Synthesis of mycobacterial phenolic glycolipids

Dijk, J.H.M. van

Synthesis of Mycobacterial Phenolic Glycolipids

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 13 oktober 2022
klokke 16:15 uur

door

Jan Hessel Michiel van Dijk

geboren te ‘s-Gravenhage
in 1992

Promotores:

Prof. dr. J.D.C. Codée

Prof. dr. G.A. van der Marel

Promotiecommissie

Prof. dr. H.S. Overkleeft	
Dr. D.V. Filippov	
Prof. dr. A. Geluk	Leids Universitair Medisch Centrum
Prof. dr. A.J. Minnaard	Rijksuniversiteit Groningen
Dr. T.L. Lowary	Academia Sinica

"The chase is better than the catch"

Scooter

Table of Contents

List of Abbreviations

Ac	Acetyl
All	Allyl
APT	Attached Proton Test
aq	Aqueous
arom	Aromatic
atm	Atmosphere
Bn	Benzyl
BSA	Bovine Serum Albumin
Bu	Butyl
Bz	Benzoyl
cat	Catalytic
Cbz	Carboxybenzyl
COSY	Correlation Spectroscopy
C_q	Quarternary carbon
CSA	Camphorsulfonic acid
d	Doublet
DABCO	Triethylenediamine
DBU	1,8-Diazabicylco[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*para*-benzoquinone
DIBAL-H	Di-*iso*-butylaluminium hydride
DIC	*N,N*-di-*iso*-propylcarbodiimide
DIPEA	*N,N*-di-*iso*-propylethylamine
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	2,2-Dimethoxypropane or Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene

EDAA	Ethyl diazoacetate
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ELISA	Enzyme-Linked ImmunoSorbent Assay
eq	Molar equivalents
Et	Ethyl
GPL	Glycopeptidolipid
HAS	Human Serum Albumin
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	Hetereonuclear Multiple Bond Correlation
HMPA	*N,N,N,N,N,N*-hexamethylphosphoramide
HOSA	Hydroxylamine-*O*-sulfonic acid
HRMS	High Resolution Mass Spectometry
HSQC	Hetereonuclear Single Quantum Coherence
IDCP	Iodonium di-*sym*-collidine perchlorate
Ig	Immunoglobuline
IL	Interleukin
IR	Infrared
J	*J*-coupling
LDA	Lithium di-*iso*-propylamide
M	Molar
m	Multiplet
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Nap	2-methylnaphtyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NTEC	*N*-thiophenyl-ε-caprolactam
p	Para
PGL	Phenolic Glycolipid

Ph	Phenyl
PIP	*para*-iodophenyl
Piv	Pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-Methoxyphenyl
PNP	*para*-Nitrophenyl
q	Quartet
quant	Quantitative
rt	Room temperature
s	Singlet
sat	Saturated
t	Tertiary
t	Triplet
TBA	Tetrabutylammonium
T-BINAP	2,2-Bis(di-*para*-tolylphosphino)-1,1-binaphtyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl or Triethylsilane
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl or Tetramethylsilane
TMU	*N,N,N,N*-tetramethylurea
TNF-α	Tumor necrosis factor α
Tol	Toluene
TRIF	Toll-interleukin-receptor-domain-containing adapter-inducing interferon β
Trt	Triphenylmethyl / Trityl

Ts	*para*-Toluenesulfonyl
TTBP	2,4,6-Tri-*tert*-butylpyrimidine
UV	Ultraviolet
δ	Chemical shift
ν	Wavenumber

Chapter 1

Developments in the synthesis of mycobacterial Phenolic Glycolipids

Part of this chapter has been published:

J. Hessel M. van Dijk, Gijs A. van der Marel, Jeroen D.C. Codée
Developments in the synthesis of mycobacterial Phenolic Glycolipids

Chem. Record 2021, 21, 3295-3312

Mycobacteria, such as those belonging to the *Mycobacterium tuberculosis* complex (MTBC) and *Mycobacterium leprae*, are arguably the most successful of all microorganisms in invading and parasitically inhabiting both animals and humans.[1] The MTBC causes tuberculosis, an infectious pulmonary disease which has plagued humanity for many centuries.[2–5] Tuberculosis (TB) claims >1.5 million lives yearly, which makes it the most deadly infectious disease globally. It is estimated that 25% of the world population has a latent infection of TB, of which 10% will progress to active disease. *Mycobacterium leprae* causes leprosy, a disease associated with loss of sensation, blindness, other lifelong handicaps and irreversible deformities.[6] Just like tuberculosis, leprosy may remain dormant in the host for years before the disease becomes active.

Mycobacteria belong to a subgroup of Gram-positive bacteria named the *Corynebacterineae*, which have an outer permeability barrier, also called the mycomembrane, which is analogous to the outer membrane of Gram-negative bacteria in an organizational manner[7] but is of a much more lipophilic character (Figure 1).[8] This highly lipophilic outer barrier is thought to be the key to the virulence and intrinsic antibiotic resistance of mycobacteria. The mycomembrane is covalently attached to arabinogalactan, a branched polysaccharide of galacto- and arabinofuranosides, which in turn is attached to peptidoglycan.

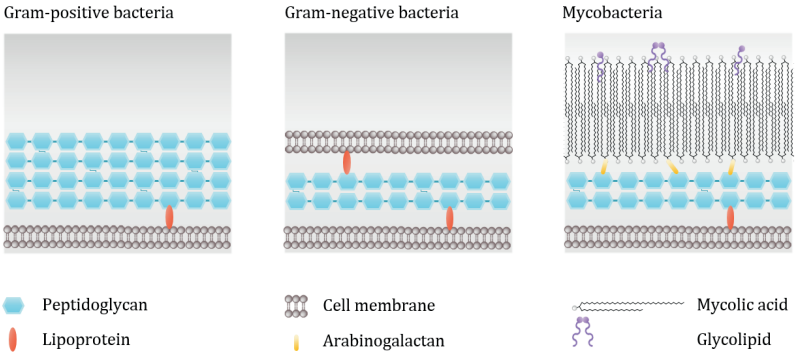
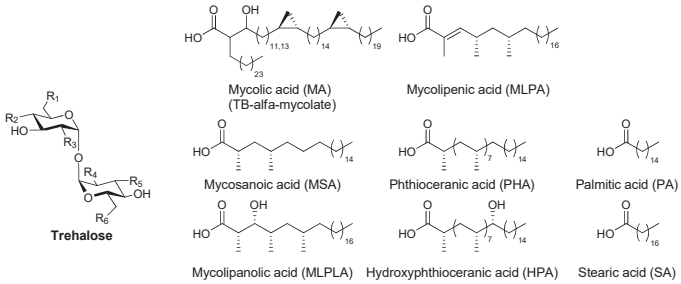


Figure 1. Schematic representation of different types of bacterial cell wall

The inner leaflet of the mycomembrane consists of mycolic acids, which are long-chain (C_{22}-C_{100}) fatty acids specific to *Corynebacterineae*.[9] The outer leaflet is composed of a variety of species-specific lipids, glycolipids (Figure 2) and proteins, which include, but are not limited to: phosphatidyl *myo*-inositol mannosides (PIMs), trehalose containing glycolipids such as lipooligosaccharides (LOS), sulfoglycolipids (SGL), trehalose monomycolate (TMM), trehalose dimycolate (TDM), diacyl-, triacyl- and pentaacyltrehalose (DAT, TAT and PAT, respectively), phthiocerol dimycocerosates (PDIM) and phenolic glycolipids (PGLs), which are phenolphthiocerol based glycolipids with a fatty acid backbone which greatly resembles PDIM.[1,10–12] The lipid content and composition of the cell wall of Mtb is important for infectivity of the bacterium and it varies during different stages of infection.[13] When the bacterium enters the lungs of the host, TLR2, TLR4 and Mincle receptors of alveolar macrophages and dendritic cells recognize TMM and TDM and this initiates an immune response.[14,15] Later in the infection cycle mycolic acid is released from TMM and TDM,[16] which dampens the immune

response, as free mycolic acid can inhibit TLR2-mediated pro-inflammatory pathways.[17] During the transition to the chronic phase of infection the host-imposed stress induces Mtb to produce more immune dampening lipids such as DAT, PAT, SGLs, PDIM and PGLs.[18–20]

PGLs and related compounds (PDIM and *p*HBAD, Figure 3) play a major role in the virulence of mycobacterial strains.[21–24] PGLs have been shown to inhibit the Toll-Like Receptor 2 (TLR2) mediated immune response, thereby reducing the production of multiple pro-inflammatory cytokines, such as TNF-α, IL-6, CCL2 and NF-κ_B.[20,25] PDIM masks other pathogen associated molecular patterns (PAMPs) on the cell wall, thereby inhibiting other pattern recognition receptor (PRR) mediated responses.[26,27] PDIM is also thought to play a role in the membrane disruption of the phagosome membrane of human lymphatic endothelial cells, allowing the bacterium to remain in the cytosol, where it can grow more rapidly.[28] PGLs are also thought to disrupt the TRIF-dependent TLR4 signaling in macrophages.[29] Furthermore, PGLs are able to recruit permissive macrophages through chemokine receptor 2 (CCR2), enabling the bacterium to travel to the lower respiratory tract.[26,30,31] If a strain of Mtb is unable to produce PGLs it will secrete an increased amount of pHBADs, biosynthetically closely related glycans, which inhibit the production of IFN-γ, thereby also dampening the immune response.[32–34]



Glycolipid	R_1	R_2	R_3	R_4	R_5	R_6
TMM	**MA**	OH	OH	OH	OH	OH
TDM	**MA**	OH	OH	OH	OH	**MA**
DAT-I	OH	OH	OH	**SA**	**MSA**	OH
DAT-II	OH	OH	OH	**SA**	**MLPLA**	OH
TAT	OH	OH	OH	**SA**	**MLPA**	**PA**
PAT	OH	**MLPA**	**MLPA**	**SA**	**MLPA**	**MLPA**
SL-I	**HPA**	OH	SO_3^-	**SA/PA**	**PHA**	**HPA**
SL-II	**HPA**	OH	SO_3^-	**SA/PA**	**HPA**	**HPA**
SL-III	OH	OH	SO_3^-	**SA/PA**	**HPA**	**HPA**
SL-IV	OH	OH	SO_3^-	**SA/PA**	**HPA**	OH

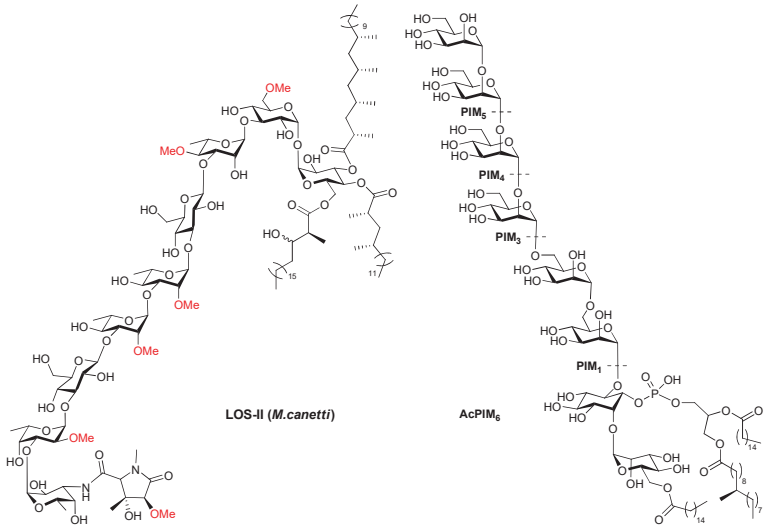


Figure 2. Schematic representation of mycobacterial glycolipids. TMM = trehalose monomycolate, TDM = trehalose dimycolate, DAT = diacyl trehalose, TAT = triacyl trehalose, PAT = pentaacyl trehalose, SL = sulfoglycolipid, LOS = lipooligosaccharide, PIM = phosphatidyl *myo*-inositol mannoside.

PGLs first occurred in the scientific literature when a lipid was found during a study of waxes of *M. bovis*,[35] characterized by an infrared spectrum, identical to one from

a lipid of *M. kansasii*[36] and these were later called mycoside B and mycoside A, respectively.[37] In 1981 Brennan and coworkers discovered a glycolipid with the same aglycone as mycoside A and B in the liver of an *M. leprae* infected armadillo in surprisingly large quantities.[38] Using gas-liquid chromatography-mass spectroscopy (GLC-MS), and later NMR studies,[39] they determined the structure to be as shown in Figure 3. The structure appeared to be unique to *M. leprae*, which makes it useful for the serological differentiation from other mycobacteria. It was at this point that they coined the name "phenolic glycolipid" (PGL) and this particular PGL was called PGL-I (Figure 3). Two more glycoforms were found shortly thereafter which seemed to differ in the methylation pattern of the glycan.[40]

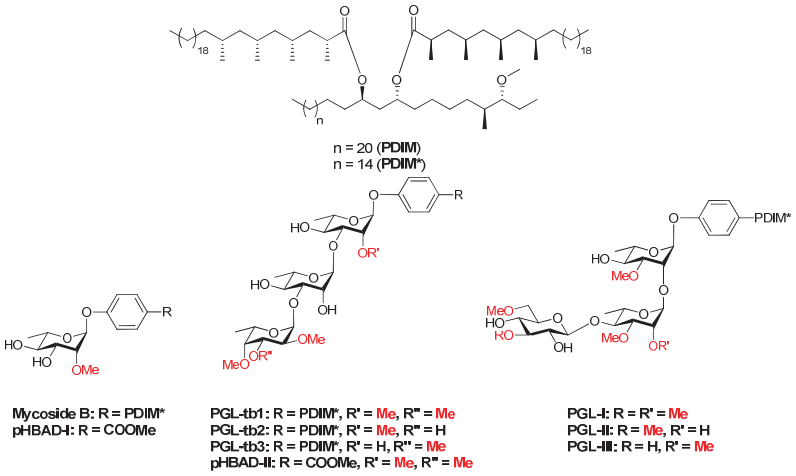
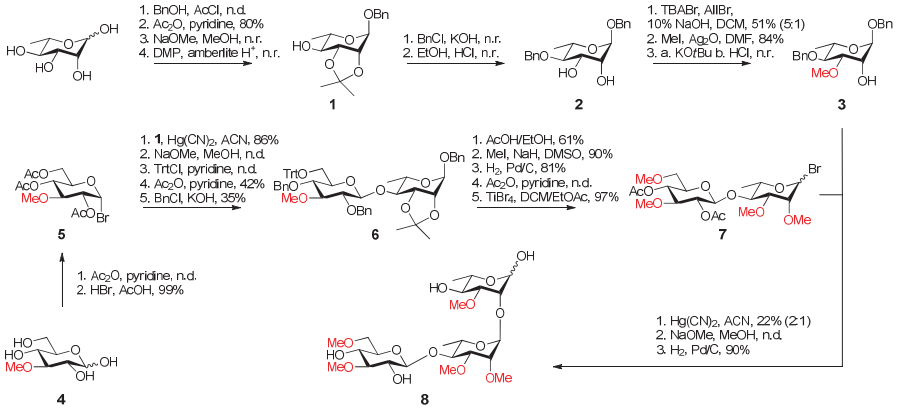


Figure 3. Phthiocerol dimycoceroserate (PDIM) and related compounds: phenolic glycolipids (PGLs) and *para*-hydroxybenzoic acid derivatives (*p*HBADs).

This chapter describes the synthetic chemistry developed to date to access *M. tuberculosis* and *M. leprae* triglycosyl PGL structures, with a focus on the assembly of the glycan part. Given the challenges associated with the complex structure of the PGLs the complete total synthesis of only a single triglycosyl PGL has been achieved so far. The first part will deal with the synthesis of *M. leprae* PGL glycans, while the second part is devoted to *M. tuberculosis* PGLs. Applications of the described synthetic glycans will be introduced.

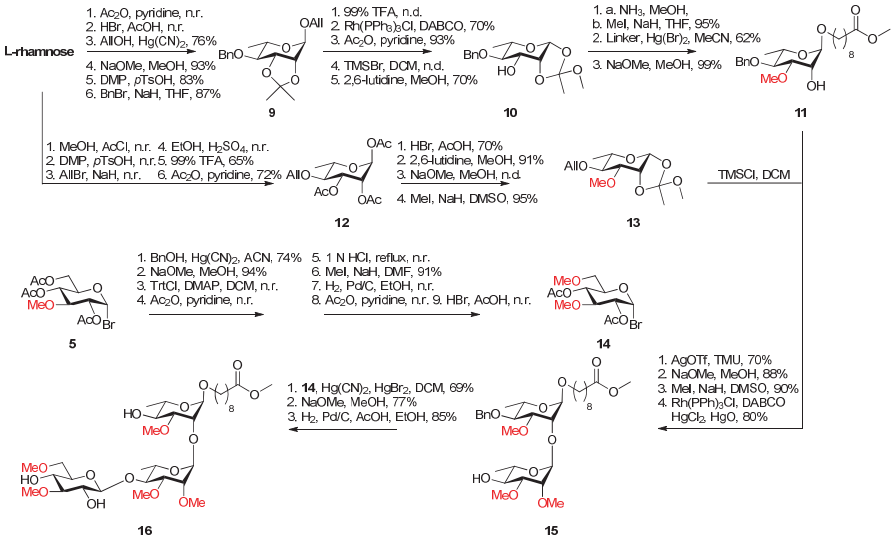
***M. leprae* PGL glycans**

The structure of the three PGL glycoforms (PGL-I, PGL-II and PGL-III) of *M. leprae* are shown in Figure 3. The general structure of *M. leprae* PGL consists of two α (1→2) linked rhamnoses which are β (1→4) linked to glucose on the non-reducing end. The reducing end rhamnoside is functionalized with a characteristic phenol, which is extended with a phthiocerol lipid, carrying two mycocerosic acids. To confirm the structures and explore their potential in serodiagnosis, Brennan and coworkers set out to synthesize the glycoforms of *M. leprae* PGLs.[41] Key in the syntheses of PGL glycans is the timing of the introduction of the multiple methyl ethers. Different strategies have been developed for the regioselective introduction of these groups both in the monosaccharide building block stage as well as in later stages of the synthesis after assembly of di- and trisaccharides. In the first PGL glycan synthesis, Brennan and co-workers[41] used building blocks **1**, **3** and **5** (Scheme 1). The regioselective methylation of the glucose building block was achieved using 1,2,5,6-di-O-isopropylideneglucofuranose as starting material, a tactic that has found wide application since. The regioselective methylation of the reducing end rhamnoside building block was accomplished by first selectively protecting the C-2 alcohol in **2** with an allyl ether, using phase-transfer catalysis conditions.[42] Next the remaining free alcohol could be methylated after which the allyl group was removed to provide the desired building block **3**. To assemble the trisaccharide, glucosyl bromide **5** and rhamnose **1** were connected under Helferich conditions using mercury cyanide.[43] Next the acid labile trityl and isopropylidene groups were removed and the liberated alcohols were methylated. The anomeric benzyl ether was then reductively removed after which acetylation and bromination provided the disaccharide donor for the next Helferich glycosylation. After connecting the disaccharide and rhamnose acceptor **3** and separating the 2:1 anomeric mixture, the acetyl groups were cleaved and the anomeric benzyl removed to provide the trisaccharide lactol **8**. As this synthesis was performed to deliver material for structure confirmation, no conjugation handle was attached to the reducing end. Nevertheless, the trisaccharide was conjugated to free lysines of BSA by means of a reductive amination and this neo-glycoconjugate was used for the detection of anti-PGL-I antibodies. While the reducing end of the trisaccharide structure was destroyed in this process, the conjugate could be used to detect anti-PGL-I antibodies.



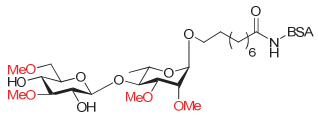
Scheme 1. First reported synthesis of the PGL-I glycan by Brennan and coworkers in 1984.[41] (n.r. = yield not reported, n.d. = yield not determined)

In 1988 Brennan and co-workers reported another synthesis of the PGL-I glycan.[44] In this synthesis they incorporated a nonyl linker on the reducing end for conjugation to BSA (Scheme 2). The regioselective methylation of the reducing end rhamnose was achieved using 1,2-orthoester building block **10**. The orthoester was then used to stereoselectively introduce the nonyl linker.[45] A similar orthoester building block (**13**, carrying a C-4 allyl ether) was transformed to the anomeric chloride by solvation in TMSCl, after which Koenigs Knorr conditions[46] were used to connect the two rhamnosides. Deacetylation then set the stage to introduce the C-2' methyl ether. Deallylation and glucosylation with glucosyl donor **14**[47] delivered the fully protected trimer, which was deprotected to provide the target PGL-I trisaccharide. The acyl azide procedure, originally developed by Lemieux and co-workers[48,49] was used for conjugation to BSA, which kept the structure of the reducing end rhamnose intact. In 1987 Fujiwara and Izumi also synthesized the PGL-I glycan using very similar chemistry. They incorporated a 3-(4-hydroxyphenyl)propionyl linker on the reducing end, more closely resembling the native structure of PGL-I.[50]



Scheme 2. Synthesis of PGL-I glycan as reported by Brennan and coworkers in 1988.[44] (n.r. = yield not reported, n.d. = yield not determined, TMU = N,N,N,N-tetramethylurea)

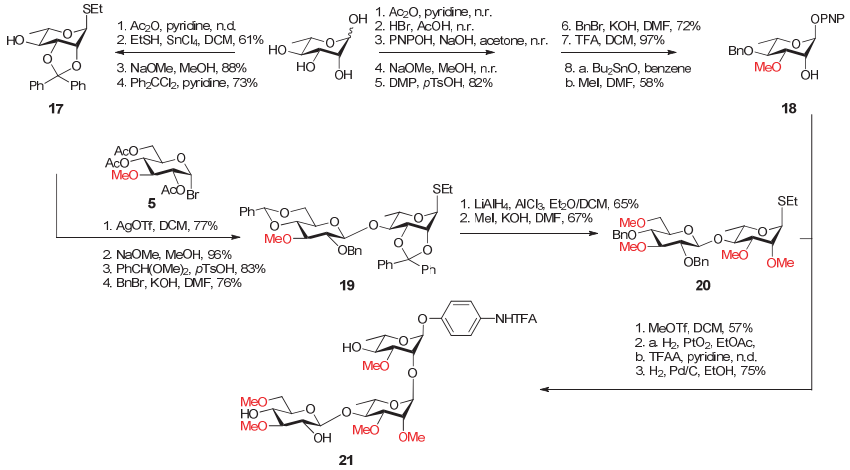
Brennan and coworkers also investigated the use of truncated PGL-I glycans for diagnostic purposes, in order to reduce the synthetic complexity and to determine structure-activity relationship with regards to antibody binding.[41,44,45,47,51] It was found that the methyl ether on the C-3 position of the terminal glucose was the most important structural determinant for antibody binding. According to their results the disaccharide based conjugate which contained the terminal glucose and central rhamnose (Natural Disaccharide – Octylcarbonyl – bovine serum albumin (ND-O-BSA)) was just as effective as the trisaccharide based conjugates for the detection of antibodies (Figure 4). Due to this ability to bind to anti-PGL-I antibodies and its synthetic simplicity this conjugate (as well as the human serum albumin version) has been the standard for leprosy diagnosis ever since.[51–54]



ND-O-BSA

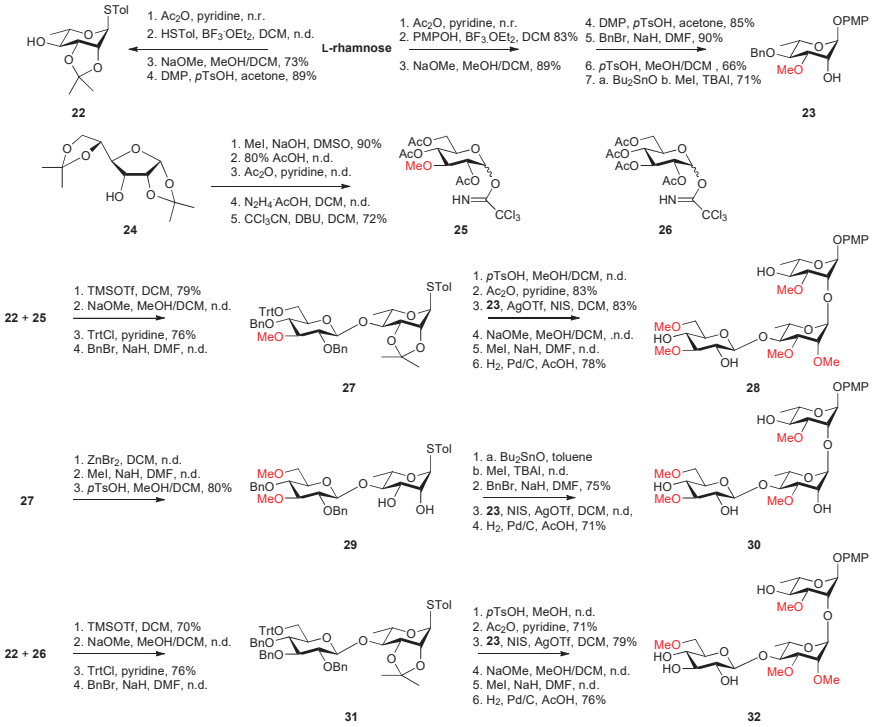
Figure 4. Natural Disaccharide - Octylcarbonyl - Bovine Serum Albumin (ND-O-BSA), the most commonly used conjugate for the detection of anti-PGL-I antibodies.

Since the reported synthesis in 1988 multiple groups have synthesized one or multiple *M. leprae* PGL glycans.[25,55–60] Líptak and coworkers investigated a new approach towards PGL-I in 1993.[60] They set out to reduce the total amount of steps required by concurrently installing multiple methyl ethers in a single step (Scheme 3). The reducing end rhamnose was selectively methylated using Bu_2SnO in refluxing benzene, and subsequent treatment of the resulting stannylidene acetal with MeI in DMF.[61] The central thiorhamnose (**17**) was to be protected with a diphenylmethylene acetal,[62] which left the C-4 alcohol free to be coupled to glucosyl bromide **5**. After the coupling and subsequent deacetylation, a benzylidene acetal was installed on the 4,6-diol of the terminal glucose. Benzylation of the remaining C-2 alcohol gave intermediate **19** which was subjected to dichloroalane, a 1:3 mixture of $LiAlH_4$ and $AlCl_3$. This mixture simultaneously liberated the primary alcohol of glucose by means of a reductive opening, while removing the diphenylmethylene acetal altogether.[63,64] The resulting three alcohols were then methylated in a single step to give thiodisaccharide **20**, which was activated with MeOTf[65] and coupling to rhamnose **18** proceeded in a stereoselective manner to give the requisite trans glycosidic linkage. The original plan was to simultaneously remove all benzyl ethers and reduce the aryl nitro group in the obtained trisaccharide with a single hydrogenation step. This proved to be more difficult than expected and a complex mixture was obtained. Therefore, they chose to first reduce the nitro moiety with Adam's catalyst (PtO_2) and acylate the resulting free amine with trifluoroacetic anhydride. The final deprotection then gave trisaccharide **21** in 25 overall steps, a big improvement over the previously reported syntheses. No further application of the obtained trisaccharide has been reported.



Scheme 3. Synthesis of PGL-I glycan as reported by Liptak and coworkers in 1993.[60] (n.r. = yield not reported, n.d. = yield not determined)

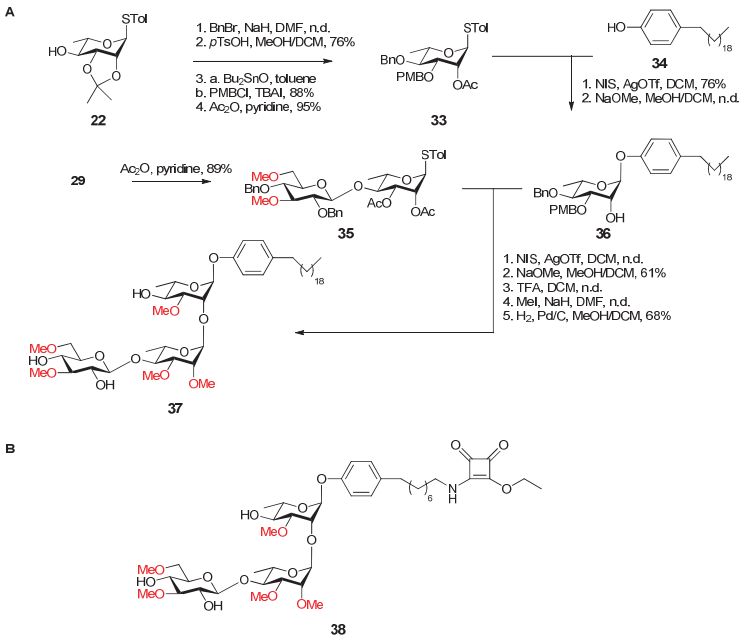
The group of Lowary synthesized all three known *M. leprae* trisaccharides in 2013 (Scheme 4).[56] In their syntheses they made use of organotin chemistry to regioselectively introduce the methyl ethers on the rhamnosides. The reducing end was capped with a *para*-methoxyphenol as an approximation of the *para*-substituted aglycone of the natural product. In a chemoselective glycosylation strategy the central rhamnose thioglycoside was glycosylated with glucosyl building block **25** or **26** to provide the thiodisaccharide. At the disaccharide stage different methylation patterns were installed, before the trisaccharides were generated in *N*-Iodosuccinimide (NIS)/AgOTf mediated glycosylation reactions.



Scheme 4. Synthesis of M.leprae PGL glycans as reported by Lowary and coworkers in 2013.[56] (n.r. = yield not reported, n.d. = yield not determined)

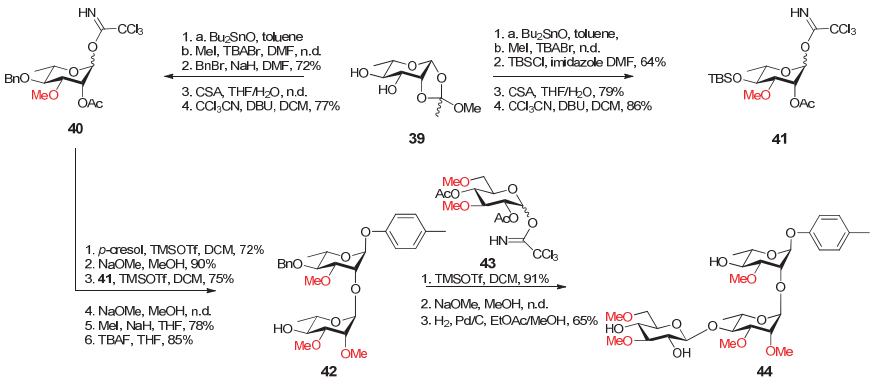
With these compounds in hand, they performed cytokine stimulation assays using THP-1 cells to find that PGL-I and the synthesized compounds could not induce cytokine production to a measurable degree. It was observed however, that they inhibited TLR2-mediated cytokine release in a concentration dependent manner. It was found that the size of the glycans and the methylation pattern were crucial for this inhibition, with the native PGL-I being the most potent. The inhibitory activity was higher when a glycan with a hydrophobic tail (**37**) was tested (Scheme 5A), which may explain why native PGL-I was the most potent inhibitor. A similar route was used by the same group to make squaramide based glycoconjugates for an array to probe the interactions of mycobacterial glycans with the innate immune system (Scheme 5B).[66] In their assay it was found that

the glycan of PGL-III binds to human Mincle, an interaction that warrants further investigation.



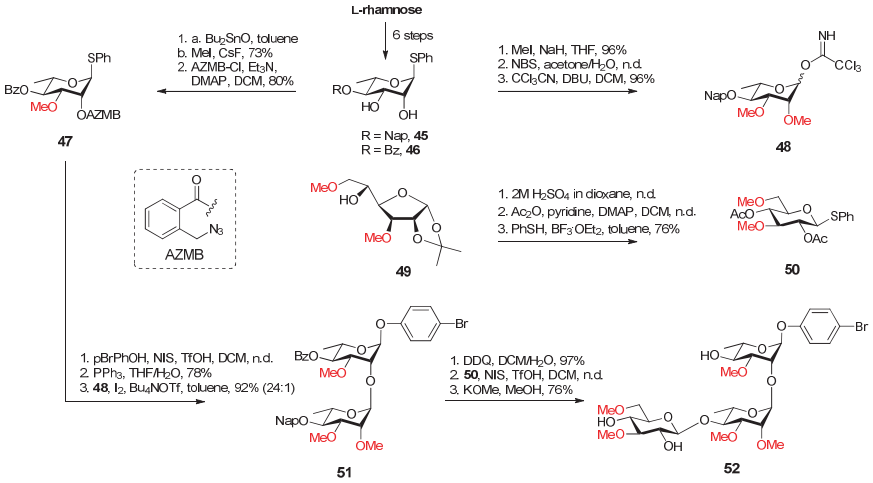
Scheme 5. A: Synthesis of PGL-I glycan with a hydrophobic anchor.[56] **B**: PGL-I glycan with a squaramide as a conjugation handle.[67] (n.r. = yield not reported, n.d. = yield not determined)

The group of Astarie-Dequeker synthesized the *M. leprae* PGL-I glycan, as well as those of Mtb and *M. bovis* in 2016 (Scheme 6).[25] The building blocks were made using a combination of orthoester and organotin chemistry. The oligosaccharides were assembled using trichloroacetimidates **40**, **41** and **43**[55] and the reducing end was capped with a *para*-cresol. The trisaccharide was used to determine possible binding to chemokine receptor 3 (CR3). It was found that CR3 could bind the glycans, but the interaction was lower than that with native PGL-I, indicating that the lipophilic aglycone enhances binding affinity. The binding of the sugar moieties is thought to be mediated by the lectin domain of CR3, which is also known to be capable of selectively binding to yeast β-(1→3)-glucans.[68] A similar route was described by Luo *et al.*, who used a *p*-aminoethylphenol on the reducing end to make a biotinylated PGL-I antigen for diagnostic purposes.[59]



Scheme 6. Synthesis of PGL-I glycan as reported by Astarie-Dequeker and coworkers in 2016.[25] (n.r. = yield not reported, n.d. = yield not determined)

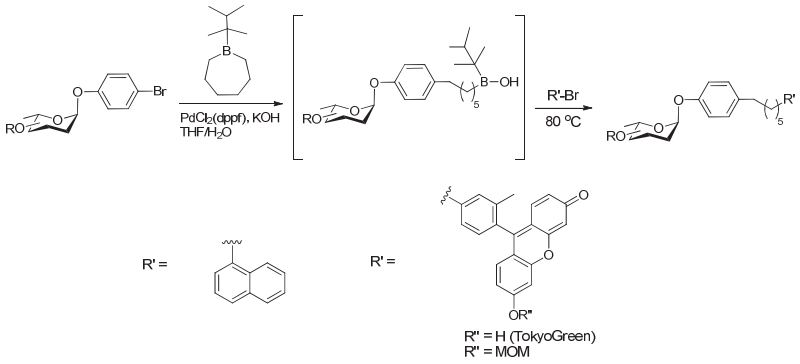
The group of Tanaka synthesized the PGL-I and PGL-tb1 glycans in 2017 (Scheme 7).[57] The reducing end rhamnose **46**[69] was selectively methylated using organotin chemistry. The C-2 position was protected with an 2-azidomethylbenzoate,[70] which could offer anchimeric assistance during the ensuing glycosylation reactions and it could be orthogonally removed in the presence of the benzoyl on the C-4 position. The thioglucose donor **50** was prepared from intermediate **49**.[71] In contrast to other syntheses discussed above, Tanaka and coworkers opted for a pre-glycosylation methylation approach for the central rhamnose moiety. The glycosylation of the 2,3-di-*O*-methyl rhamnose donor was affected under halide ion catalyzed conditions, using I_2 and Bu_4NOTf.[72] As previously reported, these conditions could be used to install the desired α-rhamnosyl linkage with good stereoselectivity, in the absence of a C-2 neighboring group.[73]



Scheme 7. Synthesis of PGL-I glycan as reported by Tanaka and coworkers in 2017. (n.r. = yield not reported, n.d. = yield not determined)

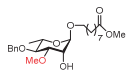
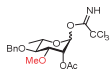
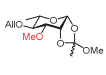
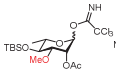
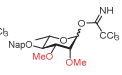
The assembled glycans were capped the with a *para*-bromophenol on the reducing end which could be used for a sequential Suzuki-Miyaura coupling with boracyclane[74,75] to attach a hydrophobic anchor or fluorophore (Scheme 8). Direct coupling with brominated TokyoGreen® did not proceed well, possibly due to the lack of solubility and reduced reactivity of the deprotonated fluorophore. Temporary protection of the phenolic alcohol in TokyoGreen® with a methoxymethyl (MOM) ether circumvented this problem and delivered the desired compounds after acidic hydrolysis. The finished compounds were tested for their immunomodulatory capabilities using bone-marrow-derived macrophages which were activated with TDM. It was observed that compounds containing just the aryl bromide on the reducing end did not inhibit TNF-α secretion. The compounds which had an aliphatic tail with a naphtyl cap as a lipid mimic on the other

hand, did inhibit cytokine secretion in a dose-dependent manner. The syntheses of PGL-I described above are summarized in Table 1.



Scheme 8. Sequential Suzuki-Miyaura coupling as reported by Tanaka et al.[57]

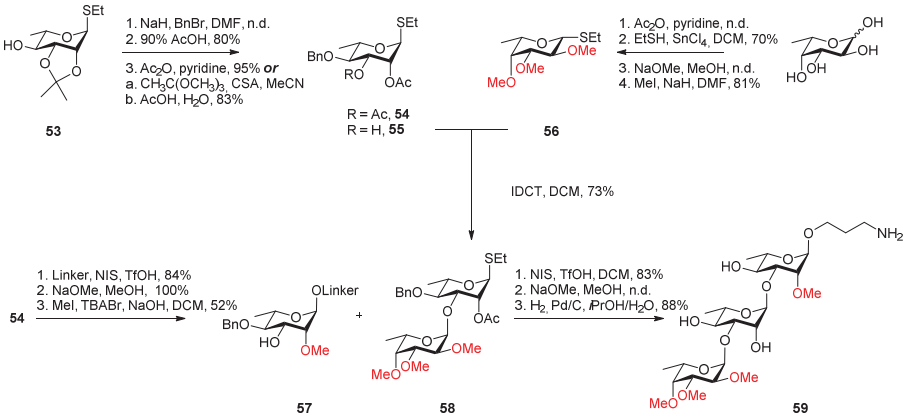
Table 1. Overview of PGL-I glycan syntheses described above.

		Brennan 1984	Brennan 1988	Liptak 1993	Lowary 2013	Astarie-Dequeker 2016	Tanaka 2017
Building blocks	1						
		9 Steps	14 Steps	8 Steps	7 Steps	7 Steps	8 Steps
	2						
		4 Steps	10 Steps	4 Steps	4 Steps	7 Steps	9 Steps
	3						
		5 Steps	14 Steps	5 Steps	6 Steps	8 Steps	8 Steps
Pre- or post-glycosylation methylation	Pre:	-	1	1	-	1,3	1,2,3
	Post:	1,2,3	2,3	2,3	1,2,3	2	-
Glycosylation method		$Hg(CN)_2$	Orthoester / $Hg(CN)_2$	AgOTf / MeOTf	TMSOTf / NIS, AgOTf	TMSOTf	NIS, TfOH / I_2, Bu_4NOTf
Glycosylation order		1 + [2 + 3]	[1 + 2] + 3	1 + [2 + 3]	1 + [2 + 3]	[1 + 2] + 3	[1 + 2] + 3
Regioselective methylation		Phase transfer catalysis	Orthoester	Bu_2SnO, MeI	Bu_2SnO MeI, TBABr	Bu_2SnO MeI, TBAI	Bu_2SnO MeI, CsF
Reducing end		Lactol	Nonyl linker	*p*-trifluoroacet-amidophenol	*p*-methoxyphenol	*p*-cresol	*p*-bromophenol
Total number of steps		28	46	25	27	27	25
Application		Structure confirmation	Detection of anti-PGL-I antibodies	None reported	THP-1 cytokine secretion assays	Tested for binding to CR3	BMM cytokine secretion assays

M. tuberculosis PGL glycans

To explore the use of *M. tuberculosis* PGLs in diagnostics, vaccine purposes and enable interaction studies at the molecular level, various syntheses of the Mtb PGLs and pHBADs have been developed as well.[25,32,57,76–80] The structures of the Mtb PGL glycoforms are depicted in Figure 3. The general structure consists of two α-(1→3)-linked rhamnoses which are α-(1→3)-linked to an L-fucose residue on the non-reducing end. The terminal fucose is 1,2-*cis* linked, which necessitates the development of effective glycosylation chemistry that cannot be built on neighboring group participation.

The group of Van Boom was the first to synthesize the PGL-tb1 trisaccharide (Scheme 9).[76] Both rhamnose building blocks were generated from the same diol intermediate, which was either diacetylated or selectively acetylated on the C-2 position using trimethylorthoformate.[81] After a linker was coupled to the diacetylated donor **54** and the product was deacetylated, the C-2-alcohol was selectively methylated using phase-transfer catalysis.[82]

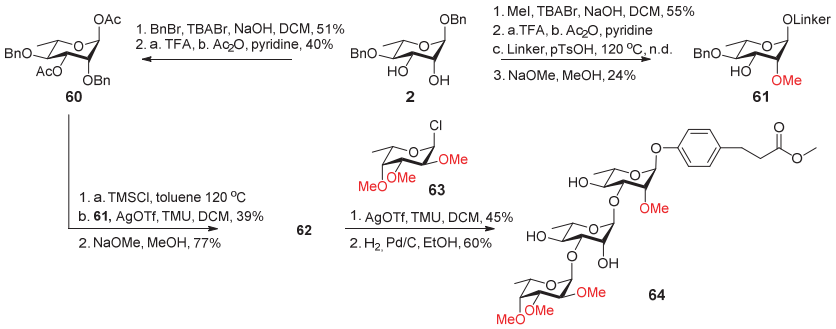


Scheme 9. Synthesis of the PGL-tb1 glycan as reported by van Boom and coworkers in 1990.[76] (n.r. = yield not reported, n.d. = yield not determined)

Monoacetylated rhamnose **55** was chemoselectively coupled to fucose donor **56** using iodonium dicollidine triflate (IDCT), which gave better results than the corresponding perchlorate salt (IDCP). This method gave a disaccharide which could be directly coupled

to monosaccharide acceptor **57**. After deprotection this route gave the desired trisaccharide **59** in only 19 steps.

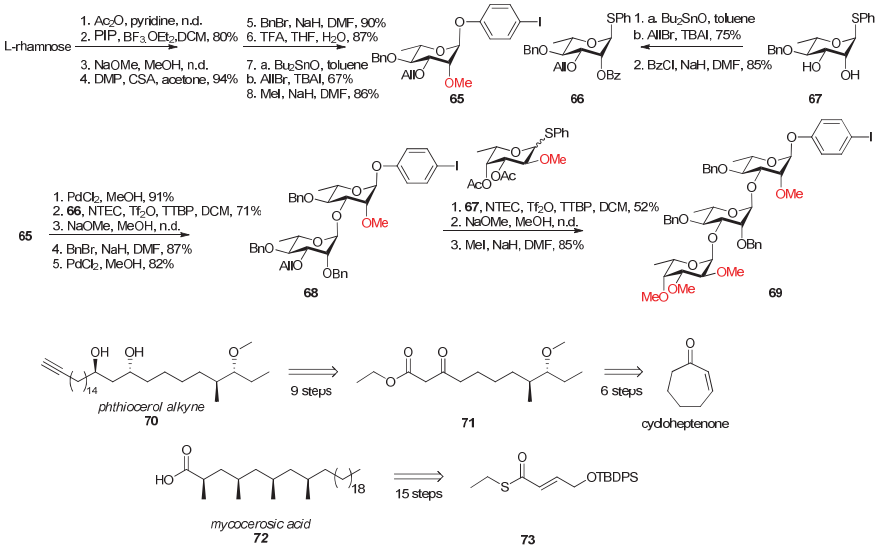
The first reported synthesis of the PGL-tb1 with a phenol on the reducing end was performed by Fujiwara (Scheme 10).[77] A 1,4-di-*O*-benzyl rhamnose intermediate, previously reported by Brennan and co-workers in 1984 for the assembly of *M. leprae* PGL-I (**2**, See Scheme 1),[41] was used as a starting point. From this intermediate phase transfer catalysis conditions were used to either install a methyl ether or a benzyl group on the C-2 position. The building blocks were glycosylated using Koenigs Knorr conditions.[46] Unfortunately both the phase transfer catalysis and glycosylation reactions provided the products with relatively low yield and selectivity. The target products could be obtained nonetheless to generate BSA conjugates in analogy to the *M. leprae* PGL conjugates. However, the Mtb PGL conjugates were not as sensitive or specific and thus not as useful for diagnostics.



Scheme 10. Synthesis of the PGL-tb1 glycan as reported by Fujiwara in 1991.[77] (n.r. = yield not reported, n.d. = yield not determined, TMU = N,N,N,N-tetramethylurea)

In 2012 Barroso *et al.* set out to synthesize the complete native PGL-tb1, including the complex phthiocerol and mycocerosic acids (Scheme 11 and 12).[79] The regioselective protection of the C-3 position of the required rhamnose building blocks was achieved using organotin chemistry.[83] The reducing end was capped with an iodophenol as this allowed for a Sonogashira coupling to attach the phthiocerol chain later in the synthesis. The glycosylation reactions were performed with a combination of *N*-thiophenyl-ε-caprolactam (NTEC) and Tf_2O as a thiophilic promoter.[84] A strategy was chosen to

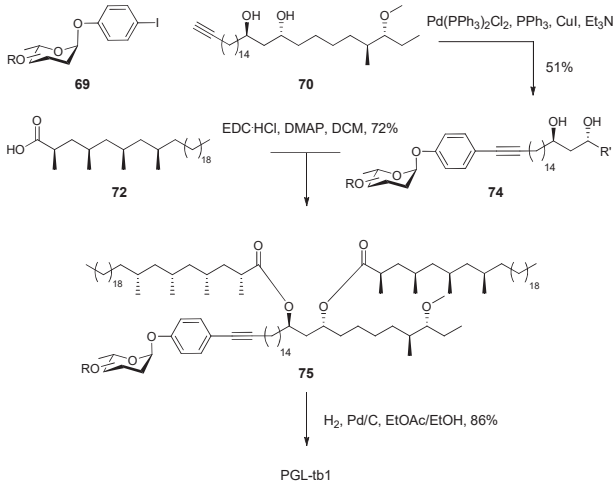
increase the stereoselectivity of the fucose donor during glycosylations by installing acetyl groups on the C-3 and C-4-alcohols.[85] This did, however, increase the number of steps required for the building block and in the trisaccharide phase of the synthesis. Key steps of the synthesis of phthiocerol include a tandem copper/phosphoramidite-catalyzed asymmetric conjugation addition to cycloheptenone to introduce the *anti*-methoxy methyl unit.[86–88] The 1,3-*anti* diol was introduced by means of an asymmetric hydrogenation of β-keto ester **71**,[89,90] followed by an Evans-Saksena reduction.[91] Mycocerosic acid was synthesized by the iterative process of copper-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated thioesters.[92–95]



Scheme 11. PGL-tb1 glycan assembly and retrosynthesis of phthiocerol and mycocerosic acid as reported by Barroso et al.[79] (n.r. = yield not reported, n.d. = yield not determined, NTEC = N-thiophenyl-ε-caprolactam)

The esters present in the target PGL-tb1 necessitated a strategy which involved the use of protecting groups that do not require acidic or basic conditions for their removal. This meant that the benzoyl group in donor **66** that was used for participation had to be swapped for a benzyl ether in the disaccharide stage (**68**) during the assembly of the trisaccharide (Scheme 11). This increased the total amount of steps required for

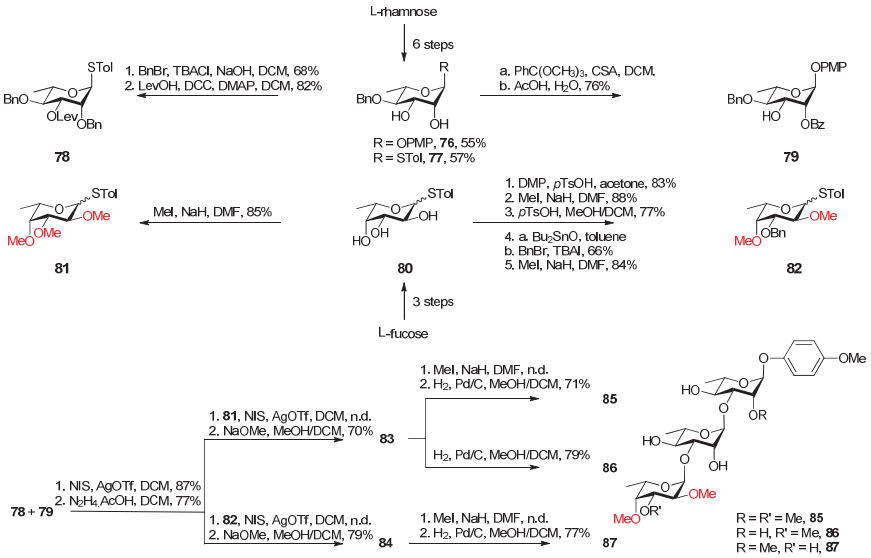
the trisaccharide but made it possible to attach phthiocerol with a Sonogashira cross coupling after which the mycocerosic acids could be attached using EDC and DMAP. During the global deprotection both the benzyl ethers and the internal alkyne, which was formed after the cross coupling, were reduced completing the highly convergent synthesis (Scheme 12). To date this has been the only PGL that has been synthesized to include the complete complex lipid. A similar approach was adopted by Meng *et al.*[78] in the generation of neo-glycoconjugates, in which the PGL-tb1 glycan, carrying a simple phenol lipid, was conjugated, through squarate chemistry, to a CRM_{197} carrier protein. It was shown that this model vaccine was capable of eliciting a high titer of anti-PGL-tb1 IgG antibodies.



Scheme 12. Final stage of assembly of PGL-tb1 as reported by Barroso et al.[79]

In 2014, the group of Lowary synthesized all three Mtb triglycosyl PGL glycans.[96] As depicted in Scheme 13, the regioselective protection of the rhamnose and fucose building blocks was achieved using orthoester chemistry, phase-transfer catalysis conditions and organotin chemistry. The reducing end was capped with a *para*-methoxyphenol and the thioglycoside donors were activated using NIS/AgOTf.[97] The selectivity of the fucosylation with the trimethylated donor was greatly enhanced by using an "inverse glycosylation procedure", in which a solution of the donor was slowly added to a mixture of the acceptor, NIS and AgOTf.[98,99] The assembled compounds were evaluated for their immunomodulatory capabilities and the structures showed a

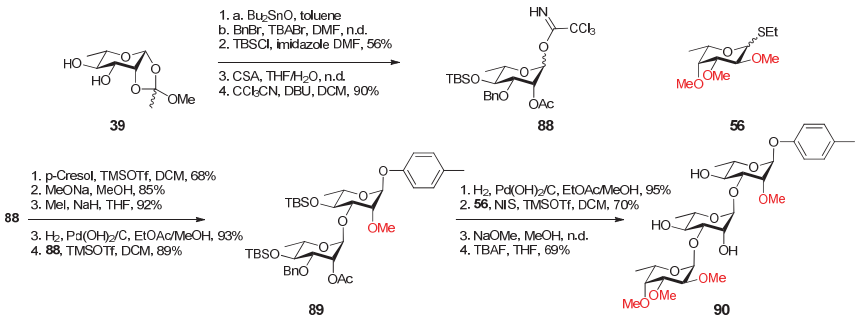
concentration-dependent inhibitory effect on the release of pro-inflammatory cytokines. PGL-tb1 turned out to be the most potent, in line with results previously obtained with *M. leprae* PGL glycans, where it was found that the structure with most methyl ethers showed the greatest inhibitory activity.[56] A similar route of synthesis was used by the same group to make squaramide based glycoconjugates, which were used to generate an array to probe the interactions of the mycobacterial glycans with lectins that play a role in the innate immune system.[66]



Scheme 13. Synthesis of Mtb PGL glycans as reported by Lowary and coworkers.[96] (n.r. = yield not reported, n.d. = yield not determined)

The group of Astarie-Dequeker synthesized the PGL-tb1 glycan in 2016[25] using a single rhamnose building block (**88**) that was assembled through a combination of orthoester and organotin chemistry (Scheme 14). A trichloroacetimidate donor was used, carrying an acetyl as a participating group, which was replaced for the required methyl ether after the first glycosylation. The reducing end was capped with a *para*-cresol moiety to mimic the natural product. Benzyl ethers were used for temporary protection and the fucosylation was performed with NIS and TMSOTf. Just two building blocks were required for this assembly and the synthesis therefore required only 19 steps in total. The PGL-tb1 glycan was able to inhibit TLR2-dependent NF-κB activation of THP-1 cells triggered by

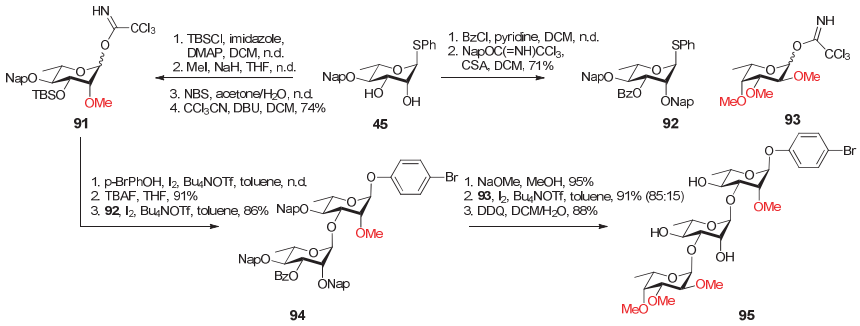
PAM_3CSK_4, which indicated that the glycans of both *M.tuberculosis* and *M.leprae* are able to antagonize TLR2. PDIM alone showed no inhibitory activity but native PGLs showed a 10 fold increase over the glycans lacking the lipid tail. It was therefore hypothesized that the trisaccharides are responsible for the specificity of binding to TLR2, but that the common lipid core enhances the affinity, possibly by improving presentation. Further investigations with a library of aglycone analogs in combination with docking studies may shed light on the interaction between PGLs and TLR2.



Scheme 14. Synthesis of the PGL-tb1 glycan as reported by Astarie-Dequeker and coworkers.[25] (n.r. = yield not reported, n.d. = yield not determined)

In 2017 Tanaka *et al.* reported the MTb PGL synthesis depicted in Scheme 15.[57] They opted for a pre-glycosylation methylation approach for the methylated rhamnose and fucose building blocks, making use of their halide ion catalyzed glycosylation chemistry using I_2 and Bu_4NOTf.[72] When they performed the synthesis of the trisaccharide with a rhamnose building block starting from intermediate **45**,[69] carrying a C-2 benzoyl ester, the final fucosylation produced an inseparable 1:1 anomeric mixture. To improve this glycosylation, they chose to rely on their halide ion based glycosylation for the disaccharide coupling. Therefore, rhamnose donor **92** was synthesized, which was selectively benzoylated on the C-3 position, after which the C-2 position was naphthylated using naphthyl imidate to prevent migration of the benzoate under basic conditions. The disaccharide coupling proceeded with a higher yield and only the α product was formed, which may be accounted for by long range participation of the C-3-*O*-benzoyl.[100] When the fucosylation was attempted with the C-2' naphthyl disaccharide acceptor the

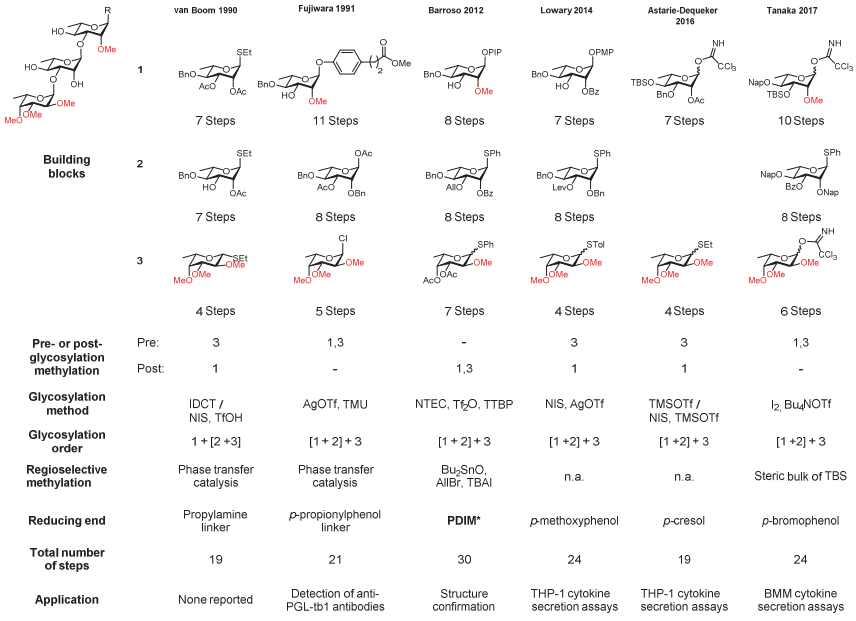
selectivity of the glycosylation was increased to a 85:15 (α/β), highlighting the importance of acceptor reactivity in the glycosylation reaction.[101,102]



Scheme 15. Synthesis of the PGL-tb1 glycan as reported by Tanaka and coworkers.[57] (n.r. = yield not reported, n.d. = yield not determined)

In contrast to results obtained by Astarie-Dequeker and co-workers, a glycan lacking the terminal trimethylated fucose showed a greater inhibition of TNF-α secretion than the corresponding trisaccharide. The syntheses of PGL-tb1 described above are summarized in Table 2.

Table 2. Overview of PGL-tb1 glycan syntheses described above. (n.a. = not applicable)



Conclusion and thesis outline

Progress in carbohydrate chemistry has enabled the efficient synthesis of the PGL glycans. The assembly of the necessary building blocks requires regioselective manipulations, which are nowadays well established. A multitude of glycosylation conditions have allowed for the stereoselective condensation of these building blocks to form the complex trisaccharides that can be used to investigate the interactions between the human immune system and the bacterial glycans. Insights acquired by these investigations has spurred the development of new ways to diagnose and treat the diseases caused by these pathogens. Although much progress has been made in synthetic carbohydrate chemistry, allowing access to the PGL trisaccharides, the synthesis of a complete PGL, including the phthiocerol and mycocerosic acids, has only once been reported. No immunological evaluation of the assembled PGL has been reported. The synthetic PGL glycans have been used to establish how the different glycosylation and methylation patterns shape the immune response. As PGLs have been reported to interact with TLR2, a PRR that binds lipopeptides, it is expected that attaching the complete

phthiocerol chain and mycocerosic acids will significantly impact the activity of the PGL. A library of complete PGLs will be required to fully understand the interaction of these molecules with the host immune system. The synthesis of this complete library and other PGL-related molecules will be described in the coming chapters. **Chapter 2** describes the synthesis of PGL conjugates of trisaccharides originating from *M. leprae* which can be used for the detection of anti-PGL-I antibodies in sera using a lateral flow assay. **Chapter 3** describes the synthesis of an alkyne derivative of phthiocerol A which can be used for the synthesis of complete PGLs. **Chapter 4** describes the synthesis of all known PGLs of the *Mycobacterium tuberculosis* Complex (MTBC). **Chapter 5** describes the synthesis of all known PGLs of *M. leprae* and *M. haemophilum* and **Chapter 6** reports the syntheses of PGLs of *M. kansasii* and *M. gastri*. In **Chapter 7** several aglycone analogues of some PGLs are synthesized which can be used to try to determine the role of lipid complexity in the binding of PGLs to receptors as well as antigen presentation. In the concluding **Chapter 8** the results described in the preceding chapters are summarized and some future prospects are presented.

References

1. Chiaradia, L. *et al.* Dissecting the mycobacterial cell envelope and defining the composition of the native mycomembrane. *Sci. Rep.* **7**, 1–12 (2017).
2. Glaziou, P., Floyd, K. & Raviglione, M. C. Global Epidemiology of Tuberculosis. *Semin. Respir. Crit. Care Med.* **39**, 271–285 (2018).
3. Young, D. B., Perkins, M. D., Duncan, K. & Barry, C. E. Confronting the scientific obstacles to global control of tuberculosis. *J. Clin. Invest.* **118**, 1255–1265 (2008).
4. Gennaro, M. L. Immunologic diagnosis of tuberculosis: A review. *Tuber. Lung Dis.* **80**, 131–140 (2000).
5. Keeler, E. *et al.* Reducing the global burden of tuberculosis: the contribution of improved diagnostics. *Nature* **444**, 49–57 (2006).
6. Fischer, M. Leprosy – an overview of clinical features, diagnosis, and treatment. *JDDG - J. Ger. Soc. Dermatology* **15**, 801–827 (2017).
7. Zuber, B. *et al.* Direct visualization of the outer membrane of mycobacteria and corynebacteria in their native state. *J. Bacteriol.* **190**, 5672–5680 (2008).
8. Vincent, A. T. *et al.* The mycobacterial cell envelope: A relict from the past or the result of recent evolution? *Front. Microbiol.* **9**, 1–9 (2018).
9. Marrakchi, H., Lanéelle, M. A. & Daffé, M. Mycolic acids: Structures, biosynthesis, and beyond. *Chem. Biol.* **21**, 67–85 (2014).
10. Daffé, M. & Draper, P. The Envelope Layers of Mycobacteria with Reference to their Pathogenicity. in *Advances in Microbial Physiology* vol. 39 131–203 (1997).
11. Dulberger, C. L., Rubin, E. J. & Boutte, C. C. The mycobacterial cell envelope — a moving target. *Nat. Rev. Microbiol.* **18**, 47–59 (2020).
12. Ouellet, H., Johnston, J. B. & Montellano, P. R. O. de. Cholesterol catabolism as a therapeutic target in Mycobacterium tuberculosis. *Trends Microbiol.* **19**, 530–539 (2011).
13. Queiroz, A. & Riley, L. W. Bacterial immunostat: Mycobacterium tuberculosis lipids and their role in the host immune response. *Rev. Soc. Bras. Med. Trop.* **50**, 9–18 (2017).
14. Khoo, K. H., Dell, A., Morris, H. R., Breman, P. J. & Chatterjee, D. Structural definition of acylated phosphatidylinositol mannosides from Mycobacterium tuberculosis: Definition of a common anchor for lipomannan and lipoarabinomannan. *Glycobiology* **5**, 117–127 (1995).
15. Sakamoto, K. *et al.* Mycobacterial trehalose dimycolate reprograms macrophage global gene expression and activates matrix metalloproteinases. *Infect. Immun.* **81**, 764–776 (2013).
16. Ojha, A. K., Trivelli, X., Guerardel, Y., Kremer, L. & Hatfull, G. F. Enzymatic hydrolysis of trehalose dimycolate releases free mycolic acids during mycobacterial growth in biofilms. *J. Biol. Chem.* **285**, 17380–17389 (2010).
17. Sequeira, P. C., Senaratne, R. H. & Riley, L. W. Inhibition of toll-like receptor 2 (TLR-2)-mediated response in human alveolar epithelial cells by mycolic acids and Mycobacterium tuberculosis mce1 operon mutant. *Pathog. Dis.* **70**, 132–140 (2014).
18. Karakousis, P. C., Bishal, W. R. & Dorman, S. E. Mycobacterium tuberculosis cell envelope lipids and the host immune response. *Cell. Microbiol.* **6**, 105–116 (2004).
19. Mendum, T. A., Wu, H., Kierzek, A. M. & Stewart, G. R. Lipid metabolism and type VII secretion systems dominate the genome scale virulence profile of Mycobacterium tuberculosis in human dendritic cells. *BMC Genomics* **16**, 1–14 (2015).
20. Blanc, L. *et al.* Mycobacterium tuberculosis inhibits human innate immune responses via the production of TLR2 antagonist glycolipids. *Proc. Natl. Acad. Sci. U. S. A.* **114**, 11205–11210 (2017).

21. Yu, J. *et al.* Both phthiocerol dimycocerosates and phenolic glycolipids are required for virulence of Mycobacterium marinum. *Infect. Immun.* **80**, 1381–1389 (2012).

22. Fournie, J. J., Adams, E., Mullins, R. J. & Basten, A. Inhibition of human lymphoproliferative responses by mycobacterial phenolic glycolipids. *Infect. Immun.* **57**, 3653–3659 (1989).

23. Barnes, D. D., Lundahl, M. L. E., Lavelle, E. C. & Scanlan, E. M. The Emergence of Phenolic Glycans as Virulence Factors in Mycobacterium tuberculosis. *ACS Chem. Biol.* **12**, 1969–1979 (2017).

24. Murry, J. P., Pandey, A. K., Sassetti, C. M. & Rubin, E. J. Phthiocerol Dimycocerosate Transport Is Required for Resisting Interferon-γ–Independent Immunity. *J. Infect. Dis.* **200**, 774–782 (2009).

25. Arbués, A. *et al.* Trisaccharides of Phenolic Glycolipids Confer Advantages to Pathogenic Mycobacteria through Manipulation of Host-Cell Pattern-Recognition Receptors. *ACS Chem. Biol.* **11**, 2865–2875 (2016).

26. Cambier, C. J. *et al.* Mycobacteria manipulate macrophage recruitment through coordinated use of membrane lipids. *Nature* **505**, 218–222 (2014).

27. Arbues, A., Lugo-Villarino, G., Neyrolles, O., Guilhot, C. & Astarie-Dequeker, C. Playing hide-and-seek with host macrophages through the use of mycobacterial cell envelope phthiocerol dimycocerosates and phenolic glycolipids. *Front. Cell. Infect. Microbiol.* **4**, 1–7 (2014).

28. Lerner, T. R. *et al.* Phthiocerol dimycocerosates promote access to the cytosol and intracellular burden of Mycobacterium tuberculosis in lymphatic endothelial cells. *BMC Biol.* **16**, 1 (2018).

29. Oldenburg, R. *et al.* Mycobacterial phenolic glycolipids selectively disable TRIF-dependent TLR4 signaling in macrophages. *Front. Immunol.* **9**, 1–12 (2018).

30. Cambier, C. J., O'Leary, S. M., O'Sullivan, M. P., Keane, J. & Ramakrishnan, L. Phenolic Glycolipid Facilitates Mycobacterial Escape from Microbicidal Tissue-Resident Macrophages. *Immunity* **47**, 552-565.e4 (2017).

31. Astarie-Dequeker, C. *et al.* Phthiocerol Dimycocerosates of *M. tuberculosis* Participate in Macrophage Invasion by Inducing Changes in the Organization of Plasma Membrane Lipids. *PLoS Pathog.* **5**, e1000289 (2009).

32. Bourke, J., Brereton, C. F., Gordon, S. V., Lavelle, E. C. & Scanlan, E. M. The synthesis and biological evaluation of mycobacterial p-hydroxybenzoic acid derivatives (p-HBADs). *Org. Biomol. Chem.* **12**, 1114–1123 (2014).

33. Hisert, K. B. *et al.* Identification of Mycobacterium tuberculosis Counterimmune (cim) Mutants in Immunodeficient Mice by Differential Screening. *Infect. Immun.* **72**, 5315–5321 (2004).

34. Stadthagen, G. *et al.* Comparative investigation of the pathogenicity of three Mycobacterium tuberculosis mutants defective in the synthesis of p-hydroxybenzoic acid derivatives. *Microbes Infect.* **8**, 2245–2253 (2006).

35. Noll, H. The chemistry of some native constituents of the purified wax of Mycobacterium tuberculosis. *J. Biol. Chem.* **224**, 149–164 (1957).

36. Smith, D. W., Randall, H. M., Gastambide-Odier, M. M. & Koevoet, A. L. The Characterization of Mycobacterial Strains by the Composition of their Lipid Extracts. *Ann. N. Y. Acad. Sci.* **69**, 145–157 (1957).

37. Smith, D. W., Randall, H. M., MacLennan, A. P. & Lederer, E. Mycosides: A new class of type-specific glycolipids of mycobacteria. *Nature* **186**, 887–888 (1960).

38. Hunter, S. W. & Brennan, P. J. A novel phenolic glycolipid from Mycobacterium leprae possibly involved in immunogenicity and pathogenicity. *J. Bacteriol.* **147**, 728–735 (1981).

39. Hunter, S. W., Fujiwara, T. & Brennan, P. J. Structure and antigenicity of the major specific glycolipid antigen of Mycobacterium leprae. *J. Biol. Chem.* **257**, 15072–15078 (1982).

40. Hunter, S. W. & Brennan, P. J. Further specific extracellular phenolic glycolipid antigens and a

related diacylphthiocerol from Mycobacterium leprae. *J. Biol. Chem.* **258**, 7556–7562 (1983).

41. Fujiwara, T., Hunter, S. W., Cho, S. N., Aspinall, G. O. & Brennan, P. J. Chemical synthesis and serology of disaccharides and trisaccharides of phenolic glycolipid antigens from the leprosy bacillus and preparation of a disaccharide protein conjugate for serodiagnosis of leprosy. *Infect. Immun.* **43**, 245–252 (1984).

42. Handa, V. K., Piskorz, C. F., Barlow, J. J. & Matta, K. L. Selective monobenzylation of methyl 4-O-benzyl-α-L-rhamnopyranoside. *Carbohydr. Res.* **74**, C5 (1979).

43. Helferich, B. & Weis, K. Zur Synthese von Glucosiden und von nicht-reduzierenden Disacchariden. *Chem. Ber.* **89**, 314–321 (1956).

44. Chatterjee, D. *et al.* Synthesis and immunoreactivity of neoglycoproteins containing the trisaccharide unit of phenolic glycolipid I of Mycobacterium leprae. *Carbohydr. Res.* **183**, 241–260 (1988).

45. Chatterjee, D., Cho, S. N., Brennan, P. J. & Aspinall, G. O. Chemical synthesis and seroreactivity of O-(3,6-di-O-methyl-β-D-glucopyranosyl)-(1→4)-O-(2,3-di-O-methyl-α-lrhamnopyranosyl)-(1→9)-oxynonanoyl-bovine serum albumin-the leprosy-specific, natural disaccharide-octyl-neoglycoprotein. *Carbohydr. Res.* **156**, 39–56 (1986).

46. HANESSIAN, S. & BANOUB, J. Innovations in Synthetic Carbohydrate Chemistry—Practical and Conceptual Approaches to Glycoside Synthesis. in *Synthetic Methods for Carbohydrates* 36–63 (1977). doi:10.1021/bk-1977-0039.ch003.

47. Chatterjee, D. *et al.* Synthesis of Neoglycoproteins containing the 3,6-di-O-methyl-β-D-glucopyranosyl epitope and their use in serodiagnosis of leprosy. *Glycoconj. J.* **2**, 187–208 (1985).

48. Lemieux, R. U., Baker, D. A. & Bundle, D. R. A methodology for the production of carbohydrate specific antibody. *Can. J. Biochem.* **55**, 507–512 (1977).

49. Lemieux, R. U., Bundle, D. R. & Baker, D. A. the Properties of a "Synthetic" Antigen Related to the Human Blood-Group Lewis a. *J. Am. Chem. Soc.* **97**, 4076–4083 (1975).

50. Fujiwara, T. & Izumi, S. Synthesis of the Neoglycoconjugates of Phenolic Glycolipid-related Trisaccharides for the Serodiagnosis of Leprosy. *Agric. Biol. Chem.* **51**, 2539–2547 (1987).

51. Zhang, J., Chatterjee, D., Brennan, P. J., Spencer, J. S. & Liav, A. A modified synthesis and serological evaluation of neoglycoproteins containing the natural disaccharide of PGL-I from Mycobacterium leprae. *Bioorganic Med. Chem. Lett.* **20**, 3250–3253 (2010).

52. Bührer, S. S., Smits, H. L., Gussenhoven, G. C., Van Ingen, C. W. & Klatser, P. R. A simple dipstick assay for the detection of antibodies to phenolic glycolipid-I of Mycobacterium leprae. *Am. J. Trop. Med. Hyg.* **58**, 133–136 (1998).

53. Buhrer-Sékula, S. *et al.* Simple and Fast Lateral Flow Test for Classification of Leprosy Patients and Identification of Contacts with High Risk of Developing Leprosy Downloaded from http://jcm.asm.org/ on June 5, 2016 by Staats-und Universitaetsbibliothek Bremen. *J. Clin. Microbiol.* **41**, 1991–1995 (2003).

54. Spencer, J. S. *et al.* Analysis of antibody responses to Mycobacterium leprae phenolic glycolipid I, lipoarabinomannan, and recombinant proteins to define disease subtype-specific antigenic profiles in leprosy. *Clin. Vaccine Immunol.* **18**, 260–267 (2011).

55. Wu, X., Mariño-Albernas, J. R., Auzanneau, F. I., Verez-Bencomo, V. & Pinto, B. M. Synthesis and NMR analysis of ^{13}C-labeled oligosaccharides corresponding to the major glycolipid from Mycobacterium leprae. *Carbohydr. Res.* **306**, 493–503 (1998).

56. Elsaidi, H. R. H., Barreda, D. R., Cairo, C. W. & Lowary, T. L. Mycobacterial phenolic glycolipids with a simplified lipid aglycone modulate cytokine levels through toll-like receptor 2. *ChemBioChem* **14**, 2153–2159 (2013).

57. Sato, K. *et al.* Synthesis and Biological Evaluation of O-Methylated Glycolipids Related to PGLs via

Direct Stereoselective Glycosidation and Sequential Suzuki–Miyaura Coupling using Boracyclane. *Chem. – A Eur. J.* **23**, 16374–16379 (2017).

58. Bock, K., Hvidt, T., Marino-Albernas, J. & Verez-Bencomo, V. An n.m.r. and conformational analysis of the terminal trisaccharide from the serologically active glycolipid of Mycobacterium leprae in different solvents. *Carbohydr. Res.* **200**, 33–45 (1990).

59. Luo, W. Y., Lu, B., Zhou, R. Y., Hu, X. & Wang, J. Chemical Synthesis of the Trisaccharide Epitope of Phenolic Glycolipid-1 Surface Antigen from Mycobacterium leprae. *J. Org. Chem.* **85**, 10973–10979 (2020).

60. Borbás, A. & Lipták, A. A new approach to the chemical synthesis of the trisaccharide, and the terminal di- and mono-saccharide units of the major, serologically active glycoplipid from Mycobacterium leprae. *Carbohydr. Res.* **241**, 99–116 (1993).

61. Augé, C., David, S. & Veyrières, A. Complete regiospecificity in the benzylation of a cis-diol by the stannylidene procedure. *J. Chem. Soc., Chem. Commun.* **14**, 375–376 (1976).

62. Lipták, A., Szabó, L. & Harangi, J. Synthesis of methyl 1-thio-L-rhamnopyranoside derivatives. *J. Carbohydr. Chem.* **7**, 687–699 (1988).

63. Hajkó, J., Borbás, A., Lipták, A. & Kajtár-Peredy, M. Preparation of dioxolane-type fluoren-9-ylidene acetals of carbohydrates and their hydrogenolysis with AlClH 2 to give axial fluoren-9-yl ethers. *Carbohydr. Res.* **216**, 413–420 (1992).

64. Lipták, A., Jodál, I. & Nánási, P. Stereoselective ring-cleavage of 3-O-benzyl- and 2,3-di-O-benzyl-4,6-O-benzylidenehexopyranoside derivatives with the LiAlH4⍰AlCl3, reagent. *Carbohydr. Res.* **44**, 1–11 (1975).

65. Lönn, H. Synthesis of a tri- and a hepta-saccharide which contain α-L-fucopyranosyl groups and are part of the complex type of carbohydrate moiety of glycoproteins. *Carbohydr. Res.* **139**, 105–113 (1985).

66. Zheng, R. B. *et al.* Insights into Interactions of Mycobacteria with the Host Innate Immune System from a Novel Array of Synthetic Mycobacterial Glycans. *ACS Chem. Biol.* **12**, 2990–3002 (2017).

67. Zheng, R. B. *et al.* Insights into Interactions of Mycobacteria with the Host Innate Immune System from a Novel Array of Synthetic Mycobacterial Glycans. *ACS Chem. Biol.* **12**, 2990–3002 (2017).

68. Malaga, W. *et al.* Deciphering the genetic bases of the structural diversity of phenolic glycolipids in strains of the Mycobacterium tuberculosis complex. *J. Biol. Chem.* **283**, 15177–15184 (2008).

69. Frihed, T. G., Pedersen, C. M. & Bols, M. Synthesis of all eight stereoisomeric 6-deoxy-L-hexopyranosyl donors - Trends in using stereoselective reductions or mitsunobu epimerizations. *European J. Org. Chem.* **2014**, 7924–7939 (2014).

70. Wada, T., Ohkubo, A., Mochizuki, A. & Sekine, M. 2-(Azidomethyl)benzoyl as a new protecting group in nucleosides. *Tetrahedron Lett.* **42**, 1069–1072 (2001).

71. Fried, J. & Walz, D. E. Streptomycin. XI. 1 Synthesis of 3,6-Dimethyl-N-methyl-D-glucosamine 2. *J. Am. Chem. Soc.* **74**, 5468–5472 (1952).

72. Lemieux, R. U., Hendriks, K. B., Stick, R. V. & James, K. Halide Ion Catalyzed Glycosidation Reactions. Syntheses of α-Linked Disaccharides. *J. Am. Chem. Soc.* **97**, 4056–4062 (1975).

73. Tanaka, H. *et al.* Efficient synthesis of the deoxysugar part of versipelostatin by direct and stereoselective glycosylation and revision of the structure of the trisaccharide unit. *Chem. - An Asian J.* **4**, 1114–1125 (2009).

74. Matos, K. & Soderquist, J. A. Alkylboranes in the Suzuki-Miyaura Coupling: Stereochemical and Mechanistic Studies. *J. Org. Chem.* **63**, 461–470 (1998).

75. Suzuki, R., Fuse, S. & Tanaka, H. Synthesis of Asymmetrical-Terminally Bifunctionlized Alkanes by Sequential Suzuki–Miyaura Coupling Using B-Thexylboracyclanes. *European J. Org. Chem.* **2016**, 3478–3481 (2016).

76. Veeneman, G. H., Leeuwen, S. H. V., Zuurmond, H. & Boom, J. H. V. Synthesis of carbohydrate-antegenic structures of mycobacterium tuberculosis using an iodonium ion promoted glycosidation approach. *J. Carbohydr. Chem.* **9**, 783–796 (1990).

77. Fujiwara, T. Synthesis of the Trisaccharide-Protein Conjugate of the Phenolic Glycolipid of Mycobacterium tuberculosis for the Serodiagnosis of Tuberculosis . *Agric. Biol. Chem.* **55**, 2123–2128 (1991).

78. Meng, X. *et al.* Synthesis and immunogenicity of PG-tb1 monovalent glycoconjugate. *Eur. J. Med. Chem.* **134**, 140–146 (2017).

79. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie Int. Ed.* **51**, 11774–11777 (2012).

80. Gurjar, M. K. & Viswanadham, G. S ynthesis of meα-L-rhap-(1→3)-2-0-me-α-L-rhap and me 2, 3, 4-tri-0-me-α-L-fucp-{1→3)-2-0-L-rhap: Oligosaccha-ride segments of phenolic glycolipids in mycobacterium bovis bcg and tuberculosis strain canetti. *J. Carbohydr. Chem.* **10**, 481–485 (1991).

81. King, J. F. & Allbutt, A. D. Remarkable stereoselectivity in the hydrolysis of dioxolenium ions and orthoesters fused to anchored six-membered rings. *Can. J. Chem.* **48**, 1754–1769 (1970).

82. Pozsgay, V. Synthesis of partially protected benzyl and methyl α-L-rhamnopyranosides by the phase-transfer technique. *Carbohydr. Res.* **69**, 284–286 (1979).

83. Guibé, F. Allylic protecting groups and their use in a complex environment Part I: Allylic protection of alcohols. *Tetrahedron* **53**, 13509–13556 (1997).

84. Durón, S. G., Polat, T. & Wong, C. N-(Phenylthio)-E-caprolactam: A New Promoter for the Activation of Thioglycosides. *Org. Lett.* 2003–2005 (2004).

85. Depré, D. *et al.* Synthesis of glycans from the glycodelins: Two undeca-, two deca-, three nona-, an octa- and a heptasaccharide. *Chem. - A Eur. J.* **5**, 3326–3340 (1999).

86. Casas-Arce, E., Ter Horst, B., Feringa, B. L. & Minnaard, A. J. Asymmetric total synthesis of PDIM A: A virulence factor of Mycobacterium tuberculosis. *Chem. - A Eur. J.* **14**, 4157–4159 (2008).

87. Guo, H. C. & Ma, J. A. Catalytic asymmetric tandem transformations triggered by conjugate additions. *Angew. Chemie - Int. Ed.* **45**, 354–366 (2006).

88. Arnold, L. A. *et al.* Enantioselective catalytic conjugate addition of dialkylzinc reagents using copper-phosphoramidite complexes; ligand variation and non-linear effects. *Tetrahedron* **56**, 2865–2878 (2000).

89. Mashima, K. *et al.* Cationic BINAP-Ru(II) Halide Complexes: Highly Efficient Catalysts for Stereoselective Asymmetric Hydrogenation of .alpha.- and .beta.-Functionalized Ketones. *J. Org. Chem.* **59**, 3064–3076 (1994).

90. Noyori, R. *et al.* Stereoselective hydrogenation via dynamic kinetic resolution. *J. Am. Chem. Soc.* **111**, 9134–9135 (1989).

91. Evans, D. A., Chapman, K. T. & Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **110**, 3560–3578 (1988).

92. ter Horst, B., Feringa, B. L. & Minnaard, A. J. Catalytic asymmetric synthesis of mycocerosic acid. *Chem. Commun.* 489–491 (2007) doi:10.1039/B612593J.

93. Ter Horst, B., Feringa, B. L. & Minnaard, A. J. Iterative strategies for the synthesis of deoxypropionates. *Chem. Commun.* **46**, 2535–2547 (2010).

94. Ter Horst, B., Feringa, B. L. & Minnaard, A. J. Catalytic asymmetric synthesis of phthioceranic acid, a heptamethyl-branched acid from Mycobacterium tuberculosis. *Org. Lett.* **9**, 3013–3015 (2007).

95. Holzheimer, M., Buter, J. & Minnaard, A. J. Chemical Synthesis of Cell Wall Constituents of Mycobacterium tuberculosis. *Chem. Rev.* **121**, 9554–9643 (2021).

96. Elsaidi, H. R. H. & Lowary, T. L. Inhibition of cytokine release by mycobacterium tuberculosis phenolic glycolipid analogues. *ChemBioChem* **15**, 1176–1182 (2014).

97. Konradsson, P., Udodong, U. E. & Fraser-Reid, B. Iodonium promoted reactions of disarmed thioglycosides. *Tetrahedron Lett.* **31**, 4313–4316 (1990).

98. Schmidt, R. R. & Toepfer, A. Glycosylation with highly reactive glycosyl donors: efficiency of the inverse procedure. *Tetrahedron Lett.* **32**, 3353–3356 (1991).

99. Toepfer, A. & Schmidt, R. R. An Efficient Synthesis Of The Lewis A (Lea) Antigen Pentasaccharide Moiety. *J. Carbohydr. Chem.* **12**, 809–822 (1993).

100. Baek, J. Y., Lee, B. Y., Jo, M. G. & Kim, K. S. β-directing effect of electron-withdrawing groups at O-3, O-4, and O-6 positions and α-directing effect by remote participation of 3-O-acyl and 6-O-acetyl groups of donors in mannopyranosylations. *J. Am. Chem. Soc.* **131**, 17705–17713 (2009).

101. van der Vorm, S., Hansen, T., Overkleeft, H. S., van der Marel, G. A. & Codée, J. D. C. The influence of acceptor nucleophilicity on the glycosylation reaction mechanism. *Chem. Sci.* **8**, 1867–1875 (2017).

102. Hansen, T. *et al.* Defining the SN1 Side of Glycosylation Reactions: Stereoselectivity of Glycopyranosyl Cations. *ACS Cent. Sci.* **5**, 781–788 (2019).

Chapter 2

Synthetic Phenolic Glycolipids for the Diagnosis of Leprosy

Part of this chapter has been published:

J. Hessel M. van Dijk#, Anouk van Hooij#, L. Melanie Groot, Jolijn Geboers, Rosita Moretti, Els Verhard-Seymonsbergen, Danielle de Jong, Gijs A. van der Marel, Paul L.A.M. Corstjens, Annemieke Geluk, and Jeroen D.C. Codée

Synthetic Phenolic Glycolipids for Application in Diagnostic Tests for Leprosy

ChemBioChem 2021, 22(8), 1487

Introduction

Leprosy is a chronic disease caused by *Mycobacterium leprae* (*M. leprae*), a bacillus with tropism for skin and peripheral nerves.[1] Although the disease can be cured with multidrug therapy (MDT), it still is a harsh reality in 145 countries mostly affecting individuals in poor socio-economic circumstances. Its late- or misdiagnosis often leads to irreversible deformities and lifelong handicaps.[2] Leprosy´s featuring aspect is the plateauing global annual number of new cases of roughly 200,000 including 10% children, which indicates that transmission is ongoing.[3] Field-friendly diagnostic tests to facilitate identification of infected individuals, will enable timely prophylactic- and therapeutic treatment. Overall, this will help prevent permanent leprosy-associated disabilities and consequently support a higher quality of life, improved long-term outcomes and reduced economic burden.

Phenolic glycolipid-I (PGL-I, Figure 1) is a cell wall component of *M. leprae* which modulates the host immune response by limiting the production of nitric oxides synthase in a complement receptor 3 (CR3) dependent manner and inhibiting the TRIF-dependent TLR4 signaling pathway in macrophages.[4] The binding to CR3 also enhances the invasion of dendritic cells and polymorphonuclear neutrophils, which further dampens the immune response.[5] Furthermore, macrophages infected with *M. marinum* expressing PGL-I (as a proxy for live *M. leprae*) induce demyelination, a process leading to nerve damage in leprosy.[6] After infection a predominantly IgM antibody response can be generated against *M. leprae* PGL-I.[7] The level of anti-PGL-I antibodies strongly correlates with bacterial load,[8] allowing identification of those who are most infectious. Moreover, antibody levels in young children can be utilized to indicate recent transmission rates in endemic areas.[9] A low complexity, point-of-care (POC) lateral flow assay based on up-converting particles (UCP-LFA) has been developed that quantitatively measures anti-PGL-I IgM levels in serum and fingerstick blood.[10–12] This assay is currently applied in field trials in Africa, to identify and treat *M. leprae* infected individuals, and evaluated for surveillance purposes of *M. leprae*-infected red squirrels in the UK.[13]

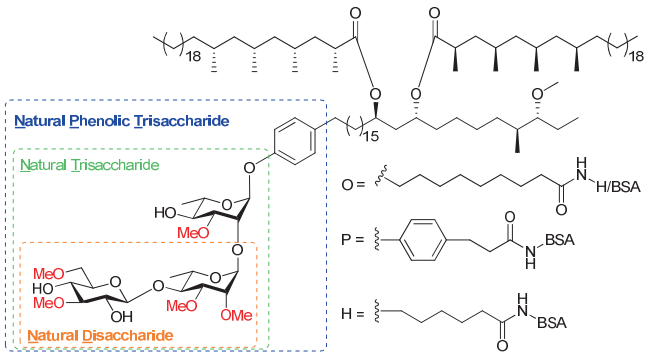


Figure 2. PGL-I and synthetic conjugates used for diagnostics.

For decades serological analyses for leprosy research have been performed using ND-O-HSA (Natural Disaccharide linked *via* an Octyl carboxylic acid linker to Human Serum Albumin, Figure 1),[7,14–16] a conjugate bearing a synthetic disaccharide antigen. This glycoconjugate contains the terminal two sugars of the naturally occurring *M. leprae* PGL-I, which has been synthesized to serve as a convenient water-soluble antigen for use in leprosy research.[17] The terminal 3,6-di-*O*-methylglucose was found to be the most

important structural determinant for antibody binding,[18] with disaccharides showing a higher sensitivity than monosaccharides.[19] Although in most sera of leprosy patients the disaccharide epitope was found to be effective for the detection of antibodies, it had been suggested that the structure of the native glycolipid needed to be more emulated to further improve the binding.[17] Therefore, the trisaccharide containing conjugate with the same octyl linker (Natural Trisaccharide linked *via* an Octyl carboxylic acid linker to Bovine Serum Albumin, NT-O-BSA) was probed by Brennan and co-workers.[20] While they found no discernable increase in sensitivity or specificity,[21] Izumi *et al*. found that a trisaccharide epitope with a phenol on the reducing end with a propyl linker (Natural Trisaccharide linked *via* an Phenol linker to Bovine Serum Albumin, NT-P-BSA) did improve the sensitivity, as well as the antigenic specificity, compared to their disaccharide (ND-P-BSA).[22] These findings were confirmed in a study, comparing ND-O-BSA to NT-O-BSA and NT-P-BSA, demonstrating that the latter provided the best sensitivity and specificity.[23] Combined, these results indicate that the phenol on the reducing end of the saccharides can increase specific antibody binding. Two additional phenolic glycolipids, PGL-II and PGL-III, differing from PGL-I in the methylation pattern of the trisaccharide, possibly because they are biosynthetic intermediates of PGL-I, are present in the cell wall of *M. leprae* as well, and can also modulate the host innate immune response against the mycobacterium.[24–26] Previous assessments by Lowary and coworkers who have described that the methylation pattern in related PGLs originating from *M. tuberculosis* and *M. kansasii* play an important role in shaping the immune response against these PGLs.[27–30]

Therefore, to investigate the binding of the *M. leprae* PGL-trisaccharides with the natural phenol anomeric appendage to human antibodies, this chapter describes the assembly of the Natural Phenolic Trisaccharides 1, 2 and 3 (NPT1, NPT2, NPT3, respectively), which are functionalized with a Hexanoic acid linker for conjugation to BSA, to provide the NPT1-H-BSA, NPT2-H-BSA and NPT3-H-BSA conjugates. These conjugates can then be evaluated using ELISAs to detect IgM antibodies against *M. leprae* in a cohort of leprosy patient sera. Since leprosy frequently occurs in remote, low resource areas the performance of these PGL conjugates will additionally be assessed in UCP-LFAs.

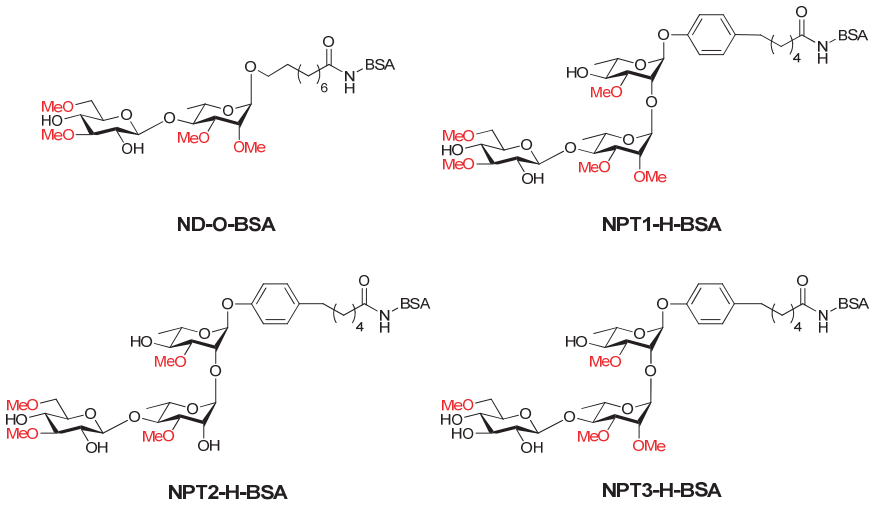


Figure 3. PGL-conjugates assembled in this chapter. Natural Disaccharide – Octyl carboxylic acid – BSA (ND-O-BSA), and Natural Phenolic Trisaccharide 1, 2 and 3 - hexyl - BSA (NPT1/2/3-H-BSA).

The strategy used for the synthesis of the trisaccharides (Figure 2) is based on an approach previously developed for the assembly of a *M. tuberculosis* phenolic glycolipid in which iodophenol glycosides were generated and subsequently functionalized with a lipid tail through a Sonogashira coupling (Figure 3).[31,32] The synthetic approach applied here can thus also be applied for the total synthesis of the natural PGL-I, PGL-II and PGL-III without any modifications. For comparison the synthesis of disaccharide epitope ND-O-BSA will also be described in this chapter.

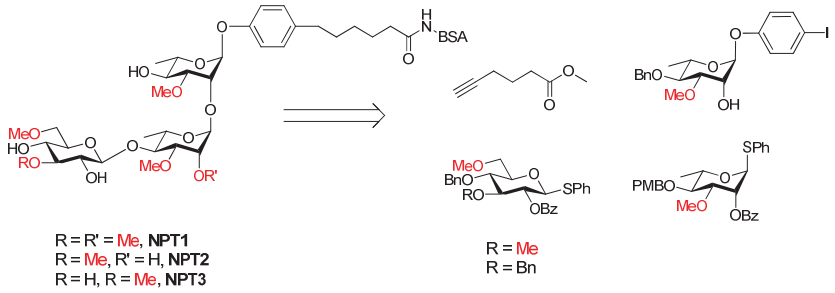
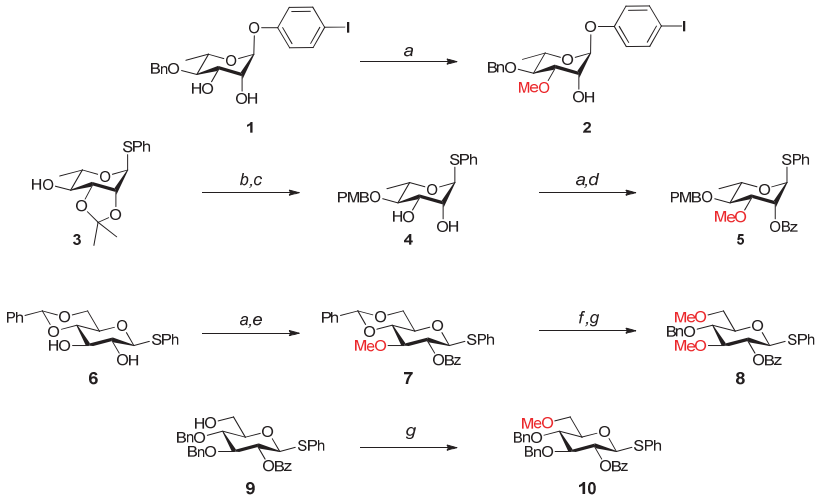


Figure 4. Retrosynthetic analysis of the desired trisaccharides.

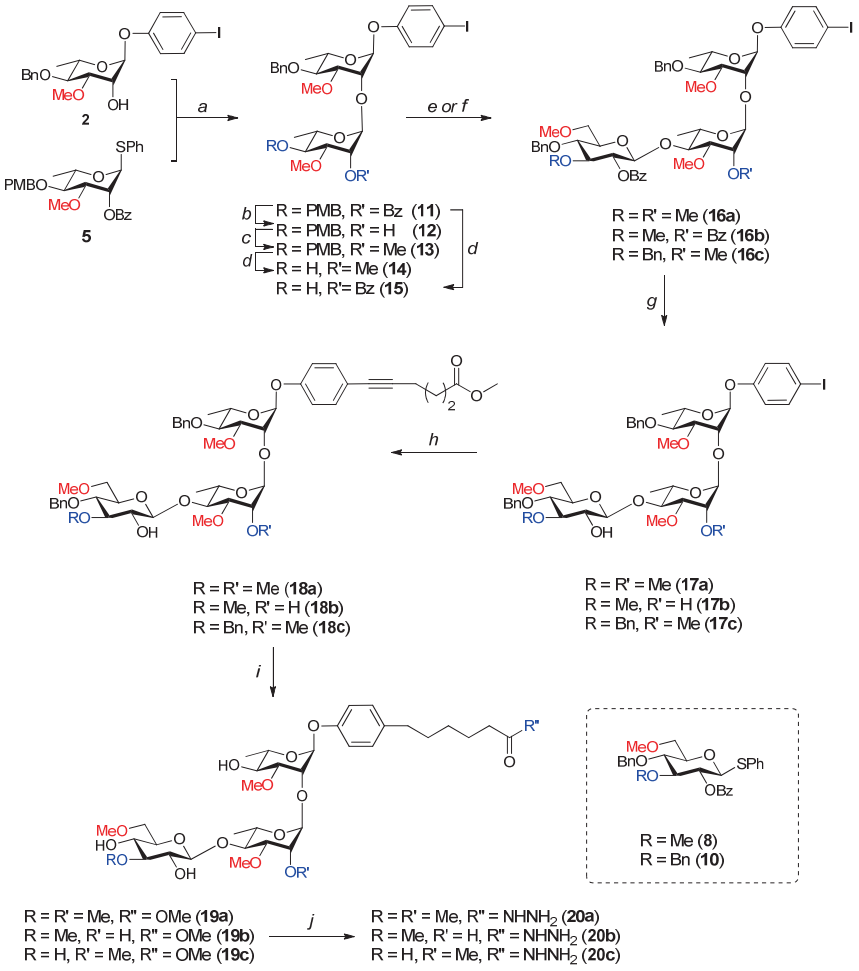
Results & Discussion

The requisite building blocks were prepared by the sequence of reactions depicted in Scheme 1. Iodoaryl acceptor **2** was synthesized by the regioselective methylation of the intermediate stannylidene complex of known[33] compound **1**. This method produced the acceptor in 91% yield as a 10:1 mixture of regioisomers. The purification of the product could be facilitated by the acetylation of the mixture, followed by separation with column chromatography and subsequent deacetylation. Donor **5** was synthesized by the protection of the C-4 position of intermediate **3**[33] with a *para*-methoxybenzyl ether, which was followed by a mild acidic hydrolysis of the isopropylidene ketal to give diol **4** in 86% yield over 2 steps. This diol was regioselectively methylated on the C-3 position as described above and subsequently benzoylated to give donor **5** in 87% yield over 2 steps. Glucose donor **8** was synthesized by the regioselective alkylation and subsequent benzoylation of known[34] benzylidene glucoside **6**. After the reductive opening of the benzylidene acetal, the newly liberated primary alcohol could be methylated to give donor **8** in 43% yield over 4 steps. Glucose **9**[35] was synthesized in a similar fashion and subsequently methylated to give donor **10** in 79% yield.



Scheme 1. Building block synthesis. Reagents and conditions: (a) 1. Bu_2SnO, toluene reflux, 2. MeI, CsF, DMF, 91% (**2**), 93% (**5**), 76% (**7**), (b) NaH, PMBCl, DMF, 0 °C -> RT, 98%, (c) AcOH/H_2O (4:1), 45 °C, 88%, (d) BzCl, pyridine, DCM, 0 °C → RT, 94%, (e) BzCl, DMAP, pyridine, 0 °C → RT, 82% (f) $BH_3 \cdot THF$, TMSOTf, DCM, 96% (g) NaH, MeI, DMF, 0 °C → RT, 72% (**8**), 79% (**10**).

Scheme 2 depicts the synthesis of the required NPT-glycans. It was found that the condensation of acceptor **2** with rhamnosyl donor **5** under the agency of *N*-iodosuccinimide (NIS) and triflic acid (TfOH) led to partial iodination of the iodoaryl ring. Therefore the diphenylsulfoxide (Ph_2SO)-triflic anhydride (Tf_2O) reagent combination was used to activate the thioglycoside.[36] Subsequent addition of acceptor **2** to the activated donor provided dirhamnoside **11** in 66% yield. The C-2' benzoyl ester was then replaced for a methyl ether and subsequently the C-4' PMB ether was removed using a catalytic amount of HCl in HFIP,[37] resulting in disaccharide acceptor **14** in 86% yield over 3 steps. This acceptor was coupled with donor **8** using the Ph_2SO/Tf_2O activator delivering the fully protected trisaccharide **16a** in 93% yield. Similarly, the condensation of **14** and donor **10** delivered trisaccharide **16c** in quantitative yield. To synthesize trisaccharide **16b**, first disaccharide acceptor **15** was generated by removal of the PMB ether in **11** using a catalytic amount of HCl in HFIP to give the required alcohol in quantitative yield. Coupling of acceptor **15** to glucose donor **8** then gave trisaccharide **16b** in 88% yield.

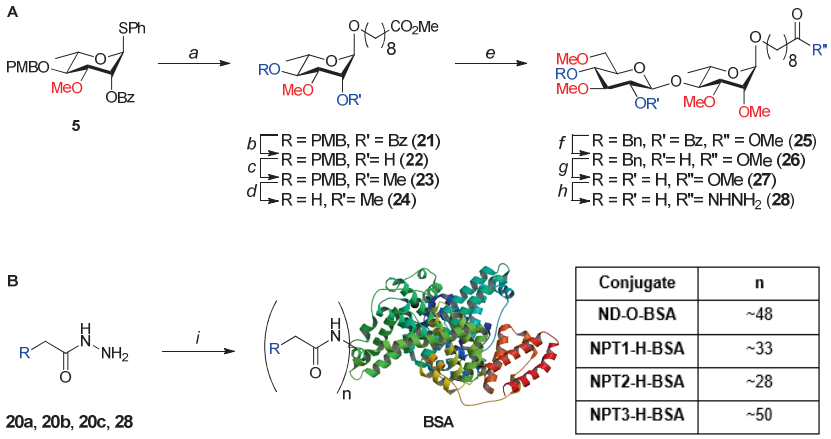


Scheme 2. Trisaccharide synthesis. Reagents and conditions: (a) Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 66%, (b) Na, MeOH/THF, 97%, (c) NaH, MeI, DMF, 0 °C → RT, 95%, (d) HCl/HFIP, HFIP/DCM, 93% (**14**), 100% (**15**), (e) Donor **8**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 93% (**16a**), 88% (**16b**), (f) Donor **10**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 100% (**16c**), (g) Na, MeOH/THF, 99% (**17a**), 84% (**17b**), 97% (**17c**), (h) Methyl hex-5-ynoate, $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, 99% (**18a**), 77% (**18b**), 82% (**18c**), (i) Pd/C, H_2, THF/MeOH, 100% (**19a**), 82% (**19b**), 90% (**19c**), (j) $N_2H_4 \cdot H_2O$, EtOH, 89% (**20a**), 100% (**20b**). 84% (**20c**).

After the benzoyl protecting groups were removed from the trisaccharides, the iodoaryl glycosides were coupled to methyl hex-5-ynoate using a Sonogashira cross-coupling. Global deprotection of the trisaccharides and reduction of the triple bond was

accomplished by a single hydrogenation reaction to provide the target trisaccharides having a methyl ester spacer, in excellent yields. The methyl esters could then be transformed into hydrazides **20a**, **20b** and **20c** which could be used for conjugation to BSA.

Scheme 3A depicts the assembly of the ND-O-disaccharide **28** which was required for comparison. The synthesis started with the coupling of rhamnose donor **5** with methyl 9-hydroxynonanoate[38] under the agency of Ph_2SO/Tf_2O, to give spacer equipped rhamnose **21** in good yield. After the C-2 benzoyl ester was removed and replaced with the required methyl ether, the C-4 PMB ether could be cleaved which provided acceptor **24** in excellent yield.



Conjugate	n
ND-O-BSA	~48
NPT1-H-BSA	~33
NPT2-H-BSA	~28
NPT3-H-BSA	~50

Scheme 3. A: Disaccharide synthesis. Reagents and conditions: (a) Methyl 9-hydroxynonanoate, Ph_2SO, Tf_2O, TTBP, DCM, -60 °C, 79%, (b), Na, MeOH/THF, 97%, (c), NaH, MeI, DMF, 91%, 0 °C → RT, (d) HCl/HFIP, HFIP/DCM, 95%, (e) Donor **8**, Ph_2SO, Tf_2O, TTBP, DCM, -60 °C, 84%, (f), Na, MeOH/THF, 82% (g) Pd/C, H_2, THF, 95%, (h) $N_2H_4 \cdot H_2O$, EtOH, 100%, **B: Conjugation of hydrazides to BSA**. Reagents and conditions: (i) 1. HCl/dioxane, *t*-BuONO, DMF, -30 °C, 2. BSA, $Na_2B_4O_7$, $NaHCO_3$, (pH = 9.2), H_2O, 0 °C.

This acceptor could be coupled to glucose donor **8**, using Ph_2SO/Tf_2O, after which the benzoate ester was cleaved by treatment with NaOMe and the benzyl ether removed with hydrogenation. Finally, the methyl ester of the linker was transformed into the corresponding hydrazide to provide the required ND-O-disaccharide **28** in quantitative yield.

The conjugation of the saccharides to BSA is depicted in Scheme 3B. First the hydrazides were transformed into the corresponding acyl azides in DMF using *tert*-butyl nitrite and HCl in dioxane at -30 °C. After complete conversion was observed, the reaction was quenched and the resulting mixture was transferred to an ice-cooled solution of BSA in aqueous $Na_2B_4O_7$ and $NaHCO_3$ (pH = 9.2). After desalting and purification by means of gel filtration the conjugates NPT1-H-BSA, NPT2-H BSA and NPT3-H-BSA were obtained, bearing 33, 28 and 50 trisaccharides per BSA, respectively and the control conjugate ND-O-BSA functionalized with 48 copies of the disaccharide on each protein, as revealed by SDS-PAGE and MALDI-TOF analyses. The synthetic route described in this chapter has also been applied in the gram scale production of NPT1-H-BSA.[39]

All newly synthesized conjugates were assessed in ELISA and UCP-LFA alongside the earlier described ND-O-HSA. ND-O-BSA, NPT1-H-BSA and NPT2-H-BSA showed a high correlation with ND-O-HSA in both ELISA and UCP-LFA, however considerably lower levels of IgM were binding to NPT3-H-BSA (Figure 4). This result shows the importance of the methylation pattern, and especially that of the C-3'' methyl, and indicates that human anti-PGL IgM binds to NPT3-H-BSA to a lesser extent.

To assess the stability of the different PGL conjugates in the UCP-LFA format, the stability was tested at seven different time points ranging from two months to thirteen months after production. Little variation was observed between the time points for test sera. Furthermore, analysis of the negative control serum sample at all time points indicated that no background signal developed in aging strips.

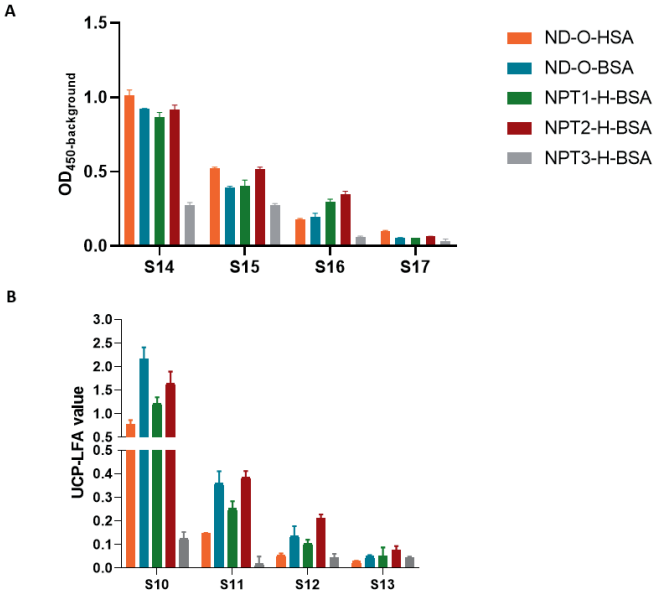


Figure 4. Comparison of IgM responses to five different synthetic PGLs in ELISA and UCP-LFA.[40] IgM responses to ND-O-HSA (orange), ND-O-BSA (blue), NPT1-H-BSA (green), NPT2-H-BSA (red) and NPT3-H-BSA were evaluated in ELISA (A) and UCP-LFA (B) using patient samples. (A) OD_{450}-background (y-axis) represents the IgM antibody levels detected by ELISA against the five different synthetic PGLs. (B) The UCP-LFA values (y-axis; arbitrary units) as determined using the UCP-LFA indicate the IgM antibody levels directed against the five different synthetic PGLs.

Conclusion

This chapter describes the synthesis of a set of BSA conjugates of *M. leprae* phenolic glycolipid trisaccharides connected to the protein via a hexanoic acid linker attached to the anomeric phenol on the reducing end, and the use of these for detection of anti-PGL IgM antibodies. The conjugates were evaluated as coating antigen both in ELISA and lateral flow format (UCP-LFA) in order to investigate the influence of the phenol on the reducing end as well as the methylation pattern of the three glycoforms. The required glycans were successfully synthesized using a route based on thioglycosides and an iodophenol bearing rhamnoside, which allowed for the functionalization with a linker through a Sonogashira coupling, a strategy which will also be applied to the total synthesis of complete PGLs. In ELISA the conjugates showed a high correlation with results obtained

with ND-O-HSA as coating antigen. Based on this data the conjugates were incorporated into the UCP-LFA format suitable for POC testing in the field. A high correlation with the results of ND-O-HSA was found here as well and therefore the conjugates are thought to be well applicable to the format. The stability of NPT1-H-BSA in the UCP-LFA format was also assessed yielding consistent results over a period of 13 months, without development of any background signal within this time frame. This is advantageous for the application of this format in low resource areas where a cold chain is not always available. When the three trisaccharides NPT1, NPT2 and NPT3 were compared, significantly lower levels of IgM were found to bind to the latter trisaccharide. This is in line with previous assessments which determined the C-3 methyl ether of the terminal glucose to be a highly important structural determinant for antibody binding.[18] In summary, the data obtained here indicates that trisaccharide conjugates represent robust targets for the detection of anti-PGL-I antibodies in point-of-care (POC) tests. The conjugates developed here can be used in future field studies in leprosy endemic areas.

Experimental

General procedures

All reactions were carried out in oven-dried glassware (80 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under N_2 atmosphere (balloon). Commercially available reagents and solvents (Aldrich Chemistry, Honeywell, Merck, Ficher Scientific, Biosolve, Fluka, VWR Chemicals, Acros Organics, Fluorochem, Brunschwig, Carbosynth) were used as received unless stated otherwise.

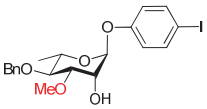
Solvents for reactions were reagent grade and dried by storage over flame dried 4 Å molecular sieves when needed. Tf_2O used in glycosylations was dried by distillation over P_2O_5 and stored under N_2 atmosphere in a Schlenk flask at -20 °C. Et_2O used for column chromatography was distilled before use and stored over iron filings. EtOAc used for column chromatography was distilled before use. NEt_3 used for Sonogashira couplings was distilled from KOH, degassed with N_2, and stored over KOH for a maximum of 24 hours.

Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, F254); visualization was carried out by irradiation with UV light (254 nm), and spraying with 20% H_2SO_4 in EtOH (w/v) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% H_2SO_4, followed by charring. Additional analysis with TLC-MS was used when needed.

Column chromatography was carried out using silica gel (Fluka, 40-63 µm mesh). The column was prepared using the apolar component mentioned in the corresponding experimental. If the apolar component was pentane the product was brought up in toluene. If the apolar component was DCM the product was brought up in DCM, possibly with a few drops of methanol if needed. Colum chromatography was performed using a gradient ranging from 0% polar component up to the ratio mentioned in the corresponding experimental in 2 to 5 steps depending on the ease of separation.

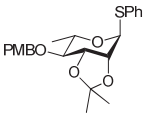
NMR spectra were recorded at ambient temperature on a Bruker AV-400LIQ spectrometer. Samples were prepared in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) in $CDCl_3$ are reported in ppm relative to Me_4Si (δ: 0.00 ppm) for ^{1}H-NMR and $CDCl_3$ (δ: 77.16 ppm) for ^{13}C-NMR. Chemical shifts in CD_3OD are reported in ppm relative to H_2O (δ: 4.87 ppm) for ^{1}H-NMR and CD_3OD (δ: 49.00 ppm) for ^{13}C-NMR. ^{13}C-APT spectra are ^{1}H decoupled and structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants (J) are given in Hz. Coupling constants of anomeric carbon atoms ($J_{H1,C1}$) were determined using HMBC-GATED experiments. MALDI measurements were carried out with a Bruker **A**utoflex Speed™ LRF. Optical rotations were measured on an Anton Paar Modular Circular Polarimeter MCP 100/150. High resolution mass spectra were recorded on a Synapt G2-Si or a Q Exactive HF Orbitrap equipped with an electron spray ion source positive mode. Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR.

4-iodophenyl 3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (2)



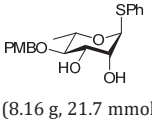
Compound **1**[33] (4.56 g, 10 mmol, 1.0 eq) was dissolved in toluene (500 mL, 0.02 M) and Bu_2SnO (2.74 g, 11 mmol, 1.1 eq) was added to the solution. The mixture was refluxed for 2 hours and then concentrated *in vacuo*. The mixture was then dissolved in dry DMF (100 mL, 0.1 M) and CsF (1.82 g, 12 mmol, 1.2 eq) and MeI (0.81 mL, 13 mmol, 1.3 eq) were added. The reaction was allowed to stir for 22 hours after which it was quenched by addition of H_2O and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (4.28 g, 9.1 mmol, 91%, 10:1 mixture of regioisomers) as a clear oil. $[\alpha]_D^{25}$ -79.9 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.54 (m, 2H, C*H*$_{arom}$); 7.36-7.24 (m, 5H, C*H*$_{arom}$); 6.84-6.80 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 4.86 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.63 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.21 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.76-3.71 (m, 2H, H-3, H-5); 3.56 (s, 3H, OC*H*$_3$); 3.44 (t, 1H, *J* = 5.2 Hz, H-4); 2.74 (bs, 1H, 2-O*H*); 1.24 (d, 3H, *J* = 6.4 Hz, H-6); ^{13}C-APT NMR (101 MHz) δ: 156.0 ($C_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.4 ($C_{q,arom}$); 128.5, 128.1, 127.9, 118.6 (*C*H$_{arom}$); 97.1 (C-1); 84.8 (*C*I$_{arom}$); 81.5 (C-3); 79.7 (C-4); 75.4 (*C*H$_{2,Bn}$); 68.2 (C-5); 67.8 (C-2); 57.8 (O*C*H$_3$); 18.0 (C-6). IR (thin film, cm^{-1}): 1026, 1095, 1133, 1177, 1233, 1452, 1484, 2927, 3408. HRMS calculated for $C_{20}H_{23}IO_5Na$ 493.0488 [M+Na]$^+$; found 493.0479.

Phenyl 2,3-*O*-isopropylidene-4-*O*-(4-methoxybenzyl)-1-thio-α-L-rhamnopyranoside (29)



Compound **3**[33] (7.45 g, 25 mmol, 1.0 eq) was dissolved in dry DMF (250 mL, 0.1 M) and PMBCl (4.8 mL, 35 mmol, 1.4 eq) was added to the solution. The mixture was cooled to 0 °C and NaH (60%, 1.40 g, 35 mmol, 1.4 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was quenched by addition of H_2O and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) gave the title compound (10.2 g, 24.5 mmol, 98%) as a pale oil. $[\alpha]_D^{25}$ -148.8 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.46-7.43 (m, 2H, C*H*$_{arom}$); 7.29-7.19 (m, 5H, C*H*$_{arom}$); 6.87-6.84 (m, 2H, C*H*$_{arom}$); 5.74 (s, 1H, H-1); 4.84 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.56 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.35-4.28 (m, 2H, H-2, H-3); 4.16-4.11 (m, 1H, H-5); 3.73 (s, 3H, C*H*$_{3,PMB}$); 3.28 (dd, 1H, *J* = 7.0, 9.8 Hz, H-4); 1.51 (s, 3H, C(C*H*$_3$)$_2$); 1.36 (s, 3H, C(C*H*$_3$)$_2$); 1.21 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.3, 133.7 ($C_{q,arom}$); 131.8 (*C*H$_{arom}$); 130.4 ($C_{q,arom}$); 130.3, 129.7, 129.1, 127.6, 113.8 (*C*H$_{arom}$); 109.5 (*C*(CH$_3$)$_2$); 83.8 (C-1); 81.0 (C-4); 78.4 (C-3); 76.7 (C-2); 72.7 (Ph*C*H$_2$); 55.1 (*C*H$_{3,PMB}$); 28.0, 26.5 (C(*C*H$_3$)$_2$); 17.7 (C-6). IR (thin film, cm^{-1}): 1035, 1057, 1086, 1108, 1220, 1248, 1513. HRMS calculated for $C_{23}H_{28}O_5SNa$ 439.1555 [M+Na]$^+$; found 439.1553.

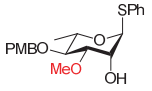
Phenyl 4-*O*-(4-methoxybenzyl)-1-thio-α-L-rhamnopyranoside (4)



Compound **29** (9.04 g, 21.7 mmol, 1.0 eq) was dissolved in AcOH/H_2O (4:1, 500 mL, 0.04 M) and stirred at 45 °C for 3h. The solvent was evaporated until a thick oil was formed. The oil was co-evaporated three times with toluene to give the title compound (8.16 g, 21.7 mmol, 100%) as a slightly yellow oil. $[\alpha]_D^{25}$ -70.8 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.42 (m, 2H, C*H*$_{arom}$); 7.31-7.22 (m, 5H, C*H*$_{arom}$); 6.91-6.88 (m, 2H, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.6 Hz, H-1); 4.71-4.63 (m, 2H, C*H*$_{2,PMB}$); 4.23-4.16 (m, 2H, H-2, H-5); 3.89 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.80 (s, 3H, C*H*$_{3,PMB}$);

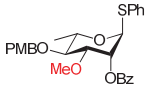
3.41 (t, 1H, *J* = 9.2 Hz, H-4); 1.34 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.6, 134.3 ($C_{q,arom}$); 131.4 (CH_{arom}); 130.3 ($C_{q,arom}$); 129.8, 129.3, 127.5, 114.2 (CH_{arom}); 87.5 (C-1); 81.5 (C-4); 74.9 (PhCH_2); 72.7 (C-2); 72.0 (C-3); 68.8 (C-5); 55.4 ($CH_{3,PMB}$); 18.0 (C-6). IR (thin film, cm^{-1}): 1036, 1065, 1097, 1250, 1513, 3328. HRMS calculated for $C_{20}H_{24}O_5SNa$ 399.1242 $[M+Na]^+$; found 399.1244.

Phenyl 3-*O*-methyl-4-*O*-(4-methoxybenzyl)-1-thio-α-L-rhamnopyranoside (30)



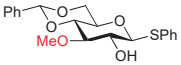
Compound **4** (8.16 g, 21.7 mmol, 1.0 eq) was dissolved in toluene (500 mL, 0.04 M) and Bu_2SnO (5.94 g, 23.9 mmol, 1.1 eq) was added to the solution. The mixture was refluxed for 2 hours and then concentrated *in vacuo*. The mixture was then dissolved in dry DMF (220 mL, 0.1 M) and CsF (3.96 g, 26 mmol, 1.2 eq) and MeI (1.8 mL, 28.2 mmol, 1.3 eq) were added. The reaction was allowed to stir for 20 hours after which it was quenched by addition of H_2O and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (7.88 g, 20.2 mmol, 93%, 10:1 mixture of regioisomers) as a pale oil. $[\alpha]_D^{25}$ = -113.8 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47-7.43 (m, 2H, CH_{arom}); 7.32-7.22 (m, 5H, CH_{arom}); 6.90-6.87 (m, 2H, CH_{arom}); 5.53 (d, 1H, *J* = 1.6 Hz, H-1); 4.78 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.56 (d, 1H, *J* = 10.4 Hz, PhCH*H*); 4.29 (dd, 1H, *J* = 1.6, 3.6 Hz, H-2); 4.18-4.14 (m, 1H, H-5); 3.80 (s, 3H, $CH_{3,PMB}$); 3.56 (dd, 1H, *J* = 3.6, 9.2 Hz, H-3); 3.52 (s, 3H, OCH_3); 3.43 (t, 1H, *J* = 9.2 Hz, H-4); 2.74 (d, 1H, *J* = 4.8 Hz, 2-O*H*); 1.28 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.4, 134.3 ($C_{q,arom}$); 131.4 (CH_{arom}); 130.6 ($C_{q,arom}$); 129.8, 129.1, 127.4, 114.0 (CH_{arom}); 87.2 (C-1); 82.1 (C-3); 79.7 (C-4); 75.0 (PhCH_2); 69.5 (C-2); 68.7 (C-5); 57.6 (OCH_3); 55.4 ($CH_{3,PMB}$); 17.9 (C-6). IR (thin film, cm^{-1}): 1035, 1083, 1097, 1249, 1513, 3450. HRMS calculated for $C_{21}H_{26}O_5SNa$ 413.1394 $[M+Na]^+$; found 413.1399.

Phenyl 2-*O*-benzoyl-3-*O*-methyl-4-*O*-(4-methoxybenzyl)-1-thio-α-L-rhamnopyranoside (5)



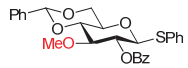
Compound **30** (0.15 g, 0.37 mmol, 1.0 eq) was dissolved in pyridine (1.9 mL, 0.2 M) and BzCl (86 µL, 0.74 mmol, 2.0 eq) was added to the solution. A catalytic amount of DMAP was added and the mixture was allowed to stir for 2 hours. The reaction was quenched by addition of MeOH and concentrated *in vacuo*. The resulting oil was dissolved in Et_2O and washed with 1M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) gave the title compound (7.88 g, 20.2 mmol, 93%) as a pale oil. $[\alpha]_D^{25}$ -120.2 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.07-8.03 (m, 2H, CH_{arom}); 7.58-7.54 (m, 1H, CH_{arom}); 7.48-7.42 (m, 4H, CH_{arom}); 7.32-7.21 (m, 5H, CH_{arom}); 6.89 (d, 2H, *J* = 8.4 Hz, CH_{arom}); 5.82 (d, 1H, *J* = 1.6 Hz, H-2); 5.55 (s, 1H, H-1); 4.74 (dd, 2H, *J* = 10.6, 95.8 Hz, PhCH_2); 4.30-4.26 (m, 1H, H-5); 3.78-3.74 (m, 4H, H-3, $CH_{3,PMB}$); 3.57 (t, 1H, *J* = 9.4 Hz, H-4); 3.50 (s, 3H, OCH_3); 1.37 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.7 (CO_{Bz}); 159.4, 134.1 ($C_{q,arom}$); 133.4, 131.8 (CH_{arom}); 130.6 ($C_{q,arom}$); 130.0 (CH_{arom}); 129.9 ($C_{q,arom}$); 129.2, 128.5, 127.7, 113.9 (CH_{arom}); 86.2 (C-1); 80.8 (C-3); 79.8 (C-4); 75.1 (PhCH_2); 70.8 (C-2); 69.1 (C-5); 57.6 (OCH_3); 55.3 ($CH_{3,PMB}$); 18.1 (C-6). IR (thin film, cm^{-1}): 1070, 1093, 1109, 1251, 1267, 1513, 1722. HRMS calculated for $C_{28}H_{30}O_6SNa$ 517.1661 $[M+Na]^+$; found 517.1663.

Phenyl 3-*O*-methyl-4,6-*O*-benzylidene-1-thio-ß-D-glucopyranoside (31)



After co-evaporation with toluene, compound **6**[41] (3.60 g, 10 mmol, 1.0 eq) was dissolved in toluene (500 mL, 0.02 M). To the solution was added Bu_2SnO (2.70 g, 11 mmol, 1.1 eq) and refluxed for 2 hours after which it was concentrated *in vacuo*. The residue was dissolved in dry DMF (100 mL, 0.1 M) and MeI (0.8 mL, 13 mmol, 1.3 eq) along with CsF (1.82 g, 12 mmol, 1.2 eq) were added. The reaction mixture was stirred overnight after which it was quenched by addition of H_2O. The aqueous phase was extracted with Et_2O (3x) after which the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-EtOAc, 7:3) gave the title compound (2.86 g, 7.64 mmol, 76%) as a white solid. ^{1}H-NMR (400 MHz) δ: 7.56-7.52 (m, 2H, C*H*$_{arom}$); 7.49-7.46 (m, 2H, C*H*$_{arom}$); 7.39-7.26 (m, 6H, C*H*$_{arom}$); 5.54 (s, 1H, PhC*H*); 4.66-4.63 (m, 1H, H-1); 4.38 (dd, 1H, *J* = 4.8, 10.4 Hz, H-6); 3.78 (t, 1H, *J* = 10.2 Hz, H-6); 3.67 (s, 3H, OC*H*3); 3.61-3.44 (m, 4H, H-2, H-3, H-4, H-5); 2.68 (s, 1H, 2-O*H*). ^{13}C NMR (100 MHz) δ: 137.2 (*C*$_{q,arom}$); 133.3 (*C*H$_{arom}$); 131.4 (*C*$_{q,arom}$); 129.2, 129.2, 128.6, 128.4, 126.1 (*C*H$_{arom}$); 101.4 (Ph*C*H); 88.6 (C-1); 83.7 (C-3); 81.2 (C-4); 72.3 (C-2); 70.8 (C-5); 68.7 (C-6); 61.2 (O*C*H$_3$). Spectroscopic data were in accordance with those previously reported in the literature[42].

Phenyl 2-*O*-benzoyl-3-*O*-methyl-4,6-*O*-benzylidene-1-thio-ß-D-glucopyranoside (7)



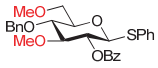
To a solution of compound **31** (2.30 g, 6.14 mmol, 1.0 eq) in pyridine (15.3 mL, 0.4 M), BzCl (1.4 mL, 12.3 mmol, 2.0 eq) was added dropwise after which it was stirred for 4.5 h. The reaction was quenched with H_2O and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with 1M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Recrystallization of the residue from EtOH afforded the title compound (2.42 g, 5.06 mmol, 82%) as a white solid. $[\alpha]_D^{25}$ 13.4 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.11-8.09 (m, 2H, C*H*$_{arom}$); 7.61 (t, 1H, *J* = 7.4 Hz, C*H*$_{arom}$); 7.50-7.43 (m, 8H, C*H*$_{arom}$); 7.40-7.35 (m, 2H, C*H*$_{arom}$); 7.31-7.25 (m, 2H, C*H*$_{arom}$); 5.59 (s, 1H, PhC*H*); 5.23 (dd, 1H, *J* = 8.4, 9.2 Hz, H-2); 4.89 (d, 1H, *J* = 10.0 Hz, H-1); 4.44-4.40 (m, 1H, H-6); 3.84 (t, 1H, *J* = 10.2 Hz, H-6); 3.77-3.67 (m, 2H, H-3, H-4); 3.61-3.55 (m, 1H, H-5); 3.51 (s, 3H, OC*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 165.3 (*C*O$_{Bz}$); 137.2 (C$_{q,arom}$); 133.4, 132.9 (*C*H$_{arom}$); 132.5 (C$_{q,arom}$); 130.0 (*C*H$_{arom}$); 129.9 (C$_{q,arom}$); 129.2, 129.1, 128.6, 128.4, 128.3, 126.2 (*C*H$_{arom}$); 101.1 (Ph*C*H); 87.2 (C-1); 82.4 (C-3); 81.1 (C-4); 72.3 (C-2); 70.8 (C-5); 68.7 (C-6); 60.9 (O*C*H$_3$). IR (thin film, cm^{-1}): 1026, 1069, 1093, 1178, 1268, 1727, 3451. HRMS calculated for $C_{27}H_{26}O_6SNa$ 501.1348 $[M+Na]^+$; found 501.1342.

Phenyl 2-*O*-benzoyl-3-*O*-methyl-4-*O*-benzyl-1-thio-ß-D-glucopyranoside (32)

Compound **7** (2.35 g, 4.91 mmol, 1.0 eq) was co-evaporated with toluene (3x) under N_2 atmosphere before it was dissolved in dry DCM (24.6 mL, 0.2 M). A 1M solution of BH_3·THF (24.6 mL, 24.6 mmol, 5 eq) in THF was added dropwise to the solution after which TMSOTf (0.13 mL, 0.74 mmol, 0.15 eq) was added to the mixture. The reaction mixture was stirred for 5 h and slowly quenched with NEt_3 (2.8 mL) followed by MeOH, which was added until the formation of H_2 ceased. The mixture was concentrated *in vacuo* and co-evaporated with MeOH (2x). Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (2.08 g, 4.33 mmol, 88%) as a white solid. $[\alpha]_D^{25}$ 32 (c = 0.4, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.12-8.10 (m, 2H, C*H*$_{arom}$); 7.62-7.58 (m, 1H, C*H*$_{arom}$); 7.50-

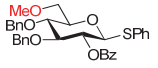
7.46 (m, 2H, C*H*$_{arom}$); 7.43-7.41 (m, 2H, C*H*$_{arom}$); 7.37-7.25 (m, 8H, C*H*$_{arom}$); 5.22-5.17 (m, 1H, H-2); 4.87-4.81 (m, 2H, H-1, PhC*H*H); 4.66 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 3.92-3.88 (m, 1H, H-6); 3.75-3.68 (m, 1H, H-6); 3.62-3.59 (m, 2H, H-3, H-4); 3.51 (s, 3H, OC*H*$_3$); 3.50-3.47 (m, 1H, H-5); 1.98 (bs, 1H, 6-O*H*). ^{13}C-APT NMR (101 MHz) δ: 165.4 (*C*O$_{Bz}$); 138.0 (C$_{q,arom}$); 133.5 (*C*H$_{arom}$); 132.9 (C$_{q,arom}$) 132.4, 132.0, 130.1 (*C*H$_{arom}$); 129.9 (C$_{q,arom}$); 129.2, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8 (*C*H$_{arom}$); 86.6 (C-3); 86.3 (C-1); 79.7 (C-5); 77.2 (C-4); 75.2 (Ph*C*H$_2$); 72.8 (C-2); 62.3 (C-6); 61.1 (O*C*H$_3$). IR (thin film, cm^{-1}): 1027, 1070, 1092, 1178, 1266, 1452, 1727, 3470. HRMS calculated for $C_{27}H_{28}O_6SNa$ 503.1504 [M+Na]$^+$; found 503.1499.

Phenyl 2-*O*-benzoyl-3,6-di-*O*-methyl-4-*O*-benzyl-1-thio-ß-D-glucopyranoside (8)



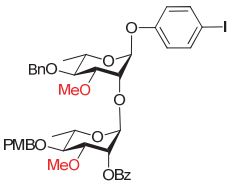
Compound **32** (0.60 g, 1.25 mmol, 1.0 eq) was dried by co-evaporation with toluene and dissolved in dry DMF (12.5 mL, 0.1 M). The solution was cooled to 0 °C after which MeI (0.16 mL, 2.51 mmol, 2.0 eq) was added. The reaction mixture was stirred for 5 minutes before NaH (60%, 84 mg, 2.51 mmol, 2.0 eq) was added and it was stirred for 5.5 hours while warming to rt. The reaction was quenched with H_2O and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O, 17:3) gave the title compound (0.45 g, 0.91 mmol, 72%) as a white solid. $[\alpha]_D^{25}$ 33.6 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.11-8.09 (m, 2H, C*H*$_{arom}$); 7.59-7.55 (m, 1H, C*H*$_{arom}$); 7.47-7.43 (m, 4H, C*H*$_{arom}$); 7.35-7.21 (m, 8H, C*H*$_{arom}$); 5.23 (t, 1H, *J* = 9.4 Hz, H-2); 4.85 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.78 (d, 1H, *J* = 10.0 Hz, H-1); 4.64 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 3.70-3.49 (m, 7H, H-3, H-4, H-5, H-6, OC*H*$_3$); 3.38 (s, 3H, OC*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 165.2 (*C*O$_{Bz}$); 138.1, 133.5 (C$_{q,arom}$); 133.3, 132.1, 129.9, 128.9, 128.5, 128.5, 128.1, 127.9, 127.7 (*C*H$_{arom}$); 86.6 (C-1); 86.5 (C-4); 79.2 (C-3); 77.5 (C-5); 75.0 (Ph*C*H$_2$); 72.6 (C-2); 71.3 (C-6); 60.9, 59.5 (O*C*H$_3$). IR (thin film, cm^{-1}): 1027, 1070, 1093, 1143, 1178, 1265, 1452, 1730. HRMS calculated for $C_{28}H_{30}O_6SNa$ 517.1661 [M+Na]$^+$; found 517.1655.

Phenyl 2-*O*-benzoyl-3-*O*-methyl-3,4-di-*O*-benzyl-1-thio-ß-D-glucopyranoside (10)



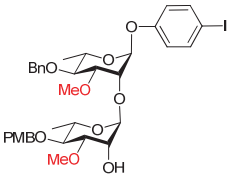
Compound **9**[35] (2.48 g, 4.31 mmol, 1.0 eq) was dried by co-evaporation with toluene and dissolved in dry DMF (43.1 mL, 0.1 M). The solution was cooled to 0 °C after which MeI (0.54 mL, 8.62 mmol, 2.0 eq) was added. The reaction mixture was stirred for 5 minutes before NaH (60%, 0.29 g, 8.62 mmol, 2.0 eq) was added and it was stirred for 5 hours while warming to rt. The reaction was quenched by addition of H_2O and the aqueous phase was extracted with Et_2O (3x). the organic layers washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O, 4:1) gave the title compound (1.94 g, 3.39 mmol, 79%) as a white solid. $[\alpha]_D^{25}$ 41.3 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.02 (d, 2H, *J* = 8.0 Hz, C*H*$_{arom}$); 7.57 (t, 1H, *J* = 7.4 Hz, C*H*$_{arom}$); 7.46-7.42 (m, 4H, C*H*$_{arom}$); 7.35-7.23 (m, 8H, C*H*$_{arom}$); 7.11 (s, 5H, C*H*$_{arom}$); 5.29 (t, 1H, *J* = 9.4 Hz, H-2); 4.84 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.79-4.72 (m, 2H, H-1, PhC*H*H); 4.66-4.63 (m, 2H, PhCH*H*, PhCH*H*); 3.84 (t, 1H, *J* = 9.4 Hz, H-3); 3.77-3.63 (m, 3H, H-4, H-6); 3.57-3.54 (m, 1H, H-5); 3.39 (s, 3H, OC*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 165.3 (*C*O$_{Bz}$); 138.1, 137.8, 133.4 (C$_{q,arom}$); 133.3, 132.4, 130.0, 128.9, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8, 127.8 (*C*H$_{arom}$); 86.6 (C-1); 84.3 (C-3); 79.4 (C-5); 77.8 (C-4); 75.4, 75.2 (Ph*C*H$_2$); 72.6 (C-2); 71.3 (C-6); 59.6 (O*C*H$_3$). IR (thin film, cm^{-1}): 1000, 1026, 1069, 1090, 1140, 1178, 1205, 1264, 1315, 1452, 1482, 1727. HRMS calculated for $C_{34}H_{34}O_6SNa$ 593.1974 [M+Na]$^+$; found 593.1968.

4-iodophenyl 2-*O*-(2-*O*-benzoyl-3-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (11)



Donor **5** (396 mg, 0.80 mmol, 1.0 eq), Ph_2SO (210 mg, 1.04 mmol, 1.3 eq) and TTBP (497 mg, 2.0 mmol, 2.5 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (16 mL, 0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -70 °C after which Tf_2O (175 µL, 1.04 mmol, 1.3 eq) was added to the solution. After stirring for 30 minutes, acceptor **2** (752 mg, 1.60 mmol, 2.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (4 mL, 0.4 M) and added to the solution at -65 °C. After stirring for 2.5 hours the reaction reached -40 °C and was quenched by addition of NEt_3 (1 mL). The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (451 mg, 0.53 mmol, 66%) as a clear oil. $[\alpha]_D^{25}$ -33.2 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.10-8.08 (m, 2H, C*H*$_{arom}$); 7.60-7.54 (m, 3H, C*H*$_{arom}$); 7.50-7.46 (m, 2H, C*H*$_{arom}$); 7.38-7.25 (m, 7H, C*H*$_{arom}$); 6.89 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 6.79 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.70 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 5.45 (d, 1H, *J* = 2.0 Hz, H-1); 5.17 (d, 1H, *J* = 1.6 Hz, H-1'); 4.92 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.84 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.66 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.59 (d, 1H, *J* = 10.4 Hz, PhCH*H*); 4.20 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.89-3.75 (m, 6H, H-3, H-3', H-5', C*H*$_{3,PMB}$); 3.71-3.67 (m, 1H, H-5); 3.53-3.45 (m, 8H, H-4, H-4', OC*H*$_3$); 1.34 (d, 3H, *J* = 6.0 Hz, H-6'); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.8 (*C*O$_{Bz}$); 159.5, 156.1, 138.5 (C$_{q,arom}$); 138.5, 133.3 (*C*H$_{arom}$); 130.6 (C$_{q,arom}$); 130.1, 130.0, 128.6, 128.5, 128.2, 127.8, 118.6, 113.9 (*C*H$_{arom}$); 99.4 (C-1'); 96.9 (C-1); 84.8 (*C*I$_{arom}$); 81.4 (C-3'); 80.1 (C-3); 79.9 (C-4'); 79.7 (C-4); 75.4, 75.2 (Ph*C*H$_2$); 73.5 (C-2); 69.2 (C-2'); 68.8 (C-5); 68.5 (C-5'); 58.1, 57.8 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 18.3 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1042, 1072, 1098, 1118, 1233, 1268, 1452, 1484, 1514, 1724. HRMS calculated for $C_{42}H_{47}IO_{11}Na$ 877.2061 $[M+Na]^+$; found 877.2055.

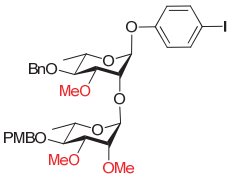
4-iodophenyl 2-*O*-(3-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (12)



Compound **11** (451 mg, 0.53 mmol, 1.0 eq) was dissolved in THF (2.6 mL, 0.2 M). A small piece of sodium was dissolved in MeOH and 2.6 mL of this solution was added. The reaction was stirred for 2 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (384 mg, 0.51 mmol, 97%) as a pale oil. $[\alpha]_D^{25}$ -63.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.53 (m, 2H, C*H*$_{arom}$); 7.34-7.25 (m, 7H, C*H*$_{arom}$); 6.91-6.87 (m, 2H, C*H*$_{arom}$); 6.80-6.76 (m, 2H, C*H*$_{arom}$); 5.42 (d, 1H, *J* = 2.0 Hz, H-1); 5.13 (d, 1H, *J* = 1.6 Hz, H-1'); 4.88 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.78 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.61 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.56 (d, 1H, *J* = 10.4 Hz, PhCH*H*); 4.21-4.19(m, 2H, H-2, H-2'); 3.81 (s, 3H, C*H*$_{3,PMB}$); 3.79-3.74 (m, 2H, H-3, H-5); 3.70-3.66 (m, 1H, H-5'); 3.60 (dd, 1H, *J* = 3.4, 9.0 Hz, H-3'); 3.57 (s, 3H, OC*H*$_3$); 3.53 (s, 3H, OC*H*$_3$); 3.43-3.34 (m, 2H, H-4, H-4'); 1.27 (d, 3H, *J* = 6.0 Hz, H-6'); 1.22 (d, 3H, *J* = 6.4 Hz, H-6).

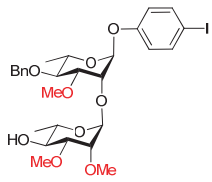
^{13}C-APT NMR (101 MHz) δ: 159.5, 156.1, 138.5 ($C_{q,arom}$); 138.5 (CH_{arom}); 130.6 ($C_{q,arom}$); 129.9, 128.5, 128.1, 127.9, 118.6, 114.0 (CH_{arom}); 100.9 (C-1'); 96.9 (C-1); 84.8 (CI_{arom}); 81.5 (C-3); 81.4 (C-3'); 80.1 (C-4); 79.6 (C-4'); 75.4, 75.1 (PhCH_2); 73.4 (C-2); 68.7 (C-5'); 68.1 (C-2'); 68.0 (C-5); 58.1, 57.7 (OCH_3); 55.4 ($CH_{3,PMB}$); 18.1 (C-6'); 18.0 (C-6). IR (thin film, cm^{-1}): 1045, 1070, 1113, 1139, 1233, 1249, 1484, 1513, 3484. HRMS calculated for $C_{36}H_{43}IO_{10}Na$ 773.1799 [M+Na]$^+$; found 773.1809.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (13)



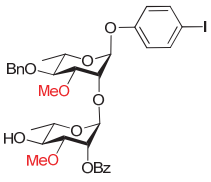
Compound **12** (196 mg, 0.26 mmol, 1.0 eq) was dissolved in dry DMF (2.6 mL, 0.1 M) and MeI (32 µL, 0.52 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C and NaH (60%, 16 mg, 0.39 mmol, 1.5 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was quenched by addition of H_2O and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (207 mg, 0.26 mmol, 100%) as a pale oil. $[\alpha]_D^{25}$ -70.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.53 (m, 2H, CH_{arom}); 7.33-7.26 (m, 7H, CH_{arom}); 6.90-6.86 (m, 2H, CH_{arom}); 6.80-6.76 (m, 2H, CH_{arom}); 5.39 (d, 1H, *J* = 1.6 Hz, H-1); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 4.88 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.83 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.64 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.54 (d, 1H, *J* = 10.4 Hz, PhCH*H*); 4.19 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.80 (s, 3H, C$H_{3,PMB}$); 3.77-3.55 (m, 14H, H-2', H-3, H-3', H-5, H-5', OCH_3); 3.46-3.38 (m, 2H, H-4, H-4'); 1.27 (d, 3H, *J* = 6.0 Hz, H-6'); 1.22 (d, 1H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.4, 156.1 ($C_{q,arom}$); 138.5 (CH_{arom}); 130.8 ($C_{q,arom}$); 129.9, 128.5, 128.1, 127.9, 118.6, 114.0 (CH_{arom}); 98.9 (C-1'); 97.0 (C-1); 84.8 (CI_{arom}); 81.7 (C-3); 81.2 (C-3'); 80.2 (C-4); 80.0 (C-4'); 77.6 (C-2'); 75.3, 75.2 (PhCH_2); 68.8 (C-5); 68.6 (C-5'); 59.2, 58.2, 58.1 (OCH_3); 55.4 ($CH_{3,PMB}$); 18.1 (C-6); 18.1 (C-6'). IR (thin film, cm^{-1}): 1035, 1052, 1072, 1093, 1120, 1173, 1233, 1248, 1484, 1514. HRMS calculated for $C_{36}H_{45}IO_{10}Na$ 787.1955 [M+Na]$^+$; found 787.1945.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (14)



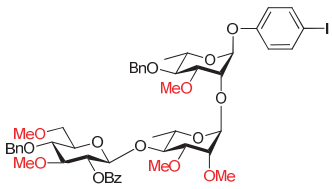
Compound **13** (199 mg, 0.26 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 2.6 mL, 0.1 M) after which a solution of HCl in HFIP (0.13 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour (~2 minutes), the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (155 mg, 0.24 mmol, 93%) as a pale oil. $[\alpha]_D^{25}$ -75.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.35-7.28 (m, 5H, C*H*$_{arom}$); 6.83-6.79 (m, 2H, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.18 (d, 1H, *J* = 1.6 Hz, H-1'); 4.77 (dd, 2H, *J* = 10.8, 65.6 Hz, PhC*H*$_2$); 4.22 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.79-3.70 (m, 4H, H-2', H-3, H-5, H-5'); 3.62-3.40 (m, 12H, H-3', H-4, H-4', OC*H*$_3$); 2.34 (bs, 4'-OH); 1.30 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.4 (C$_{q,arom}$); 128.5, 128.1, 127.9, 118.6 (*C*H$_{arom}$); 99.1 (C-1'); 97.0 (C-1); 84.9 (*C*I$_{arom}$); 81.6 (C-3); 80.8 (C-3'); 80.0 (C-4); 75.9 (C-2'); 75.2 (Ph*C*H$_2$); 73.5 (C-2); 71.7 (C-4'); 68.9 (C-5); 68.8 (C-5'); 59.1, 58.2, 57.1 (O*C*H$_3$); 18.2 (C-6'); 17.9 (C-6). IR (thin film, cm^{-1}): 1013, 1017, 1032, 1050, 1073, 1089, 1122, 1139, 1233, 1262, 1484, 2909, 2929, 3481. HRMS calculated for $C_{28}H_{37}IO_9Na$ 667.1380 $[M+Na]^+$; found 667.1374.

4-iodophenyl 2-*O*-(2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (15)



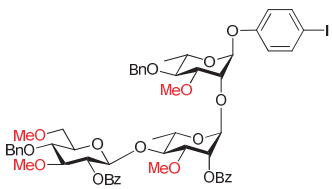
Compound **11** (88 mg, 0.10 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 1 mL, 0.1 M) after which a solution of HCl in HFIP (50 μL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour (~2 minutes), the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (80 mg, 0.10 mmol, 100%) as a pale oil. $[\alpha]_D^{25}$ -57.1 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.09-8.06 (m, 2H, C*H*$_{arom}$); 7.60-7.55 (m, 3H, C*H*$_{arom}$); 7.48-7.44 (m, 2H, C*H*$_{arom}$); 7.39-7.25 (m, 5H, C*H*$_{arom}$); 6.83-6.80 (m, 2H, C*H*$_{arom}$); 5.70 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2'); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.22 (d, 1H, *J* = 1.6 Hz, H-1'); 4.80 (dd, 2H, *J* = 11.0, 103.4 Hz, PhC*H*$_2$); 4.24 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.90-3.86 (m, 1H, H-5'); 3.79 (dd, 1H, *J* = 2.8, 9.2 Hz, H-3); 3.75-3.62 (m, 3H, H-3', H-4', H-5); 3.56-3.47 (m, 7H, H-4, OC*H*$_3$); 2.60 (bs, 1H, 4'-O*H*); 1.37 (d, 3H, *J* = 6.0 Hz, H-6'); 1.27 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.7 (*C*O$_{Bz}$); 156.1, 138.5 (C$_{q,arom}$); 138.5, 133.4, 130.0 (*C*H$_{arom}$); 129.8 (C$_{q,arom}$); 128.6, 128.5, 128.2, 127.9, 118.6 (*C*H$_{arom}$); 99.6 (C-1'); 97.0 (C-1); 84.9 (*C*I$_{arom}$); 81.4 (C-3); 79.9 (C-4); 79.6 (C-3'); 75.4 (C-2); 73.6 (C-4'); 68.9 (C-5); 68.9 (C-5'); 68.0 (C-2'); 58.2, 57.5 (O*C*H$_3$); 18.2 (C-6); 18.1 (C-6'). IR (thin film, cm^{-1}): 1040, 1073, 1096, 1119, 1176, 1202, 1232, 1271, 1316, 1385, 1452, 1484, 1585, 1724, 2931, 3446. HRMS calculated for $C_{34}H_{39}IO_{10}Na$ 757.1486 $[M+Na]^+$; found 757.1480.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzoyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (16a)



Donor **8** (103 mg, 0.21 mmol, 1.5 eq), Ph_2SO (50 mg, 0.23 mmol, 1.7 eq) and TTBP (103 mg, 0.42 mmol, 3.0 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (2.8 mL, 0.08 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -60 °C after which Tf_2O (35 µL, 0.23 mmol, 1.7 eq) was added to the solution. After stirring for 30 minutes, acceptor **14** (90 mg, 0.14 mmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.4 mL, 0.4 M) and added to the solution. After stirring for 1.5 hours the reaction was quenched by addition of NEt_3 (0.14 mL). The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (140 mg, 0.14 mmol, 98%) as a slightly yellow oil. $[\alpha]_D^{25}$ -74.9 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.16-8.14 (m, 2H, C*H*$_{arom}$); 7.58-7.56 (m, 3H, C*H*$_{arom}$); 7.47 (t, 1H, *J* = 7.8 Hz, C*H*$_{arom}$); 7.36-7.26 (m, 11H, C*H*$_{arom}$); 6.82-6.80 (m, 2H, C*H*$_{arom}$); 5.40 (d, 1H, *J* = 1.6 Hz, H-1); 5.17-5.12 (m, 2H, H-1', H-2''); 4.85-4.80 (m, 3H, H-1'', PhC*H*H, PhC*H*H); 4.66 (d, 1H, *J* = 11.2 Hz), PhCH*H*); 4.58 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.17 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.74-3.39 (m, 19H, H-2', H-3, H-3', H-3'', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 3.35-3.30 (m, 2H, H-4, H-4'); 3.13 (s, 3H, OC*H*$_3$); 1.29 (d, 3H, *J* = 6.0 Hz, H-6''); 1.20 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.3 (*C*O$_{Bz}$); 156.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.5, 138.4 (C$_{q,arom}$); 133.2 (*C*H$_{arom}$); 130.3 (C$_{q,arom}$); 130.0, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 118.6 (*C*H$_{arom}$); 101.4 (C-1''); 98.4 (C-1'); 96.8 (C-1''); 85.4 (C-3''); 84.8 (*C*I$_{arom}$); 81.8 (C-3); 80.5 (C-4'); 80.0 (C-4); 77.7 (C-3'); 77.5 (C-4''); 76.6 (C-2'); 75.2, 75.0 (Ph*C*H$_2$); 74.9 (C-5''); 74.3 (C-2''); 73.1 (C-2); 71.2 (C-6''); 68.8 (C-5'); 68.0 (C-5); 60.8, 59.8, 59.0, 58.3, 57.2 (O*C*H$_3$); 18.1 (C-6 and C-6'). IR (thin film, cm^{-1}): 1027, 1055, 1072, 1092, 1119, 1140, 1233, 1268, 1484, 1734, 2928. HRMS calculated for $C_{50}H_{61}IO_{15}Na$ 1051.2953 $[M+Na]^+$; found 1051.2947.

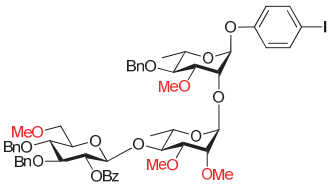
4-iodophenyl 2-*O*-(2-*O*-benzoyl-3-*O*-methyl-4-*O*-(2-*O*-benzoyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (16b)



Donor **8** (69 g, 0.14 mmol, 1.5 eq), Ph_2SO (37 mg, 0.18 mmol, 2.0 eq) and TTBP (86 mg, 0.35 mmol, 3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (2.8 mL, 0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -60 °C after which Tf_2O (30 µL, 0.18 mmol, 2.0 eq) was added to the solution. After stirring for 30 minutes, acceptor **15** (68 mg, 93 µmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.3 mL, 0.3 M) and added to the solution. After stirring for 2 hours the reaction was quenched by addition of NEt_3 (0.1 mL). The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-

pentane-Et_2O 3:7) gave the title compound (92 mg, 82 µmol, 88%) as a pale oil. $[\alpha]_D^{25}$ -42.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.14-8.12 (m, 2H, C*H*$_{arom}$); 8.07-8.05 (m, 2H, C*H*$_{arom}$); 7.59-7.54 (m, 4H, C*H*$_{arom}$); 7.49-7.42 (m, 4H, C*H*$_{arom}$); 7.35-7.25 (m, 10H, C*H*$_{arom}$); 6.81 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 2.0 Hz, H-1); 5.16-5.14 (m, 2H, H-1', H-2''); 4.87-4.83 (m, 3H, H-1'', PhC*H*H, PhC*H*H); 4.65 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.59 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.18 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.72-3.53 (m, 7H, H-3, H-4', H-4'', H-5, H-5', H-6''); 3.52-3.40 (m, 13H, H-3', H-3'', H-4, H-5'', OC*H*$_3$); 3.10 (s, 3H, OC*H*$_3$); 1.38 (d, 3H, *J* = 6.4 Hz, H-6'); 1.23 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.7, 165.3 (*C*O$_{Bz}$); 138.5 (*C*H$_{arom}$); 138.3 (C$_{q,arom}$); 133.4, 133.3 (*C*H$_{arom}$); 130.2 (C$_{q,arom}$); 130.1, 130.0, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 118.7 (*C*H$_{arom}$); 101.5 (C-1''); 99.1 (C-1'); 96.8 (C-1); 85.4 (C-3''); 84.9 (*C*I$_{arom}$); 81.5 (C-3); 79.9 (C-4); 79.4 (C-3'); 78.2 (C-4'); 77.6 (C-4''); 75.3, 75.0 (Ph*C*H$_2$); 74.9 (C-5''); 74.2 (C-2''); 73.0 (C-2); 71.5 (C-6''); 68.9 (C-5); 68.4 (C-2'); 68.0 (C-5'); 60.8, 59.8, 58.2, 57.4 (O*C*H$_3$); 18.3 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1000, 1027, 1070, 1096, 1112, 1140, 1178, 1233, 1268, 1452, 1484, 1723, 2931. HRMS calculated for $C_{56}H_{63}IO_{16}Na$ 1141.3059 $[M+Na]^+$; found 1141.3064.

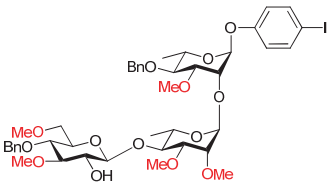
4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (16c)



Donor **10** (204 mg, 0.41 mmol, 1.5 eq), Ph_2SO (92 mg, 0.45 mmol, 1.7 eq) and TTBP (205 mg, 0.83 mmol, 3.0 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (5.5 mL, 0.07 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -70 °C after which Tf_2O (76 µL, 0.45 mmol, 1.7 eq) was added to the solution. After stirring for 20 minutes, acceptor **14** (177 mg, 0.27 mmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.6 mL, 0.4 M) and added to the solution. After stirring for 1 hour the reaction was quenched by addition of pyridine (0.28 mL). The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (284 g, 0.26 mmol, 93%) as a slightly yellow oil. $[\alpha]_D^{25}$ -76.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.12-8.10 (m, 2H, C*H*$_{arom}$); 7.62-7.58 (m, 3H, C*H*$_{arom}$); 7.49-7.45 (m, 2H, C*H*$_{arom}$); 7.37-7.32 (m, 10H, C*H*$_{arom}$); 7.16-7.13 (m, 5H, C*H*$_{arom}$); 6.85-6.83 (m, 2H, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 2.0 Hz, H-1); 5.27 (t, 1H, *J* = 8.4 Hz, H-2''); 5.16 (d, 1H, *J* = 2.0 Hz, H-1'); 4.88-4.84 (m, 3H, H-1'', PhC*H*H, PhC*H*H); 4.79 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.72-4.67 (m, 2H, PhCH*H*, PhCH*H*); 4.61 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.21 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.83-3.62 (m, 9H, H-2', H-3, H-3', H-3'', H-4'', H-5, H-5', H-6''); 3.55 (s, 3H, OC*H*$_3$); 3.50 (s, 4H, H-5'', OC*H*$_3$); 3.43 (s, OC*H*$_3$); 3.38-3.30 (m, 2H, H-4, H-4'); 3.15 (s, 3H, OC*H*$_3$); 1.33 (d, 3H, *J* = 5.6 Hz, H-6'); 1.24 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.2 (*C*O$_{Bz}$); 156.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.3, 138.1 (C$_{q,arom}$); 133.1 (*C*H$_{arom}$); 130.3 (C$_{q,arom}$); 130.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 118.6 (*C*H$_{arom}$); 101.5 (C-1''); 98.4 (C-1'); 96.8 (C-1); 84.8 (*C*I$_{arom}$); 83.1 (C-3''); 81.8 (C-4''); 80.5 (C-4); 80.0 (C-4'); 78.1 (C-3); 77.7 (C-3'); 76.6 (C-2'); 75.2, 75.2, 75.1 (Ph*C*H$_2$); 75.0 (C-5''); 74.3 (C-2''); 73.1 (C-2); 71.2 (C-6''); 68.8 (C-5'); 68.0 (C-5); 59.9, 59.0, 58.2, 57.2 (O*C*H$_3$); 18.1 (C-6'); 18.1 (C-

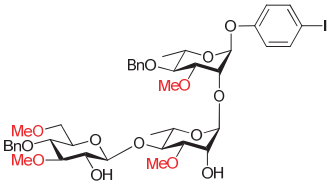
6). IR (thin film, cm^{-1}): 1000, 1027, 1055, 1072, 1095, 1120, 1140, 1233, 1268, 1452, 1484, 1731, 2931. HRMS calculated for $C_{56}H_{65}IO_{15}Na$ 1127.3266 $[M+Na]^+$; found 1127.3260.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (17a)



Compound **16a** (102 mg, 0.1 mmol, 1.0 eq) was dissolved in THF (0.49 mL, 0.2 M) and the solution was diluted with MeOH (0.49 mL). A small piece of sodium was added to the solution and the reaction was stirred for 2 hours. The reaction was then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (92 mg, 0.1 mmol, 100%) as a pale oil. $[\alpha]_D^{25}$ -27.4 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.56 (m, 2H, C*H*$_{arom}$); 7.36-7.26 (m, 10H, C*H*$_{arom}$); 6.82-6.79 (m, 2H, C*H*$_{arom}$); 5.40 (d, 1H, *J* = 1.6 Hz, H-1); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 4.89-4.83 (m, 2H, PhC*H*H, PhC*H*H); 4.66-4.60 (m, 2H, PhCH*H*, PhCH*H*); 4.37 (d, 1H, *J* = 8.0 Hz, H-1''); 4.18 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.90 (bs, 1H, 2''-O*H*); 3.79-3.75 (m, 3H, H-2', H-3, H-5); 3.71-3.58 (m, 6H, H-3', H-5', H-5'', OCH_3); 3.56-3.50 (m, 11H, H-4'', H-6'', OCH_3); 3.46-3.36 (m, 6H, H-2'', H-4, H-4', OCH_3); 3.29 (t, 1H, *J* = 8.8 Hz, H-3''); 1.35 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.4 (C$_{q,arom}$); 128.6, 128.5, 128.1, 128.1, 127.9, 118.6 (*C*H$_{arom}$); 105.8 (C-1''); 98.8 (C-1'); 96.9 (C-1); 86.4 (C-3''); 84.9 (*C*I$_{arom}$); 81.8 (C-5''); 81.6 (C-3); 80.3 (C-3'); 80.0 (C-4); 77.3 (C-4''); 75.8 (C-2'); 75.6 (C-2''); 75.3 (Ph*C*H$_2$); 75.2 (C-4'); 75.0 (Ph*C*H$_2$); 71.3 (C-6''); 68.7 (C-5'); 68.4 (C-5); 61.0, 59.5, 59.1, 58.3, 56.7 (O*C*H$_3$); 18.2 (C-6'); 17.7 (C-6). IR (thin film, cm^{-1}): 1000, 1002, 1030, 1032, 1052, 1071, 1120, 1233, 1455, 1485, 2896, 2923, 3445. HRMS calculated for $C_{43}H_{57}IO_{14}Na$ 947.2691 $[M+Na]^+$; found 947.2709.

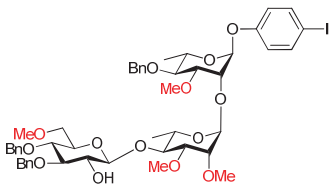
4-iodophenyl 2-*O*-(3-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (17b)



Compound **16b** (90 mg, 80 µmol, 1.0 eq) was dissolved in THF (0.4 mL, 0.2 M). A small piece of sodium was dissolved in MeOH and 0.4 mL of this solution was added. The reaction was stirred for 4 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (DCM-EtOAc 7:3) gave the title compound (61 mg, 67 µmol, 84%) as a pale oil. $[\alpha]_D^{25}$ -65.2 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.36-7.28 (m, 10H, C*H*$_{arom}$); 6.82-6.79 (m, 2H, C*H*$_{arom}$); 5.41 (d, 1H, *J* = 1.6 Hz, H-1); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 4.89-4.86 (m, 2H, PhC*H*H, PhC*H*H); 4.63-4.61 (m, 2H, PhCH*H*, PhCH*H*); 4.35 (d, 1H, *J* = 7.6 Hz, H-1''); 4.25 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2'); 4.19 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.85-3.79 (m, 1H, H-5'); 3.78-3.59 (m, 9H, H-3, H-3', H-4', H-5, H-6'', OCH_3); 3.55-3.50 (m, 7H, H-4'', OCH_3); 3.47-3.36 (m, 8H, H-2'', H-5'', OCH_3); 3.30 (t, 1H, *J* = 9.2 Hz, H-3''); 1.35 (d, 3H, *J* = 6.4 Hz, H-6'); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101

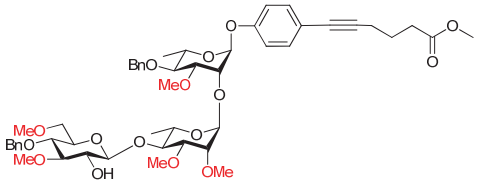
MHz) δ: 156.0 ($C_{q,arom}$); 138.5 (CH_{arom}); 138.5, 138.4 ($C_{q,arom}$); 128.6, 128.5, 128.1, 128.1, 127.9, 127.9, 118.6 (CH_{arom}); 105.7 (C-1''); 100.8 (C-1'); 96.9 (C-1); 86.2 (C-3''); 84.9 (CI_{arom}); 81.5 (C-3); 81.2 (C-4'); 80.6 (C-3'); 80.1 (C-4); 77.3 (C-4''); 75.6 (C-2''); 75.3 (PhCH_2); 75.3 (C-5''); 75.0 (PhCH_2); 73.6 (C-2); 71.3 (C-6''); 68.7 (C-5); 67.9 (C-5'); 66.9 (C-2'); 61.1, 59.5, 58.2, 56.9 (OCH_3); 18.1 (C-6); 17.6 (C-6'). IR (thin film, cm^{-1}): 1069, 1116, 1232, 1454, 1484, 2928, 3451. HRMS calculated for $C_{42}H_{55}IO_{14}Na$ 933.2534 $[M+Na]^+$; found 933.2529.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (17c)



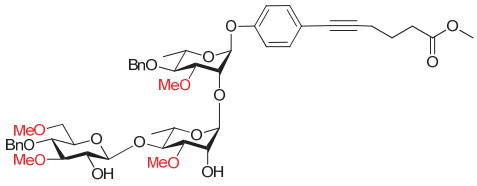
Compound **16c** (95 mg, 86 µmol, 1.0 eq) was dissolved in THF (0.8 mL, 0.1 M) and the solution was diluted with MeOH (0.8 mL). A small piece of sodium was added to the solution and the reaction was stirred for 2 hours. The reaction was then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (85 mg, 85 µmol, 99%) as a pale oil. $[\alpha]_D^{25}$ -41.4 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 2H, CH_{arom}); 7.42-7.40 (m, 1H, CH_{arom}); 7.37-7.25 (m, 14H, CH_{arom}); 6.82-6.79 (m, 2H, CH_{arom}); 5.41 (d, 1H, *J* = 2.0 Hz, H-1); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 5.02 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.89-4.82 (m, 3H, PhC*H*H, PhC*H*H, PhCH*H*); 4.66-4.59 (m, 2H, PhCH*H*, PhCH*H*); 4.40 (d, 1H, *J* = 6.8 Hz, H-1''); 4.19 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.79-3.72 (m, 4H, H-2', H-3, H-5', 2''-O*H*); 3.70-3.51 (m, 17H, H-2'', H-3', H-3'', H-4'', H-5, H-5'', H-6'', OCH_3); 3.42-3.38 (m, 2H, H-4, H-4'); 3.35 (s, 3H, OCH_3); 1.36 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.0, 139.0 ($C_{q,arom}$); 138.4 (CH_{arom}); 138.4 ($C_{q,arom}$); 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 118.6 (CH_{arom}); 105.7 (C-1''); 98.8 (C-1'); 96.9 (C-1); 84.8 (CI_{arom}); 84.8 (C-4''); 81.7 (C-3''); 81.6 (C-3); 80.3 (C-3'); 80.0 (C-4'); 77.1 (C-2''); 76.2 (C-4); 75.8 (C-2'); 75.2 (C-5''); 75.2, 75.2, 75.0 (PhCH_2); 73.7 (C-2); 71.3 (C-6''); 68.7 (C-5'); 68.4 (C-5); 59.5, 59.1, 58.3, 56.7 (OCH_3); 18.2 (C-6'); 17.7 (C-6). IR (thin film, cm^{-1}): 1053, 1070, 1089, 1119, 1232, 1454, 1484, 2928, 3454. HRMS calculated for $C_{49}H_{61}IO_{14}Na$ 1023.3004 $[M+Na]^+$; found 1023.2998.

Methyl 6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)phenylhex-5-ynoate (18a)



Compound **17a** (67 mg, 72 µmol, 1.0 eq) was dissolved in freshly distilled NEt_3 (2 mL, 0.04 M) together with methyl hex-5-ynoate (28 µL, 0.22 mmol, 3.0 eq). A cocktail of $Pd(PPh_3)_2Cl_2$ (28 mg), PPh_3 (22 mg) and CuI (15 mg) in freshly distilled NEt_3 was stirred for 15 minutes at 40 °C . Of this cocktail 0.18 mL was added to the reaction mixture, amounting to 0.1 eq $Pd(PPh_3)_2Cl_2$, 0.2 eq PPh_3 and 0.2 eq CuI. The reaction was left to stir overnight at 40 °C after which it was diluted with Et_2O and washed with 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (DCM-EtOAc 6:4) gave the title compound (66 mg, 72 µmol, 99%) as a yellow oil. $[\alpha]_D^{25}$ -56.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.36-7.26 (m, 12H, C*H*$_{arom}$); 6.95-6.92 (m, 2H, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 4.90-4.83 (m, 2H, PhC*H*H, PhC*H*H); 4.66-4.60 (m, 2H, PhCH*H*, PhCH*H*); 4.38 (d, 1H, *J* = 7.6 Hz, H-1''); 4.19 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.90 (bs, 1H, 2''-O*H*); 3.79-3.70 (m, 3H, H-2', H-3, H-5); 3.69-3.66 (m, 9H, H-3', H-5', H-5'', OC*H*$_3$, COOC*H*$_3$); 3.64-3.59 (m, 2H, H-6''); 3.56-3.50 (m, 10H, H-4'', OC*H*$_3$); 3.46-3.37 (m, 6H, H-2'', H-4, H-4', OC*H*$_3$); 3.36 (s, 3H, OC*H*$_3$); 3.29 (t, 1H, *J* = 8.6 Hz, H-3''); 2.53-2.45 (m, 4H, C*H*$_{2,linker}$, C*H*$_{2,linker}$); 1.92 (quint, 2H, *J* = 7.2 Hz, C*H*$_{2,linker}$); 1.36 (d, 3H, *J* = 6.0 Hz, H-6'); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 Mz) δ: 173.8 (*C*OOCH$_3$); 155.6, 138.4, 138.4 (C$_{q,arom}$); 133.0, 128.7, 128.5, 128.5, 128.1, 128.1, 127.9 (*C*H$_{arom}$); 117.6 (C$_{q,arom}$); 116.1 (*C*H$_{arom}$); 105.8 (C-1''); 98.8 (C-1'); 87.8 (C$_{q,alkyne}$); 86.4 (C-3''); 81.8 (C-3); 81.6 (C-5''); 81.0 (C$_{q,alkyne}$); 80.3 (C-3'); 80.1 (C-2''); 77.3 (C-4''); 75.8 (C-2'); 75.6 (C-4); 75.2 (C-4'); 75.2, 75.0 (Ph*C*H$_2$); 73.7 (C-2); 71.3 (C-6''); 68.7 (C-5'); 68.4 (C-5); 61.0, 59.5, 59.1, 58.3, 56.7 (O*C*H$_3$); 51.7 (COO*C*H$_3$); 33.0, 24.0, 19.0 (*C*H$_{2,linker}$); 18.1 (C-6'); 17.7 (C-6). IR (thin film, cm^{-1}): 1005, 1016, 1030, 1053, 1070, 1088, 1120, 1140, 1233, 1507, 1739, 2930, 3420. HRMS calculated for $C_{50}H_{66}O_{16}Na$ 945.4249 $[M+Na]^+$; found 945.4244.

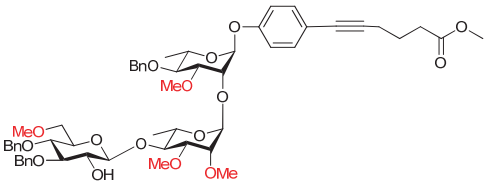
Methyl 6-(4-(2-*O*-(3-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)phenylhex-5-ynoate (18b)



Compound **17b** (61 mg, 67 µmol, 1.0 eq) was dissolved in freshly distilled NEt_3 (1 mL, 0.07 M) together with methyl hex-5-ynoate (28 µL, 0.20 mmol, 3.0 eq). A cocktail of $Pd(PPh_3)_2Cl_2$ (14 mg), PPh_3 (11 mg) and CuI (7 mg) in freshly distilled NEt_3 was stirred for 15 minutes at 40 °C . Of this cocktail 0.34 mL was added to the reaction mixture, amounting to 0.1 eq $Pd(PPh_3)_2Cl_2$, 0.2 eq PPh_3 and 0.2 eq CuI. The reaction was left to stir overnight at 40 °C after which it was diluted with Et_2O, filtered over celite and washed with 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (DCM-EtOAc 7:3) gave the title compound (47 mg, 52 µmol, 77%) as a yellow oil. $[\alpha]_D^{25}$ -60.5 (c = 1.0, $CHCl_3$). ^{1}H-

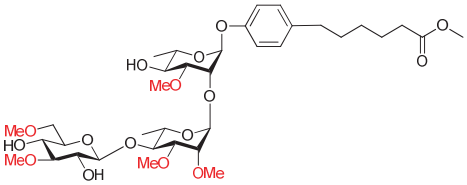
NMR (400 MHz) δ: 7.36-7.26 (m, 12H, C*H*$_{arom}$); 6.93 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 2.0 Hz, H-1); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 4.89-4.84 (m, 2H, PhC*H*H, PhC*H*H); 4.64-4.61 (m, 2H, PhCH*H*, PhCH*H*); 4.35 (d, 1H, *J* = 7.6 Hz, H-1''); 4.25 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2'); 4.20 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.88-3.80 (m, 1H, H-5'); 3.78 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.71-3.60 (m, 11H, H-3', H-4', H-5, H-6'', COOC*H*$_3$, OC*H*$_3$); 3.54-3.50 (m, 7H, H-4'', OC*H*$_3$); 3.47-3.36 (m, 6H, H-2'', H-4, H-5'', OC*H*$_3$); 3.30 (t, 1H, *J* = 9.0 Hz, H-3''); 2.51 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 2.47 (t, 2H, *J* = 6.8 Hz, C*H*$_{2,linker}$); 1.92 (quint, 2H, *J* = 7.2 Hz, C*H*$_{2,linker}$); 1.35 (d, 3H, *J* = 6.0 Hz, H-6'); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 173.8 (*C*OOCH$_3$); 155.6, 138.5, 138.4 (C$_{q,arom}$); 133.1, 128.6, 128.5, 128.1, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 117.6 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 105.7 (C-1''); 100.8 (C-1'); 96.8 (C-1); 87.9 (C$_{q,alkyne}$); 86.3 (C-3''); 81.6 (C-3); 81.2 (C-4'); 81.1 (C$_{q,alkyne}$); 80.7 (C-3'); 80.1 (C-4); 77.4 (C-4''); 75.6 (C-2''); 75.3 (C-5''); 75.0, 75.0 (Ph*C*H$_2$); 73.6 (C-2); 71.3 (C-6''); 68.7 (C-5); 67.9 (C-5'); 66.9 (C-2'); 61.1, 59.5, 58.2, 57.0 (O*C*H$_3$); 51.8 (COO*C*H$_3$); 33.1, 24.1, 19.0 (*C*H$_{2,linker}$); 18.2 (C-6); 17.6 (C-6'). IR (thin film, cm^{-1}): 1049, 1069, 1139, 1233, 1454, 1508, 1560, 1736, 2923, 3464. HRMS calculated for $C_{49}H_{64}O_{16}Na$ 931.4092 [M+Na]$^+$; found 931.4087.

Methyl 6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)phenylhex-5-ynoate (18c)



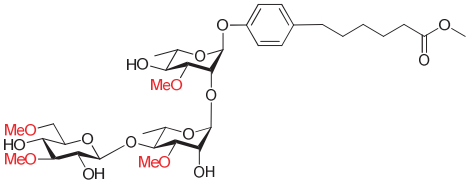
Compound **17c** (85 mg, 85 µmol, 1.0 eq) was dissolved in freshly distilled NEt$_3$ (1.79 mL, 0.05 M) together with methyl hex-5-ynoate (33 µL, 0.26 mmol, 3.0 eq). A cocktail of Pd(PPh$_3$)$_2$Cl$_2$ (28 mg), PPh$_3$ (22 mg) and CuI (15 mg) in freshly distilled NEt$_3$ was stirred for 15 minutes at 40 °C . Of this cocktail 0.21 mL was added to the reaction mixture, amounting to 0.1 eq Pd(PPh$_3$)$_2$Cl$_2$, 0.2 eq PPh$_3$ and 0.2 eq CuI. The reaction was left to stir overnight at 40 °C after which it was diluted with Et$_2$O and washed with 1 M HCl, sat. aq. NaHCO$_3$ and brine. The organic layer was dried with MgSO$_4$ and concentrated *in vacuo*. Purification by means of column chromatography (DCM-EtOAc 7:3) gave the title compound (70 mg, 70 µmol, 82%) as a yellow oil. [α]$_D^{25}$ -67.5 (c = 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz) δ: 7.42-7.26 (m, 17H, C*H*$_{arom}$); 6.93 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 2.0 Hz, H-1); 5.16 (d, 1H, *J* = 1.6 Hz, H-1'); 5.02 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.90-4.82 (m, 3H, PhCH*H*, PhC*H*H, PhC*H*H); 4.66-4.59 (m, 2H, PhCH*H*, PhCH*H*); 4.40 (d, 1H, *J* = 6.8 Hz, H-1''); 4.19 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.83-3.65 (m, 4H, H-2', H-3, H-5', 2''-O*H*); 3.62-3.53 (m, 20H, H-2'', H-3', H-3'', H-4, H-4'', H-5, H-6'', OC*H*$_3$); 3.42-3.38 (m, 2H, H-4', H-5''); 3.35 (s, 3H, OC*H*$_3$); 2.53-2.45 (m, 4H, C*H*$_{2,Linker}$); 1.95-1.90 (m, 2H, C*H*$_{2,Linker}$); 1.36 (d, 3H, *J* = 6.0 Hz, H-6'); 1.25 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 173.8 (*C*OOCH$_3$); 155.6, 139.1, 138.5, 138.4 (C$_{q,arom}$); 133.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.6 (*C*H$_{arom}$); 117.6 (C$_{q,arom}$); 116.1 (*C*H$_{arom}$); 105.7 (C-1''); 96.8 (C-1'); 96.8 (C-1); 87.9 (C$_{q,alkyne}$); 84.8 (C-4''); 81.7 (C-3); 81.6 (C-3'); 81.1 (C$_{q,alkyne}$); 80.4 (C-3''); 80.1 (C-4'); 77.3 (C-2''); 76.2 (C-4); 75.9 (C-2'); 75.3 (C-5''); 75.2, 75.2, 75.0 (Ph*C*H$_2$); 73.8 (C-2); 71.4 (C-6''); 68.7 (C-5); 68.4 (C-5'); 59.5, 59.1, 58.3, 56.7 (O*C*H$_3$); 51.7 (COO*C*H$_3$); 33.0, 24.1, 19.0 (*C*H$_{2,Linker}$); 18.2 (C-6); 17.8 (C-6'). IR (thin film, cm^{-1}): 1000, 1055, 1070, 1120, 1203, 1233, 1286, 1454, 1507, 1605, 1736, 2932, 3453. HRMS calculated for $C_{56}H_{70}O_{16}Na$ 1021.4562 [M+Na]$^+$; found 1021.4556.

Methyl 6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranosyl)phenylhexanoate (19a)



Compound **18a** (66 mg, 72 µmol, 1.0 eq) was dissolved in a mixture of THF and MeOH (1:1, 3 mL, 0.03 M) and the solution was purged with N_2. Palladium on carbon (10%, 15 mg, 14 µmol, 0.2 eq) was added to the solution. The solution was then purged with H_2 and stirred for 40 hours under H_2 atmosphere. The mixture was then purged with N_2, diluted with EtOAc, filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 1:19) gave the title compound (53 mg, 72 µmol, 100%) as a pale oil. $[\alpha]_D^{25}$ -46.6 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.09 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.97-6.94 (m, 2H, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 1.6 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.41 (d, 1H, *J* = 7.6 Hz, H-1''); 4.23 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2); 3.90 (bs, 1H, 2''-O*H*); 3.79-3.72 (m, 3H, H-2', H-5, H-5'); 3.68-3.60 (m, 11H, H-3, H-3', H-4', H-6'', OC*H*$_3$, COOC*H*$_3$); 3.58-3.49 (m, 11H, H-4, H-4'', OC*H*$_3$); 3.48-3.38 (m, 5H, H-2'', H-5'', OC*H*$_3$); 3.17 (t, 1H, *J* = 9.0 Hz, H-3''); 2.56 (t, 2H, *J* = 7.8 Hz, C*H*$_{2,linker}$); 2.31 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 1.70-1.57 (m, 4H, C*H*$_{2,linker}$, C*H*$_{2,linker}$); 1.40-1.27 (m, 5H, C*H*$_{2,linker}$, H-6'); 1.25 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 154.3, 136.5 (C$_{q,arom}$); 129.5, 116.2 (*C*H$_{arom}$); 105.7 (C-1''); 98.5 (C-1'); 97.4 (C-1); 85.6 (C-3''); 81.7, 81.5 (C-3 and C-3'); 80.3 (C-4'); 75.8 (C-2'); 75.1, 74.2 (C-2'' and C-5''); 72.9 (C-6''); 72.2 (C-2); 71.9 (C-4); 71.2 (C-4''); 69.1, 68.4 (C-5 and C-5'); 60.7, 59.7, 59.2, 57.8, 56.7 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 35.0, 34.1, 31.3, 28.8, 24.9 (*C*H$_{2,linker}$); 17.9 (C-6); 17.7 (C-6'). IR (thin film, cm^{-1}): 1009, 1067, 1120, 1201, 1228, 1454 1510, 1736, 1933, 3436. HRMS calculated for $C_{36}H_{58}O_{16}Na$ 769.3623 $[M+Na]^+$; found 769.3617.

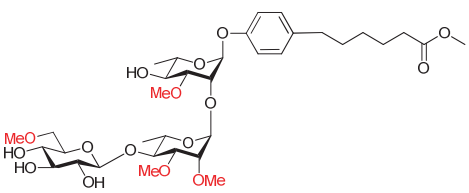
Methyl (6-(4-(2-*O*-(3-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-L-rhamnopyranosyl)phenylhexanoate (19b)



Compound **18b** (35 mg, 38 µmol, 1.0 eq) was dissolved in a mixture of THF and MeOH (1:1, 3.8 mL, 0.01 M) and the solution was purged with N_2. Palladium on carbon (10%, 8 mg, 8 µmol, 0.2 eq) was added to the solution. The solution was then purged with H_2 and stirred overnight under H_2 atmosphere. The mixture was then purged with N_2, diluted with EtOAc, filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 3:17) gave the title compound (23 mg, 31 µmol, 82%) as a pale oil. $[\alpha]_D^{25}$ -63.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.09 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.94 (dd, 2H, *J* = 2.2, 6.6 Hz, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 1.6 Hz, H-1); 5.08 (d, 1H, *J* = 1.6 Hz, H-1'); 4.39 (d, 1H, *J* = 8.0 Hz, H-1''); 4.22-4.19 (m, 2H, H-2, H-2'); 3.83-3.72 (m, 2H, H-5, H-5'); 3.69-3.53 (m, 13H, H-3, H-3', H-4, H-4', H-4'', H-6'', OC*H*$_3$, COOC*H*$_3$); 3.51 (s, 6H, OC*H*$_3$); 3.45-3.39 (m, 5H, H-2'', H-5'', OC*H*$_3$); 3.18 (t, 1H, *J* = 9.0 Hz, H-3''); 2.91 (bs, 1H, O*H*); 2.56 (t, 2H, *J* = 7.8 Hz, C*H*$_{2,linker}$); 2.42 (bs, 1H, O*H*); 2.31 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,lnker}$); 1.70-1.57 (m, 4H, C*H*$_{2,linker}$, C*H*$_{2,linker}$); 1.40-1.32 (m, 5H, H-6, C*H*$_{2,linker}$); 1.27 (d, 3H, *J* = 6.4 Hz, H-6'). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 154.4, 136.5 (C$_{q,arom}$); 129.5, 116.2

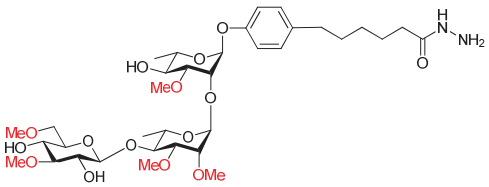
(*C*H$_{arom}$); 105.6 (C-1''); 100.7 (C-1'); 97.4 (C-1''); 85.5 (C-3''); 81.3, 81.1 (C-3 and C-3'); 75.2, 74.3 (C-2'' and C-5''); 72.9 (C-6''); 72.5 (C-2); 71.8 (C-4); 71.3 (C-4''); 69.1 (C-5); 67.9 (C-5'); 66.9 (C-2'); 60.7, 59.8, 57.7, 56.9 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 35.0, 34.1, 31.4, 28.9, 24.9 (*C*H$_{2,linker}$); 17.9 (C-6); 17.6 (C-6'). IR (thin film, cm^{-1}): 1013, 1065, 1122, 1202, 1228, 1261, 1455, 1510, 1736, 2858, 2931, 3426. HRMS calculated for $C_{35}H_{56}O_{16}Na$ 755.3466 [M+Na]$^+$; found 755.3457.

Methyl 6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranosyl))phenylhexanoate (19c)



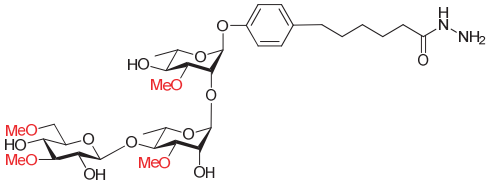
Compound **18c** (70 mg, 70 µmol, 1.0 eq) was dissolved in a mixture of THF and MeOH (1:1, 7 mL, 0.01 M) and the solution was purged with N_2. Palladium on carbon (10%, 15 mg, 14 µmol, 0.2 eq) was added to the solution. The solution was then purged with H_2 and stirred overnight under H_2 atmosphere. The mixture was then purged with N_2, diluted with EtOAc, filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 3:17) gave the title compound (46 mg, 63 µmol, 90%) as a pale oil. $[\alpha]_D^{25}$ -51.6 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.96-6.94 (m, 2H, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.45 (d, 1H, *J* = 7.6 Hz, H-1''); 4.22 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2); 3.79-3.72 (m, 3H, H-2', H-5, H-5'); 3.70-3.61 (m, 8H, H-3, H-3', H-4, H-6'', COOC*H*$_3$); 3.58-3.48 (m, 12H, H-3'', H-4', H-5'', OC*H*$_3$); 3.45-3.34 (m, 5H, H-2'', H-4'', OC*H*$_3$); 2.56 (t, 2H, *J* = 7.8 Hz, C*H*$_{2,linker}$); 2.31 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 1.70-1.57 (m, 4H, C*H*$_{2,linker}$, C*H*$_{2,linker}$); 1.40-1.32 (m, 5H, H-6, C*H*$_{2,linker}$); 1.27 (d, 3H, *J* = 6.0 Hz, H-6'). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 154.3, 136.5 (C$_{q,arom}$); 129.5, 116.2 (*C*H$_{arom}$); 105.2 (C-1''); 98.5 (C-1'); 97.4 (C-1); 81.5, 81.3 (C-3 and C-4'); 80.2 (C-3'); 76.6 (C-3''); 75.9 (C-2'); 74.8 (C-2''); 74.3 (C-4''); 72.9 (C-6''); 72.3 (C-2); 71.9 (C-4); 71.5 (C-5''); 69.1, 68.3 (C-5 and C-5'); 59.8, 59.1, 57.8, 56.7 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 35.0, 34.1, 31.3, 28.8, 24.9 (*C*H$_{2,linker}$); 17.9, 17.7 (C-6 and C-6'). IR (thin film, cm^{-1}): 1007, 1067, 1118, 1201, 1229, 1457, 1508, 1736, 2931, 3413. HRMS calculated for $C_{35}H_{56}O_{16}Na$ 755.3466 [M+Na]$^+$; found 755.3461.

6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranosyl)phenylhexanohydrazide (20a)



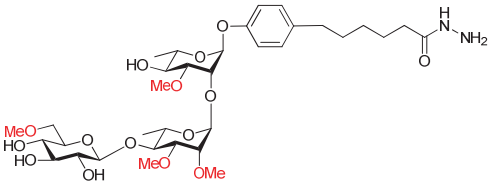
Compound **19a** (51 mg, 68 µmol, 1.0 eq) was dissolved in a mixture of EtOH and $N_2H_4 \cdot H_2O$ (1:2, 3 mL, 0.02 M) and stirred for 3 hours after which it was concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 1:9) gave the title compound (45 mg, 60 µmol, 82%) as a pale oil. $[\alpha]_D^{25}$ -64.5 (c = 1.0, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.94-6.92 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 2.0 Hz, H-1); 5.09 (d, 1H, *J* = 2.0 Hz, H-1'); 4.54 (d, 1H, *J* = 8.0 Hz, H-1''); 4.22 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.78-3.74 (m, 2H, H-2', H-5'); 3.68-3.54 (m, 12H, H-3, H-3', H-4', H-5, H-6'', OC*H*$_3$, COOC*H*$_3$); 3.49-3.44 (m, 7H, H-4, OC*H*$_3$); 3.37 (s, 3H, OC*H*$_3$); 3.34-3.29 (m, 2H, H-4'', H-5''); 3.19 (t, 1H, *J* = 7.6 Hz, H-2''); 3.09 (t, 1H, *J* = 8.4 Hz, H-3''); 2.55 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 2.13 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.62-1.58 (m, 4H, C*H*$_{2,linker}$); 1.32-1.27 (m, 4H, C*H*$_{2,linker}$); 1.24-1.21 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 175.3 (*C*ONHNH$_2$); 155.9, 137.8 (C$_{q,arom}$); 130.5, 117.4 (*C*H$_{arom}$); 104.8 (C-1''); 100.4 (C-1'); 98.9 (C-1); 87.6 (C-3''); 82.1, 81.9 (C-3 and C-3'); 79.1 (C-4'); 77.7 (C-2'); 76.7 (C-5''); 76.0 (C-2); 75.4 (C-2''); 73.3 (C-4); 73.0 (C-6''); 71.2 (C-4''); 70.7 (C-5); 69.1 (C-5'); 61.0, 59.8, 59.1, 58.5, 57.5 (O*C*H$_3$); 35.8, 34.9, 32.4, 29.7, 26.7 (*C*H$_{2,linker}$); 18.3, 18.2 (C-6 and C-6'). IR (thin film, cm^{-1}): 1068, 1119, 1201, 1228, 1294, 1387, 1452, 1510, 2931, 3398. HRMS calculated for $C_{35}H_{58}N_2O_{15}Na$ 769.3735 $[M+Na]^+$; found 769.3729.

6-(4-(2-*O*-(3-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranosyl))phenylhexanohydrazide (20b)



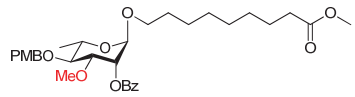
Compound **19b** (23 mg, 31 µmol, 1.0 eq) was dissolved in a mixture of EtOH and $N_2H_4 \cdot H_2O$ (1:2, 3 mL, 0.01 M) and stirred for 3 hours after which it was concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 1:4) gave the title compound (23 mg, 31 µmol, 100%) as a pale oil. $[\alpha]_D^{25}$ -52.9 (c = 1.0, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.93 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 4.98 (d, 1H, *J* = 1.6 Hz, H-1'); 4.56 (d, 1H, *J* = 8.0 Hz, H-1''); 4.20 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 4.13 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2'); 3.80-3.76 (m, 1H, H-5'); 3.70-3.45 (m, 15H, H-3, H-3', H-4, H-5, H-6'', OC*H*$_3$); 3.37-3.29 (m, 5, H-4'', H-5'', OC*H*$_3$); 3.20 (dd, 1H, *J* = 7.8, 9.0 Hz, H-2''); 3.07 (t, 1H, *J* = 8.2 Hz, H-3''); 2.55 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 2.13 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.64-1.58 (m, 4H, C*H*$_{2,linker}$); 1.39-1.21 (m, 8H, H-6, H-6', C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 175.4 (*C*ONHNH$_2$); 155.9, 137.8 (C$_{q,arom}$); 130.5, 117.4 (*C*H$_{arom}$); 105.0 (C-1''); 103.5 (C-1'); 98.9 (C-1); 87.6 (C-3''); 82.1 (C-3'); 81.7 (C-3); 79.1 (C-4'); 76.8 (C-5''); 75.7 (C-2); 75.5 (C-2''); 73.2 (C-4); 73.0 (C-6''); 71.2 (C-4''); 70.7 (C-5); 69.1 (C-5'); 67.8 (C-2'); 60.9, 59.8, 58.3, 57.0 (O*C*H$_3$); 35.8, 34.9, 32.4, 29.7, 26.7 (*C*H$_{2,linker}$); 18.2 (C-6); 18.2 (C-6'). IR (thin film, cm^{-1}): 1017, 1063, 1116, 1228, 1248, 1268, 1454, 1510, 1637, 2926, 3386. HRMS calculated for $C_{34}H_{56}N_2O_{15}Na$ 755.3578 $[M+Na]^+$; found 733.3754.

6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranosyl))phenylhexano-hydrazide (20c)



Compound **19c** (46 mg, 63 µmol, 1.0 eq) was dissolved in a mixture of EtOH and $N_2H_4 \cdot H_2O$ (1:2, 3 mL, 0.02 M) and stirred for 3 hours after which it was concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 1:4) gave the title compound (39 mg, 53 µmol, 84%) as a pale oil. $[\alpha]_D^{25}$ -42.9 (c = 1.0, MeOH). ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.95-6.92 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.54 (d, 1H, *J* = 7.6 Hz, H-1''); 4.22 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.78-3.74 (m, 2H, H-2, H-5); 3.70-3.54 (m, 9H, H-3, H-3', H-4, H-5, H-6'', OC*H*$_3$); 3.49-3.44 (m, 7H, H-4', OC*H*$_3$); 3.37-3.24 (m, 6H, H-3'', H-4'', H-5'', OC*H*$_3$); 3.15 (dd, 1H, *J* = 8.0, 8.8 Hz, H-2''); 2.55 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 2.13 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.66-1.56 (m, 4H, C*H*$_{2,linker}$, C*H*$_{2,linker}$); 1.36-1.27 (m, 2H, C*H*$_{2,linker}$); 1.25-1.21 (m, 6H, H-6, H-6'); ^{13}C-APT NMR (101 MHz) δ: 175.3 (*C*OOCH$_3$); 155.9, 137.8 (C$_{q,arom}$); 130.5, 117.4 (*C*H$_{arom}$); 104.8 (C-1''); 100.4 (C-1'); 98.9 (C-1); 82.1, 81.9 (C-3 and C-3'); 79.0 (C-4); 77.9 (C-4''); 77.7 (C-2'); 76.9 (C-3''); 76.0 (C-2); 75.5 (C-2''); 73.3 (C-4'); 73.1(C-6''); 71.7 (C-5''); 70.7 (C-5'); 69.1 (C-5); 59.8, 59.1, 58.5, 57.5 (O*C*H$_3$); 35.8, 32.4, 29.7, 26.7 (*C*H$_{2,linker}$); 18.3 (C-6); 18.2 (C-6'). IR (thin film, cm^{-1}): 1012, 1066, 1116, 1201, 1228, 1387, 1457, 1510, 1656, 1731, 2932, 3380. HRMS calculated for $C_{34}H_{57}N_2O_{15}$ 733.3759 $[M+H]^+$; found 733.37462.

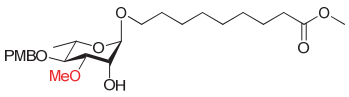
Methyl 9-(2-*O*-benzoyl-3-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)nonanoate (21)



Donor **5** (148 mg, 0.30 mmol, 1.0 eq), Ph_2SO (79 mg, 0.39 mmol, 1.3 eq) and TTBP (186 mg, 0.75 mmol, 2.5 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (6 mL, 0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -60 °C after which Tf_2O (65 µL, 0.39 mmol, 1.3 eq) was added. After stirring for 30 minutes, methyl 9-hydroxylnonanoate[38] (282 mg, 1.5 mmol, 5.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (3.8 mL, 0.4 M) and added to the solution. After stirring for 1 hour the reaction was quenched by addition of NEt_3 (0.3 mL). The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (136 mg, 0.24 mmol, 79%) as a pale oil. $[\alpha]_D^{25}$ -5.6 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.11-8.09 (m, 2H, C*H*$_{arom}$); 7.58-7.56 (m, 1H, C*H*$_{arom}$); 7.48-7.44 (m, 2H, C*H*$_{arom}$); 7.31-7.26 (m, 2H, C*H*$_{arom}$); 6.90-6.86 (m, 2H, C*H*$_{arom}$); 5.52 (dd, 1H, *J* = 1.8, 3.4 Hz, H-2); 4.85-4.81 (m, 2H, H-1, PhC*H*H); 3.80-3.75 (m, 5H, H-3, H-5, OC*H*$_3$); 3.68-3.62 (m, 4H, C*H*H$_{linker}$, OC*H*$_3$); 3.48-3.37 (m, 5H, H-4, CH*H*$_{linker}$, OC*H*$_3$); 2.30 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.64-1.53 (m, 4H, C*H*$_{2,linker}$); 1.35-1.26 (m, 12H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 165.9 (*C*O$_{Bz}$); 159.4 (C$_{q,arom}$); 133.3 (*C*H$_{arom}$); 130.8, 130.1 (C$_{q,arom}$); 130.0, 129.9, 128.5, 113.9 (*C*H$_{arom}$); 97.7 (C-1); 80.4 (C-4); 79.9 (C-3); 75.1 (Ph*C*H$_2$); 69.3 (C-2); 68.0 (O*C*H$_{2,linker}$); 67.6 (C-5); 57.5 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 34.2, 29.5, 29.3, 29.2, 29.2, 26.2, 25.0 (*C*H$_{2,linker}$); 18.3 (C-6). IR (thin film, cm^{-1}): 1003, 1027, 1070, 1099,

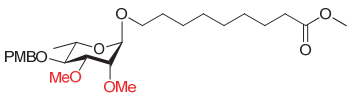
1112, 1173, 1193, 1251, 1269, 1319, 1364, 1452, 1514, 1724, 2855, 2925. HRMS calculated for $C_{32}H_{44}O_9Na$ 595.2883 $[M+Na]^+$; found 595.2879.

Methyl 9-(3-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)nonanoate (22)



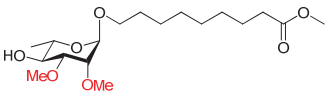
Compound **21** (264 mg, 0.46 mmol, 1.0 eq) was dissolved in THF (2.3 mL, 0.2 M). A small piece of sodium was dissolved in MeOH and 2.3 mL of this solution was added and the reaction was stirred for 2 hours. The reaction was then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (Et_2O) gave the title compound (210 mg, 0.45 mmol, 97%) as a pale oil. $[\alpha]_D^{25}$ -36.5 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.30-7.26 (m, 2H, C*H*$_{arom}$); 6.90-6.86 (m, 2H, C*H*$_{arom}$); 4.78 (s, 1H, H-1); 4.66 (dd, 2H, *J* = 10.6, 87.4 Hz, PhC*H*$_2$); 4.02 (dd, 1H, *J* = 1.6, 3.6 Hz, H-2); 3.81 (s, 3H, C*H*$_{3,PMB}$); 3.69-3.59 (m, 5H, H-5, OC*H*H$_{linker}$, COOC*H*$_3$); 3.56-3.51 (m, 4H, H-3, OC*H*$_3$); 3.41-3.31 (m, 2H, H-4, OCH*H*$_{linker}$); 2.41 (bs, 1H, 2-O*H*); 2.30 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.61 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,linker}$); 1.53 (t, 2H, *J* = 6.6 Hz, C*H*$_{2,linker}$); 1.29-1.27 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.5 (*C*OOCH$_3$); 159.4, 130.8 (C$_{q,arom}$); 129.8, 113.9 (*C*H$_{arom}$); 99.1 (C-1); 81.9 (C-3); 79.7 (C-4); 75.1 (Ph*C*H$_2$); 68.2 (C-2); 67.7 (O*C*H$_{2,linker}$); 67.2 (C-5); 57.6 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 51.6 (COO*C*H$_3$); 34.2, 29.6, 29.3, 29.3, 29.2, 26.2, 25.1 (*C*H$_{2,linker}$); 18.0 (C-6). IR (thin film, cm^{-1}): 1073, 1079, 1083, 1109, 1113, 1251, 1457, 1514, 1734, 2916, 3490. HRMS calculated for $C_{25}H_{40}O_8Na$ 491.2621 $[M+Na]^+$; found 491.2615.

Methyl 9-(2,3-di-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)nonanoate (23)



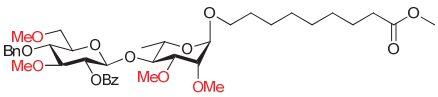
Compound **22** (105 mg, 0.22 mmol, 1.0 eq) was dissolved in dry DMF (1.5 mL, 0.15 M) and MeI (42 µL, 0.67 mmol, 3.0 eq) was added to the solution. The mixture was cooled to 0 °C and NaH (60%, 27 mg, 0.67 mmol, 3.0 eq) was then added. The reaction mixture was warmed to rt while stirring for 1 hour after which it was quenched by addition of MeOH and partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (3x) and the organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (98 mg, 0.20 mmol, 91%) as a pale oil. $[\alpha]_D^{25}$ -41.5 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.30-7.27 (m, 2H, C*H*$_{arom}$); 6.89-6.86 (m, 2H, C*H*$_{arom}$); 4.83 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.81 (s, 1H, H-1); 4.53 (d, 1H, *J* = 10.4 Hz, PhCH*H*); 3.80 (s, 3H, C*H*$_{3,PMB}$); 3.66-3.42 (m, 13H, H-2, H-3, H-5, OC*H*H$_{linker}$, COOC*H*$_3$, OC*H*$_3$); 3.40-3.34 (m, 2H, H-4, OCH*H*$_{linker}$); 2.30 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 1.62 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,linker}$); 1.54 (t, 2H, *J* = 6.4 Hz, C*H*$_{2,linker}$); 1.30-1.27 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 159.3, 131.0 (C$_{q,arom}$); 129.8, 113.9 (*C*H$_{arom}$); 96.9 (C-1); 81.7 (C-3); 80.3 (C-4); 77.7 (C-2); 75.1 (*C*H$_{3,PMB}$); 67.7 (O*C*H$_{2,linker}$); 67.7 (C-5); 59.2, 57.9 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 51.6 (COO*C*H$_3$); 34.2, 29.6, 29.3, 29.3, 29.2, 26.2, 25.0 (*C*H$_{2,linker}$); 18.0 (C-6). IR (thin film, cm^{-1}): 1036, 1072, 1093, 1120, 1142, 1173, 1198, 1249, 1457, 1464, 1514, 1739, 2932. HRMS calculated for $C_{26}H_{42}O_8Na$ 505.2777 $[M+Na]^+$; found 505.2771.

Methyl 9-(2,3-di-*O*-methyl-α-L-rhamnopyranosyl)nonanoate[43] (24)



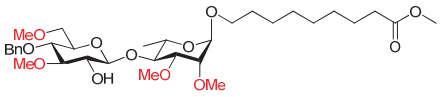
Compound **23** (98 mg, 0.20 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 2 mL, 0.1 M) after which a solution of HCl in HFIP (0.1 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour (~2 minutes), the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (70 mg, 0.19 mmol, 95%) as a pale oil. ^{1}H-NMR (400 MHz) δ: 4.85 (d, 1H, *J* = 1.2 Hz, H-1); 3.70-3.60 (m, 6H, H-2, H-5, OC*H*H$_{linker}$, COOC*H*$_3$); 3.56 (t, 1H, *J* = 9.4 Hz, H-4); 3.50 (s, 3H, OC*H*$_3$); 3.47 (s, 3H, OC*H*$_3$); 3.44-3.37 (m, 2H, H-3, OCH*H*$_{linker}$); 2.31 (t, 2H, *J* = 7.6 Hz, OC*H*$_{2,linker}$); 1.64-1.54 (m, 4H, C*H*$_{2,linker}$); 1.38-1.31 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.5 (*C*OOCH$_3$); 97.2 (C-1); 81.2 (C-3); 76.1 (C-2); 71.9 (C-4); 68.2 (C-5); 67.8 (O*C*H$_{2,linker}$); 59.1, 57.1 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 34.2, 29.6, 29.4, 29.3, 29.2, 26.3, 25.1 (*C*H$_{2,linker}$); 17.8 (C-6).

Methyl 9-(2,3-di-*O*-methyl-4-O-(2-*O*-benzoyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)nonanoate (25)



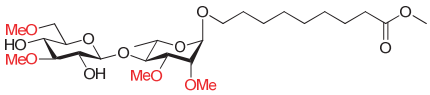
Donor **8** (230 mg, 0.47 mmol, 1.5 eq), Ph_2SO (123 mg, 0.61 mmol, 2.0 eq) and TTBP (291 mg, 1.17 mmol, 3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (9 mL, 0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -60 °C after which Tf_2O (102 µL, 0.61 mmol, 2.0 eq) was added to the solution. After stirring for 30 minutes, acceptor **24** (122 mg, 0.31 mmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.75 mL, 0.4 M) and added to the solution. After stirring for 1.5 hours the reaction was quenched by addition of NEt_3 (0.3 mL). The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (194 mg, 0.26 mmol, 84%) as a pale oil. $[\alpha]_D^{25}$ -29.5 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.14-8.12 (m, 2H, C*H*$_{arom}$); 7.59-7.55 (m, 1H, C*H*$_{arom}$); 7.47-7.44 (m, 2H, C*H*$_{arom}$); 7.35-7.27 (m, 5H, C*H*$_{arom}$); 5.14 (dd, 1H, *J* = 8.0, 9.6 Hz, H-2'); 4.85-4.82 (m, 2H, H-1', PhC*H*H); 4.77 (d, 1H, *J* = 1.6 Hz, H-1); 4.66 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 3.72-3.40 (m, 21H, H-2, H-3, H-3', H-4', H-5, H-5', H-6', OC*H*H$_{linker}$, COOC*H*$_3$, OC*H*$_3$); 3.34-3.27 (m, 2H, H-4, OCH*H*$_{linker}$); 3.08 (s, 3H, OC*H*$_3$); 2.30 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.62 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,linker}$); 1.52 (t, 2H, *J* = 6.6 Hz, C*H*$_{2,linker}$); 1.31-1.25 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOC*H*$_3$); 165.3 (*C*O$_{Bz}$); 138.4 (C$_{q,arom}$); 133.1 (*C*H$_{arom}$); 130.3 (C$_{q,arom}$); 129.9, 128.5, 128.5, 128.2, 127.9 (*C*H$_{arom}$); 101.4 (C-1'); 96.6 (C-1); 85.3 (C-3'); 80.9 (C-4); 77.8 (C-5'); 77.5 (C-3); 76.6 (C-2); 75.0 (Ph*C*H$_2$); 74.8 (C-4'); 74.3 (C-2'); 71.2 (C-6'); 67.8 (O*C*H$_{2,linker}$); 60.8, 59.8, 59.0, 56.7 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 34.2, 29.8, 29.4, 29.3, 29.2, 29.2, 26.1, 25.0 (*C*H$_{2,linker}$); 18.0 (C-6). IR (thin film, cm^{-1}): 1029, 1057, 1072, 1090, 1116, 1143, 1268, 1733. HRMS calculated for $C_{40}H_{58}O_{13}Na$ 769.3775 $[M+Na]^+$; found 769.3770.

Methyl 9-(2,3-di-*O*-methyl-4-O-(3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)nonanoate (26)



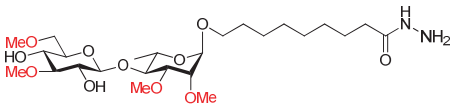
Compound **25** (116 mg, 0.155 mmol, 1.0 eq) was dissolved in THF (0.8 mL, 0.2 M). A small piece of sodium was dissolved in MeOH and 0.8 mL of this solution was added. The reaction was stirred for 2 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 3:7) gave the title compound (82 mg, 0.128 mmol, 82%) as a pale oil. $[\alpha]_D^{25}$ -21.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.34-7.27 (m, 5H, C*H*$_{arom}$); 4.86-4.82 (m, 2H, H-1, PhC*H*H); 4.61 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.37 (d, 1H, *J* = 7.6 Hz, H-1'); 3.91 (bs, 1H, 2'-O*H*); 3.68-3.54 (m, 13H, H-2, H-3, H-4, H-5, H-6', OC*H*$_3$, COOC*H*$_3$); 3.51-3.35 (m, 12H, H-2', H-4', H-5', OC*H*$_3$); 3.28 (t, 1H, *J* = 9.0 Hz, H-3'); 2.31 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 1.65-1.35 (m, 4H, C*H*$_{2,linker}$); 1.31-1.23 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 138.4 (C$_{q,arom}$); 128.5, 128.1, 127.9 (*C*H$_{arom}$); 105.8 (C-1'); 96.9 (C-1); 86.5 (C-3'); 82.0 (C-3); 80.7 (C-4); 77.3 (C-4'); 76.0 (C-2); 75.6 (C-2'); 75.2 (C-5'); 75.0 (Ph*C*H$_2$); 71.3 (C-6'); 67.9 (O*C*H$_{2,linker}$); 67.6 (C-5); 61.0, 59.5, 59.1 56.6 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 34.2, 29.6, 29.3, 29.2, 29.2, 26.2, 25.0 (*C*H$_{2,linker}$); 17.7 (C-6). IR (thin film, cm^{-1}): 1029, 1070, 1118, 1143, 1192, 1251, 1269, 1454, 1736, 2856, 2928, 3476. HRMS calculated for $C_{33}H_{54}O_{12}Na$ 665.3513 [M+Na]$^+$; found 665.3500.

Methyl 9-(2,3-di-*O*-methyl-4-O-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)nonanoate[43] (27)



Compound **26** (49 mg, 76 µmol, 1.0 eq) was dissolved in THF (1.5 mL, 0.05 M) and the solution was purged with N_2. Palladium on carbon (10%, 8 mg, 7.6 µmol, 0.1 eq) was added to the solution. The solution was then purged with H_2 and stirred overnight under H_2 atmosphere. The mixture was then purged with N_2, diluted with EtOAc, filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 1:19) gave the title compound (40 mg, 72 µmol, 95%) as a pale oil. ^{1}H NMR (400 MHz) δ: 4.82 (d, 1H, *J* = 1.2 Hz, H-1); 4.41 (d, 1H, *J* = 7.6 Hz, H-1'); 3.68-3.60 (m, 13 H, H-2, H-3, H-4, H'-5, H-6', OC*H*H$_{linker}$, OC*H*$_3$, COOC*H*$_3$); 3.55 (t, 1H, *J* = 9.2 Hz, H-4'); 3.49 (s, 3H, OC*H*$_3$); 3.47 (s, 3H, OC*H*$_3$); 3.45-3.35 (m, 6H, H-2', H-5', OCH*H*$_{linker}$); 3.17 (t, 1H, *J* = 9.0 Hz, H-3'); 2.13 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,linker}$); 1.63 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,linker}$); 1.55 (t, 2H, *J* = 6.4 Hz, C*H*$_{2,linker}$); 1.36-1.25 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*OOCH$_3$); 105.8 (C-1'); 96.9 (C-1); 85.7 (C-3'); 82.1 (C-3); 80.7 (C-4); 76.0 (C-2); 75.1, 74.2 (C-2'and C-5'); 72.9 (C-6'); 71.2 (C-4'); 67.9 (O*C*H$_{2,linker}$); 67.6 (C-5); 60.6, 59.7, 59.2, 56.5 (O*C*H$_3$); 51.6 (COO*C*H$_3$); 34.2, 29.6, 29.3, 29.2, 29.2, 26.2, 25.0 (*C*H$_{2,linker}$); 17.6 (C-6).

9-(2,3-di-*O*-methyl-4-O-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl nonanohydrazide[43] (28)



Compound **27** (17 mg, 31 µmol, 1.0 eq) was dissolved in a mixture of EtOH and $N_2H_4 \cdot H_2O$ (1:2, 1.5 mL, 0.02 M) and stirred for 3 hours after which it was concentrated *in vacuo*. Purification by means of column chromatography (MeOH-DCM 1:9) gave the title compound (17 mg, 31 µmol, 100%) as a pale oil. ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.80 (d, 1H, *J* = 1.6 Hz, H-1); 4.53 (d, 1H, *J* = 7.6 Hz, H-1'); 3.68-3.54 (m, 9H, H-2, H-3, H-4, H-6', OC*H*H$_{linker}$, OC*H*$_3$); 3.44-3.40 (m, 7H, OCH*H*$_{linker}$, OC*H*$_3$, OC*H*$_3$); 3.37 (s, 3H, OC*H*$_3$); 3.35-3.20 (m, 2H, H-4', H-5'); 3.18 (dd, 1H, *J* = 8.0, 9.2 Hz, H-2''); 3.06 (dd, 1H, *J* = 8.4, 9.2 Hz, H-3'); 2.13 (t, 2H, *J* = 7.4 Hz, C*H*$_{2,linker}$); 1.63-1.54 (m, 4H, C*H*$_{2,linker}$); 1.39-1.21 (m, 11H, H-6, C*H*$_{2,linker}$). ^{13}C-APT NMR (101 MHz) δ: 175.3 (*C*ONHNH$_2$); 104.9 (C-1'); 98.3 (C-1); 87.6 (C-3'); 82.4 (C-3); 79.4 (C-4); 77.8 (C-2); 76.7 (C-5'); 75.5 (C-2'); 73.0 (C-6'); 71.2 (C-4'); 68.8 (O*C*H$_{2,linker}$); 68.5 (C-5); 61.0, 59.8, 59.1 (O*C*H$_3$); 35.0, 30.6, 30.3, 30.2, 29.3, 26.8 (*C*H$_{2,linker}$); 18.3 (C-6).

Study cohorts

HIV-negative, treated and untreated leprosy patients and controls were recruited on a voluntary basis at the Dept. Dermatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands. This study was performed according to the Helsinki Declaration. All patients received treatment according to national guidelines. Ethical approval for the study was obtained from the ethical boards in The Netherlands (MEC-2012-589).

Conjugation[43]

Hydrazide (100 eq) was dissolved in DMF (0.05 M) and cooled to -30 °C (DCE bath, liquid N_2). a solution of *t*-BuONO in DMF (1:10, 400 eq) was then added, followed by HCl in dioxane (400 eq). The reaction was stirred until the starting material was converted to a higher running spot on TLC (MeOH-DCM 1:9) after which DIPEA (1000 eq) was added. The cold solution was then transferred to a 0 °C solution of BSA (1.0 eq) in borax buffer (0.1 mM, pH = 9.2) and stirred overnight while slowly warming to rt. The buffered solution was diluted (1:14) with miliQ and spun down using a 3kDa MWCO filter. The retentate was diluted to 4 mL with miliQ and transferred to a 10kDa MWCO filter. After spinning down the new retentate was purified by means of gel filtration with sephadex G-75 medium in miliQ. The product in the void volume was lyophilized and used without further purification.

Quality control for synthesized conjugates

The conjugates were analyzed with SDS-PAGE with BSA as a reference and stained with Coumassie brilliant blue to ensure no unconjugated protein was present. The amount of sugars per BSA was determined using MALDI-TOF analysis. The measurement procedure was as follows:
1 µL of sample solution (2 mg/mL in 7:3 MeCN:H_2O + 0.1% TFA) was mixed together with 1 µL of 3,5-dimethoxy-4-hydroxycinnamic acid and the dried-droplet sample preparation method was applied. Spectra were assembled from 2000 shots in the linear mode with a 1 kHz laser.

PGL-I ELISA

The PGL-I ELISA was performed as previously described.[8] Briefly, 200 ng synthetic PGL was coated per well in 50 µl in 0.1 M Na_2CO_3/$NaHCO_3$ buffer (pH 9.6) at 4 °C overnight. After blocking with 200 µl PBS/1%BSA/0.05% Tween-80 per well for 1 hour, 50 µl of 1:400 diluted sample was added and incubated for 2 hours at room temperature. Then, 50 µl per well of a 1:8000 dilution of anti-human IgM-HRP, (A6907, Sigma-Aldrich, St. Louis, Missouri, USA) in 0.05%Tween 20/PBS was incubated for 2 hours. In between each step the wells were washed 3 times with PBS/0,05% Tween-20. 50 µl of 3,3',5,5'-Tetramethylbenzidine (TMB) was added and the color reaction was stopped using H_2SO_4 after 10–15 minutes. Absorbance was determined at a wavelength of 450 nm.

ND-O-HSA

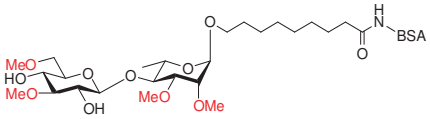
The disaccharide epitope (3,6-di-*O*-methyl-β-D-glucopyranosyl(1→4)2,3-di-*O*-methyl-α-L-rhamnopyranoside) coupled to human serum albumin (designated ND-O-HSA) was obtained through the Biodefense and Emerging Infections Research Resources Repository (https://www.beiresources.org/).

UCP-LFAs

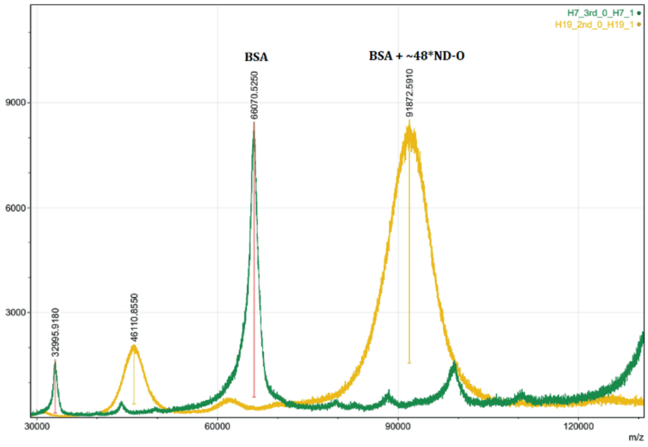
PGL-I lateral flow strips were produced as described earlier.[10] In short, the test line consists of 100 ng synthetic PGL-I and the flow control line of 100 ng Rabbit-anti-Goat (RαG; G4018, Sigma-Aldrich). Conjugates of UCP particles with goat anti-human IgM (I0759, Sigma-Aldrich, St. Louis, Missouri, USA) at a concentration of 50 µg antibody per mg UCP were applied to the sample/conjugate pad at a density of 400 ng. Samples were diluted 50-fold in high salt finger stick buffer supplemented with 1% (v/v) Triton X-100 (HSFS; 100mM Tris pH 8, 270mM NaCl, 1% (w/v) BSA). 50 µl of diluted sample was added to microtiterplate wells before LF strips were placed in the corresponding wells. Immunochromatography was allowed to continue for at least 30 min until dry. LF strips were analyzed using a UCP dedicated benchtop reader (UPCON; Labrox, Finland). Test results are displayed as an arbitrary value with Test signal normalized to the Flow-Control signal based on fluorescence units (RFUs) measured at the respective lines. Strips were stored in containers with silica dry packs at room temperature. Containers were sealed with parafilm.

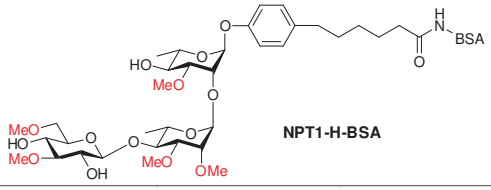
Statistical analysis

Graphpad Prism version 8.00 for Windows (GraphPad Software, San Diego CA, USA) was used to determine the correlation (R^2) between the different tests performed. The statistical significance level used was $p \leq 0.05$.

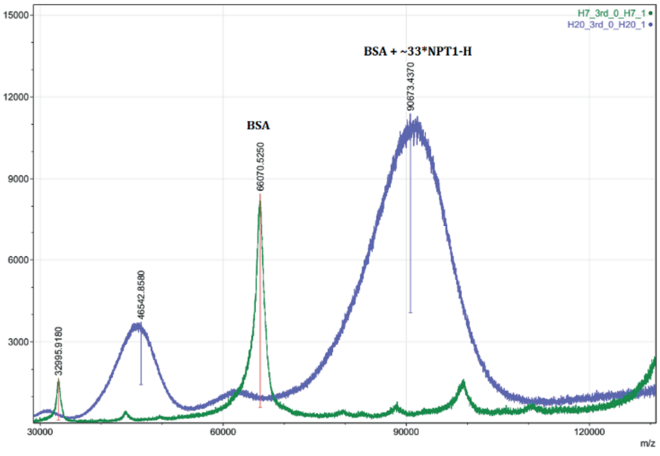


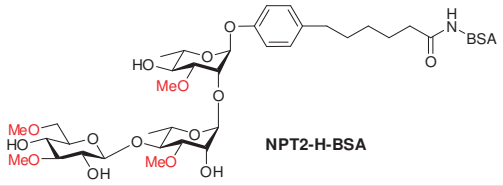
ND-O-BSA



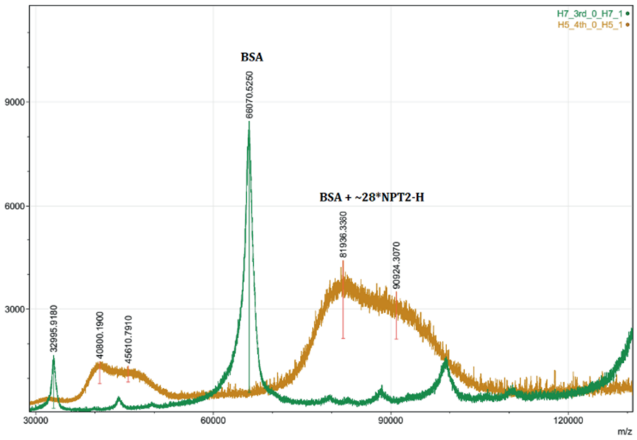


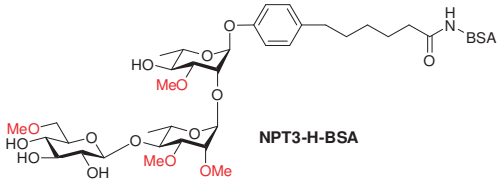
NPT1-H-BSA



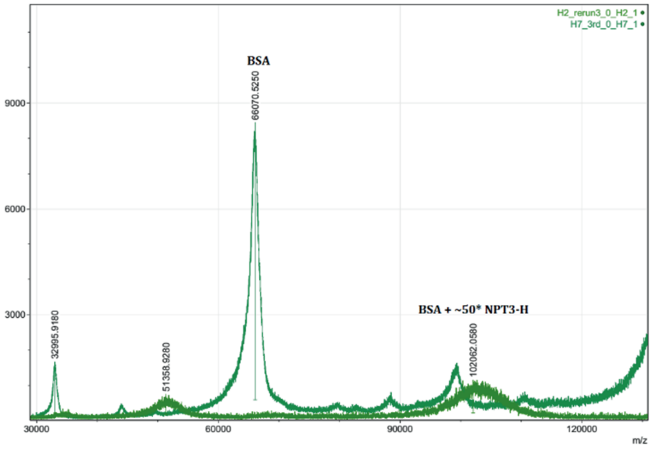


NPT2-H-BSA





NPT3-H-BSA



References

1. Fischer, M. Leprosy – an overview of clinical features, diagnosis, and treatment. *JDDG - J. Ger. Soc. Dermatology* **15**, 801–827 (2017).
2. Scollard, D. M. *et al.* The continuing challenges of leprosy. *Clin. Microbiol. Rev.* **19**, 338–381 (2006).
3. Barreto, J. G. *et al.* Leprosy in Children. *Curr. Infect. Dis. Rep.* **19**, (2017).
4. Oldenburg, R. *et al.* Mycobacterial phenolic glycolipids selectively disable TRIF-dependent TLR4 signaling in macrophages. *Front. Immunol.* **9**, 1–12 (2018).
5. Doz-Deblauwe, É. *et al.* CR3 Engaged by PGL-I Triggers Syk-Calcineurin-NFATc to Rewire the Innate Immune Response in Leprosy. *Front. Immunol.* **10**, 1–15 (2019).
6. Madigan, C. A. *et al.* A Macrophage Response to Mycobacterium leprae Phenolic Glycolipid Initiates Nerve Damage in Leprosy. *Cell* **170**, 973-985.e10 (2017).
7. Spencer, J. S. *et al.* Analysis of antibody responses to Mycobacterium leprae phenolic glycolipid I, lipoarabinomannan, and recombinant proteins to define disease subtype-specific antigenic profiles in leprosy. *Clin. Vaccine Immunol.* **18**, 260–267 (2011).
8. Van Hooij, A. *et al.* Field-friendly serological tests for determination of M. Leprae-specific antibodies. *Sci. Rep.* **7**, 1–8 (2017).
9. Van Beers, S., Hatta, M. & Klatser, P. R. Seroprevalence rates of antibodies to phenolic glycolipid-I among school children as an indicator of leprosy endemicity. *Int. J. Lepr. Other Mycobact. Dis.* **67**, 243–249 (1999).
10. Corstjens, P. L. A. M. *et al.* Fingerstick test quantifying humoral and cellular biomarkers indicative for *M. leprae* infection. *Clin. Biochem.* **66**, 76–82 (2019).
11. Corstjens, P. L. A. M. *et al.* Field-Friendly Test for Monitoring Multiple Immune Response Markers during Onset and Treatment if Exacerbated Immunity in Leprosy. *Clin. Vaccine Immunol.* **23**, 515–519 (2016).
12. Bobosha, K. *et al.* Field-Evaluation of a New Lateral Flow Assay for Detection of Cellular and Humoral Immunity against Mycobacterium leprae. *PLoS Negl. Trop. Dis.* **8**, (2014).
13. Schilling, A. K. *et al.* Detection of humoral immunity to mycobacteria causing leprosy in Eurasian red squirrels (Sciurus vulgaris) using a quantitative rapid test. *Eur. J. Wildl. Res.* **65**, 1–5 (2019).
14. Bührer, S. S., Smits, H. L., Gussenhoven, G. C., Van Ingen, C. W. & Klatser, P. R. A simple dipstick assay for the detection of antibodies to phenolic glycolipid-I of Mycobacterium leprae. *Am. J. Trop. Med. Hyg.* **58**, 133–136 (1998).
15. Bührer-Sékula, S. *et al.* Simple and Fast Lateral Flow Test for Classification of Leprosy Patients and Identification of Contacts with High Risk of Developing Leprosy. *J. Clin. Microbiol.* **41**, 1991–1995 (2003).
16. Spencer, J. S. & Brennan, P. J. The role of Mycobacterium leprae phenolic glycolipid I (PGL-I) in serodiagnosis and in the pathogenesis of leprosy. *Lepr. Rev.* **82**, 344–357 (2011).
17. Chatterjee, D., Cho, S. N., Brennan, P. J. & Aspinall, G. O. Chemical synthesis and seroreactivity of O-(3,6-di-O-methyl-β-D-glucopyranosyl)-(1→4)-O-(2,3-di-O-methyl-α-lrhamnopyranosyl)-(1→9)-oxynonanoyl-bovine serum albumin-the leprosy-specific, natural disaccharide-octyl-neoglycoprotein. *Carbohydr. Res.* **156**, 39–56 (1986).
18. Fujiwara, T., Hunter, S. W., Cho, S. N., Aspinall, G. O. & Brennan, P. J. Chemical synthesis and serology of disaccharides and trisaccharides of phenolic glycolipid antigens from the leprosy bacillus and preparation of a disaccharide protein conjugate for serodiagnosis of leprosy. *Infect. Immun.* **43**, 245–252 (1984).
19. Chatterjee, D. *et al.* Synthesis of Neoglycoproteins containing the 3,6-di-O-methyl-β-D-glucopyranosyl epitope and their use in serodiagnosis of leprosy. *Glycoconj. J.* **2**, 187–208 (1985).

20. Fujiwara, T., Aspinall, G. O., Hunter, S. W. & Brennan, P. J. Chemical synthesis of the trisaccharide unit of the species-specific phenolic glycolipid from Mycobacterium leprae. *Carbohydr. Res.* **163**, 41–52 (1987).

21. Chatterjee, D. *et al.* Synthesis and immunoreactivity of neoglycoproteins containing the trisaccharide unit of phenolic glycolipid I of Mycobacterium leprae. *Carbohydr. Res.* **183**, 241–260 (1988).

22. Fujiwara, T. & Izumi, S. Synthesis of the Neoglycoconjugates of Phenolic Glycolipid-related Trisaccharides for the Serodiagnosis of Leprosy. *Agric. Biol. Chem.* **51**, 2539–2547 (1987).

23. Chanteau, S. *et al.* Comparison of synthetic antigens for detecting antibodies to phenolic glycolipid i in patients with leprosy and their household contacts. *J. Infect. Dis.* **157**, 770–776 (1988).

24. Arbues, A., Lugo-Villarino, G., Neyrolles, O., Guilhot, C. & Astarie-Dequeker, C. Playing hide-and-seek with host macrophages through the use of mycobacterial cell envelope phthiocerol dimycocerosates and phenolic glycolipids. *Front. Cell. Infect. Microbiol.* **4**, 1–7 (2014).

25. Arbués, A. *et al.* Trisaccharides of Phenolic Glycolipids Confer Advantages to Pathogenic Mycobacteria through Manipulation of Host-Cell Pattern-Recognition Receptors. *ACS Chem. Biol.* **11**, 2865–2875 (2016).

26. Cambier, C. J., O'Leary, S. M., O'Sullivan, M. P., Keane, J. & Ramakrishnan, L. Phenolic Glycolipid Facilitates Mycobacterial Escape from Microbicidal Tissue-Resident Macrophages. *Immunity* **47**, 552-565.e4 (2017).

27. Elsaidi, H. R. H. & Lowary, T. L. Effect of phenolic glycolipids from Mycobacterium kansasii on proinflammatory cytokine release. A structure - activity relationship study. *Chem. Sci.* **6**, 3161–3172 (2015).

28. Elsaidi, H. R. H. & Lowary, T. L. Inhibition of cytokine release by mycobacterium tuberculosis phenolic glycolipid analogues. *ChemBioChem* **15**, 1176–1182 (2014).

29. Elsaidi, H. R. H., Barreda, D. R., Cairo, C. W. & Lowary, T. L. Mycobacterial phenolic glycolipids with a simplified lipid aglycone modulate cytokine levels through toll-like receptor 2. *ChemBioChem* **14**, 2153–2159 (2013).

30. Zheng, R. B. *et al.* Insights into Interactions of Mycobacteria with the Host Innate Immune System from a Novel Array of Synthetic Mycobacterial Glycans. *ACS Chem. Biol.* **12**, 2990–3002 (2017).

31. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie Int. Ed.* **51**, 11774–11777 (2012).

32. Barroso, S., Geerdink, D., Ter Horst, B., Casas-Arce, E. & Minnaard, A. J. Total synthesis of the phenolic glycolipid mycoside B and the glycosylated p-hydroxybenzoic acid methyl ester HBAD-I, virulence markers of mycobacterium tuberculosis. *European J. Org. Chem.* 4642–4654 (2013) doi:10.1002/ejoc.201300437.

33. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie* **124**, 11944–11947 (2012).

34. Raju, R. *et al.* Synthesis and evaluation of 3″- and 4″-deoxy and -fluoro analogs of the immunostimulatory glycolipid, KRN7000. *Bioorganic Med. Chem. Lett.* **19**, 4122–4125 (2009).

35. Kobayashi, S., Furukawa, J. I., Sakai, T. & Sakairi, N. Preparation and diastereomeric separation of an (*S*)- and (R)-1-(methoxycarbonyl)tridec-10-yl glucoside derivative, a precursor for a monosaccharide constituent of resin glycosides. *Carbohydr. Res.* **337**, 1047–1053 (2002).

36. Codée, J. D. C. *et al.* Ph2SO/Tf2O: A powerful promotor system in chemoselective glycosylations using thioglycosides. *Org. Lett.* **5**, 1519–1522 (2003).

37. Volbeda, A. G. *et al.* Chemoselective Cleavage of p-Methoxybenzyl and 2-Naphthylmethyl Ethers Using a Catalytic Amount of HCl in Hexafluoro-2-propanol. *J. Org. Chem.* **80**, 8796–8806 (2015).

38. Darwish, T. A. *et al.* Synthesis of deuterated [D32]oleic acid and its phospholipid derivative

[D64]dioleoylsn- glycero-3-phosphocholine. *J. Label. Compd. Radiopharm.* **56**, 520–529 (2013).

39. Unpublished results.

40. van Dijk, J. H. M. *et al.* Synthetic Phenolic Glycolipids for Application in Diagnostic Tests for Leprosy. *ChemBioChem* **22**, 1487–1493 (2021).

41. Janczuk, A. J., Zhang, W., Andreana, P. R., Warrick, J. & Wang, P. G. The synthesis of deoxy-α-Gal epitope derivatives for the evaluation of an anti-α-Gal antibody binding. *Carbohydr. Res.* **337**, 1247–1259 (2002).

42. Bourgeaux, E. & Combret, J. C. General access to asymmetric γ-cyclodextrins for gas chromatographic applications by insertion of a selectively modified sugar unit. *Tetrahedron Asymmetry* **11**, 4189–4205 (2000).

43. Zhang, J., Chatterjee, D., Brennan, P. J., Spencer, J. S. & Liav, A. A modified synthesis and serological evaluation of neoglycoproteins containing the natural disaccharide of PGL-I from Mycobacterium leprae. *Bioorganic Med. Chem. Lett.* **20**, 3250–3253 (2010).

Chapter 3

Synthesis of Phthiocerol alkyne

Introduction

Phthiocerol is a methoxyglycol that was first isolated from chloroform extracts of *Mycobacterium tuberculosis*,[1,2] and its structure was later established to be the methoxydiol shown in Figure 1, using infrared spectroscopy, GC-MS and degradative experiments.[3–6] Minor variations such as phthiotriol and phthiodiolone in which the methyl ether is replaced by either an alcohol or a ketone, respectively, and shorter versions (B) have also been found (Figure 1).[7–11] Phthiocerol is the backbone of Phthiocerol Dimycocerosate[12] (PDIM) and Phenolic Glycolipids (PGLs) which are phenolphthiocerol dimycocerosate based glycolipids.

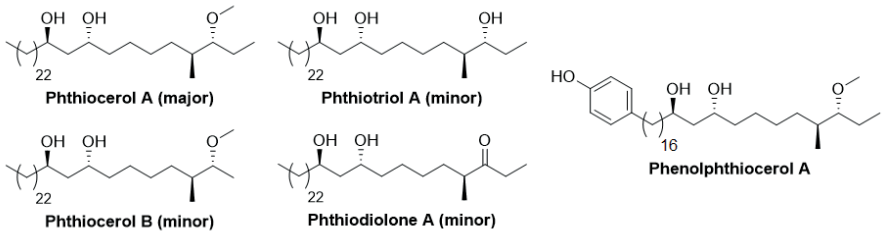


Figure 1. Phthiocerol and variations thereof.

Phenolic glycolipids have a well preserved lipid structure among mycobacteria with an *anti*-diol on the phthiocerol backbone and multiple *R*-configured *C*-methyls on

mycocerosic acid, with 4 methyls being the most prevalent.[13–16] *M. marinum* and *M. ulcerans* on the other hand contain phenolic glycolipids with a *syn*-diol on the phthiocerol backbone and *S*-configured methyls on mycocerosic acid (Figure 2).[17–20]

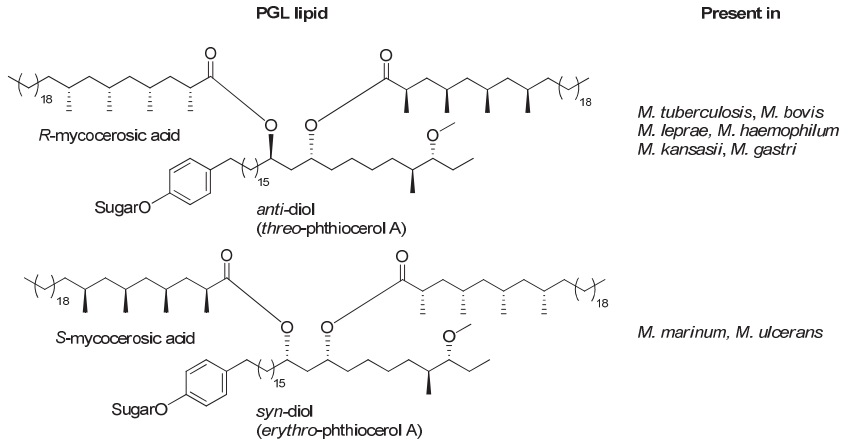
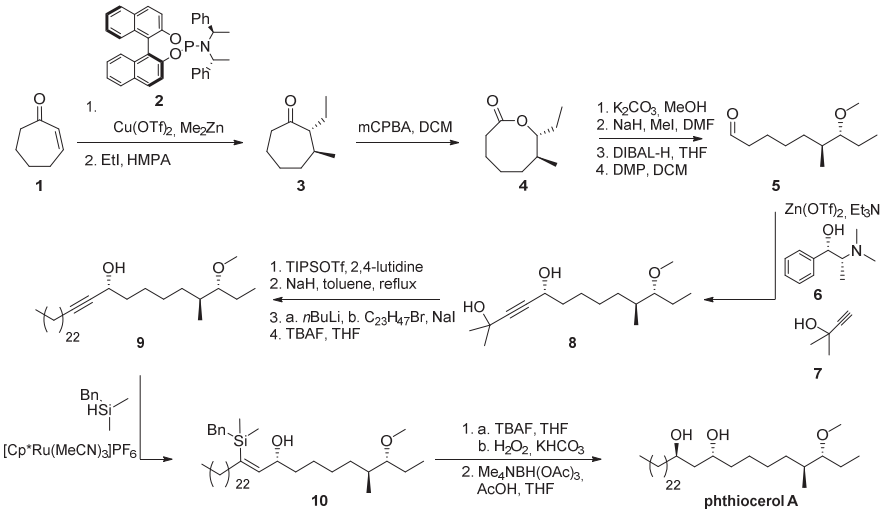


Figure 2. Lipid backbones of PGLs and the corresponding mycobacteria.

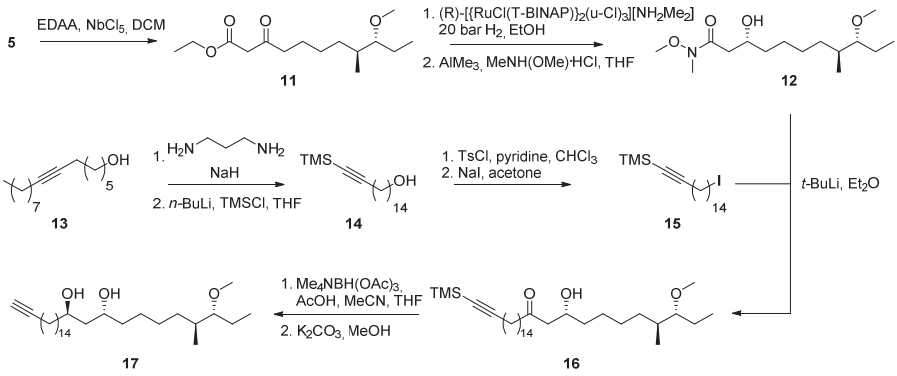
In order to confirm its structure, the chemical synthesis of PDIM A, and thereby also phthiocerol A, has been performed by Minnaard and coworkers in 2008 (Scheme 1).[21,22] Their synthetic strategy was based on a tandem copper/phosphoramidite-catalyzed asymmetric conjugation addition to cycloheptenone providing the *anti*-methoxy methyl unit in phthiocerol.[21,23–25] After a Baeyer-Villiger oxidation, opening of the resulting 8-membered lactone **4**, methylation of the freed alcohol and reduction and oxidation of the methyl ester gave aldehyde **5**, alkyne **7** could then stereoselectively be added to the aldehyde using a procedure developed by Carreira and co-workers.[26] The secondary alcohol that was formed was protected with a silyl ether, whereafter the alkyne was deprotected under basic conditions and elongated by alkylating the corresponding alkynyllithium compound with $CH_3(CH_2)_{22}Br$ in the presence of NaI. After removal of the silyl ether, compound **9** was hydrosilylated with benzyldimethylsilane catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$.[27,28] The mixture of silanes was treated with TBAF and subjected to a Fleming-Tamao oxidation with H_2O_2 and $KHCO_3$ to give the corresponding hydroxy ketones that were separated by chromatography.[29] Thereafter an Evans-Saksena reduction[30] of the β–hydroxy ketone selectively produced the *anti*-diol which was then

coupled to mycocerosic acid[22] using Steglich esterification conditions[31] to complete the first total synthesis of PDIM A.



Scheme 1. Synthesis of phthiocerol A as performed by Casas-Arce et al.[32]

While this was an efficient synthesis of PDIM A, the phthiocerol that was synthesized was not suited for conjugation to glycans, which is required to synthesize complete PGLs. Therefore when Minnaard and coworkers set out to synthesize PGL-tb1, a new route had to be designed which would yield phthiocerol derivative **17** with a terminal alkyne as a conjugation handle (Scheme 2).[33] This route also made use of key aldehyde **5** which was elongated with ethyl diazoacetate and $NbCl_5$[34] to give β-keto ester **11**. This ketone was then stereoselectively reduced using a chiral ruthenium catalyst[35,36] and the resulting β-hydroxy ester was transformed to a Weinreb amide.



Scheme 16. Synthesis of phthiocerol containing a terminal alkyne as performed by Barroso et al.[33]

Iodide **15** was made in 4 steps from hexadec-7-yn-1-ol (**13**) by means of a Zipper reaction,[37] protection of the terminal alkyne with a TMS group[38] and the substitution of the primary alcohol with an iodide. Coupling of lithiated iodide **15** to Weinreb amide **12** produced β-hydroxy ketone **16** which was stereoselectively transformed to the *anti*-diol by means of an Evans-Saksena reduction similarly as described above in the synthesis of phthiocerol by Casas-Arce et al.[30] After deprotection of the terminal alkyne this phthiocerol derivative **17** could be connected through a Sonogashira cross-coupling to a glycan bearing an iodophenol on the reducing end. Esterification of the resulting diol with mycocerosic acid[22] and subsequent global deprotection produced the first total synthesis of PGL-tb1.

In order to synthesize all PGLs outlined in this thesis, a large amount of the phthiocerol alkyne derivative is needed. Unfortunately, hexadec-7-yn-1-ol was difficult to obtain commercially, especially in large quantities. Therefore, a new synthesis had to be devised. A route was envisaged which introduced the terminal alkyne of iodide **15** by means of a homologation of an aldehyde which in turn could be produced in large amounts from pentadecanolide (Figure 3). A potential method for this reaction could be the Seyferth-Gilbert homologation, which makes use of dimethyl (diazomethyl)phosphonate.[39] While this method produces the alkyne in a single step from the aldehyde, the terminal alkyne would then have to be protected in a separate step. Another disadvantage of this method is that the required reagent is not shelf stable. The

more stable Bestmann-Ohira reagent (dimethyl diazo-2-oxopropylphosphonate)[40,41] could be used, but this reagent needs to be synthesized beforehand with relatively expensive reagents, compromising scaling up of the synthesis. Therefore, a route was chosen which uses the Corey-Fuchs reaction[42] to transform the aldehyde to a 1,1-dibromoalkene with PPh_3 and CBr_4. This alkene could then be transformed to an alkyne via an *n*-Buli mediated 1,2-hydride shift (Fritsch-Buttenberg-Wiechell rearrangement)[43–46] and the resulting alkynyllithium intermediate could react with TMSCl in the same pot. For the homologation reaction the primary alcohol would have to be protected with a moiety that could withstand the extremely basic conditions required for the hydride shift and possible nucleophilic attack by PPh_3. Furthermore, because of the TMS-protected terminal alkyne the protecting group should not require hydrogenation, protic bases or fluoride-based conditions to be removed. It was therefore opted to use a *para*-methoxybenzyl (PMB) or benzyl ether as these groups can be removed with oxidative conditions or alternatively in the case of the PMB ether with mild acidic conditions.[47,48]

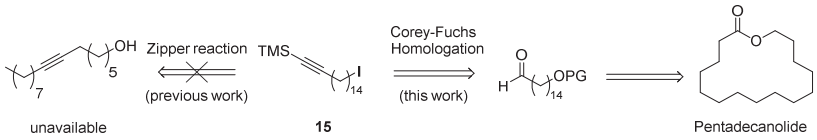
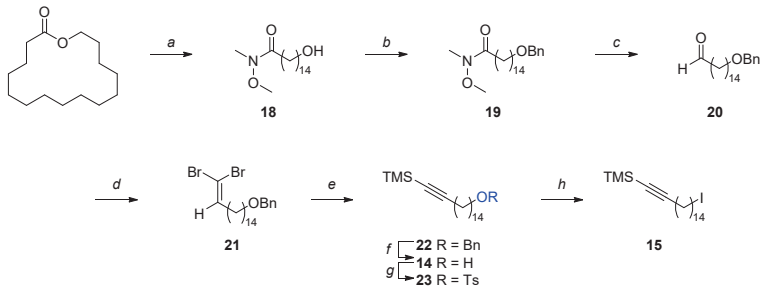


Figure 3. Retrosynthetic analysis of iodide **15**. (PG = protecting group)

Results and discussion

The successful synthesis of iodide **15** is depicted in Scheme 3. The opening of pentadecanolide with *N,O*-dimethyl hydroxylamine hydrochloride and *iso*-propylmagnesium chloride in THF[49] gave Weinreb amide **18** in near quantitative yield. At first, the resulting free alcohol was protected with a PMB-ether. Later on in the synthesis, when acidic conditions were used to remove this group, only moderate yields were obtained. A DDQ mediated oxidation proceeded smoothly but the *p*-anisaldehyde which was liberated as a side-product had the same retention factor as the product during column chromatography, which greatly hindered purification. Therefore, a benzyl ether was then tried as an alternative protecting group. Thus, Weinreb amide **18** was protected with a benzyl ether using BnBr and NaH in DMF to give **19** in 77% yield. The protected Weinreb amide was then reduced with $LiAlH_4$ to give aldehyde **20** in quantitative yield. It

was found that this reaction is best performed in Et_2O instead of THF, as this significantly facilitates the work-up, leading to an improved yield. Using a 1 M HCl washing step instead of Rochelle's salt further improved the work-up as the latter resulted in a thick gel that was very difficult to separate into two layers.

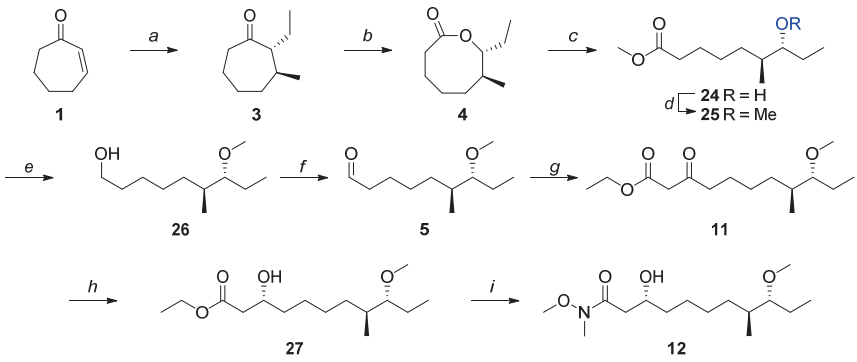


Scheme 3 Synthesis of iodide **16**. Reagents and conditions: (a) *N,O*-dimethylhydroxylamine hydrochloride, *iso*-propylMgCl, THF, 99%, (b) NaH, BnBr, DMF, 0 °C → RT, 77%, (c) $LiAlH_4$, Et_2O, 0 °C → RT, 100%, (d) CBr_4, PPh_3, DCM, 0 °C → RT, 91%, (e) *n*-BuLi, TMSCl, Et_2O, 0 °C, 94%, (f) DDQ, DCM/H_2O, 86%, (g) *p*-TsCl, pyridine, $CHCl_3$, 95%, (h) NaI, acetone, 96%.

Next, aldehyde **20** could be transformed to dibromoalkene **21** with PPh_3 and CBr_4, a reaction which could easily be scaled up to >25 grams. The Fritsch-Buttenberg-Wiechell rearrangement and subsequent TMS protection were first attempted at -78 °C, but at this temperature, the starting material partially precipitates which hampered the reaction. When the reaction was performed at 0 °C, the starting material was well soluble and the reaction produced protected alkyne **22** in 89% yield. As noted before in the reduction of the Weinreb amide to the aldehyde, the use of Et_2O instead of THF improved the yield. The benzyl ether was then removed using DDQ to produce primary alcohol **15** in 86% yield. The tosylation and iodide substitution that followed produced iodide **16** in 90% yield over two steps.

The synthesis of Weinreb amide **12** (Scheme 4) was performed as reported by Barroso *et al.*[33] with only minor modifications. It was attempted to improve the Baeyer-Villiger oxidation of **3** by using other oxidative reagents (TFPAA, 2-iodobenzenesulfonic acid together with Oxone) but these attempts were to no avail. Direct reduction of ester **25** to the aldehyde **5** with DIBAL-H was attempted but overreduction occurred. Therefore, reduction of the ester with $LiAlH_4$ to the alcohol was followed by an oxidation with Dess-

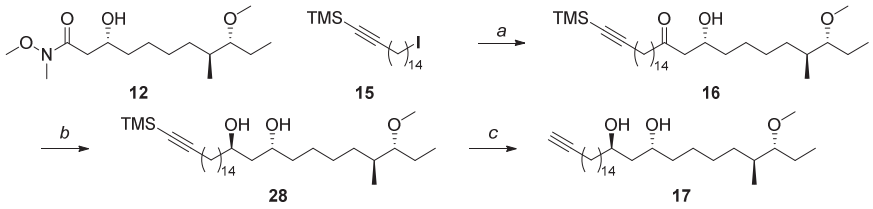
Martin Periodinane to give aldehyde **5** in 82% yield over 2 steps. The coupling of this aldehyde with ethyl diazoacetate under the agency of $NbCl_5$ produced ß-keto ester **11** in 86% yield. Because $NbCl_5$ is highly hygroscopic, the best results were obtained if the reagent was not weighted. Next the asymmetric hydrogenation was performed with (*R*)-[(RuCl(tol-BINAP))$_2$(μ-Cl)$_3$][NH_2Me_2] as catalyst, which gave ß-hydroxy ester **27** in 87% yield. This ester was transformed to the corresponding Weinreb amide with *N,O*-dimethylhydroxylamine hydrochloride and $AlMe_3$ in 89% yield.



Scheme 4. Synthesis of Weinreb amide **13**. Reagents and conditions: (a) 1. Phosphoramidite **2**, $Cu(OTf)_2$, Me_2Zn, -25 °C, toluene 2. EtI, HMPA, 0 °C. (b) *m*CPBA, DCM reflux, (c) K_2CO_3, MeOH, 43% over 3 steps, (d) NaH, MeI, DMF, 0 °C → RT, 84%, (e) $LiAlH_4$, Et_2O, 0 °C, 98%, (f), DMP, DCM, 84%, (g) ethyl diazoacetate, $NbCl_5$, DCM, 86%, (h) (R)-[(RuCl(tol-BINAP))$_2$(μ-Cl)$_3$[NH_2Me_2], H_2, EtOH, 87%, (i) *N,O*-dimethylhydroxylamine hydrochloride, $AlMe_3$, THF, 0 °C → RT, 89%.

The final steps of the synthesis of the phthiocerol alkyne are depicted in Scheme 5. Coupling of lithiated **15** to Weinreb amide **12** turned out to be a challenge. Iodide **15** partially precipitates at the low temperatures required for the reaction, hampering the reaction. Two equivalents of *t*-BuLi per iodide are required to activate it and more than two equivalents of the activated species are required for the coupling because the first equivalent will deprotonate the alcohol in **12**. However, if too much *t*-BuLi is added a *tert*-butyl ketone can be formed. It was observed that this *tert*-butyl ketone has the same retention factor as product **16**, complicating purification of **16** but also of **28** and **17**, generated in the next two steps. Despite these challenges ß-hydroxy ketone **16** was obtained in 60% yield and it could be reduced with $NMe_4BH(OAc)_3$ to stereoselectively

produce 1,3-*anti* diol **28** in 80% yield. Thereafter, removal of the TMS-group using basic conditions gave the desired phthiocerol alkyne derivative in 97% yield.



Scheme 5. Synthesis of phthiocerol alkyne **18**. Reagents and conditions: (a) *t*-BuLi, Et_2O -78 °C, 60%, (b) $NMe_4BH(OAc)_3$, THF/MeCN/AcOH, 0 °C, 80%, (c) K_2CO_3, MeOH, 97%.

Conclusion

In conclusion, in order to synthesize phthiocerol alkyne derivative **17**, a new route had to be devised for iodide **15** which did not rely on hexadec-7-yn-1-ol. A route was chosen which started from pentadecanolide to give the desired molecule in 51% yield over 8 steps, with a Corey-Fuchs reaction as the key step, which could be easily scaled up. Weinreb amide **12** was synthesized from cycloheptenone in 19% yield over 9 steps according to previously reported procedures. After the coupling of these two building blocks and the final reduction and deprotection, phthiocerol alkyne derivative **17** was successfully synthesized in 4.3 % over 20 steps and could be used for the total synthesis of phenolic glycolipids as will be reported in the coming chapters of this thesis.

EXPERIMENTAL:

General procedures

All reactions were carried out in oven-dried glassware (80 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under N_2 atmosphere (balloon). Commercially available reagents and solvents (Aldrich Chemistry, Honeywell, Merck, Fisher Scientific, Biosolve, Fluka, VWR Chemicals, Acros Organics, Fluorochem, Brunschwig, Carbosynth) were used as received unless stated otherwise.

Solvents for reactions were reagent grade and dried by storage over flame dried 4 Å molecular sieves when needed. Et_2O used for column chromatography was distilled before use and stored over iron filings.

Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, F254); visualization was carried out by irradiation with UV light (254 nm), and spraying with 20% H_2SO_4 in EtOH (w/v) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% H_2SO_4, followed by charring. Additional analysis with TLC-MS was used when needed.

Column chromatography was carried out using silica gel (Fluka, 40-63 μm mesh). The column was prepared using the apolar component mentioned in the corresponding experimental. If the apolar component was pentane the product was brought up in toluene. If the apolar component was DCM the product was brought up in DCM, possibly with a few drops of methanol if needed. Colum chromatography was performed using a gradient ranging from 0% polar component up to the ratio mentioned in the corresponding experimental in 2 to 5 steps depending on the ease of separation.

NMR spectra were recorded at ambient temperature on a Bruker AV-400LIQ spectrometer. Samples were prepared in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) in $CDCl_3$ are reported in ppm relative to Me_4Si (δ: 0.00 ppm) for ^{1}H-NMR and $CDCl_3$ (δ: 77.16 ppm) for ^{13}C-APT NMR. Chemical shifts in CD_3OD are reported in ppm relative to H_2O (δ: 4.87 ppm) for ^{1}H-NMR and CD_3OD (δ: 49.00 ppm) for ^{13}C-APT NMR. ^{13}C-APT spectra are ^{1}H decoupled and structural assignments were achieved using HH-COSY and HSQC 2D experiments. Coupling constants (*J*) are given in Hz. Coupling constants of anomeric carbon atoms ($J_{H1,C1}$) were determined using HMBC-GATED experiments. Optical rotations were measured on an Anton Paar Modular Circular Polarimeter MCP 100/150. High resolution mass spectra were recorded on a Synapt G2-Si or a Q Exactive HF Orbitrap equipped with an electron spray ion source positive mode. Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR.

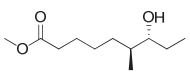
(2*R*)-ethyl-(3*S*)-methylcycloheptanone (3)

(S,R,R)-Leggy phosphoramidite (**2**, 200 mg, 0.37 mmol, 0.6 mol%) and $Cu(OTf)_2$ (65 mg, 0.18 mmol, 0.3 mol%) were dissolved in dry toluene (60 ml) and stirred for 15 min under nitrogen at room temperature. The mixture was cooled to -25 °C and Me_2Zn (2 M in toluene, 50 ml, 100 mmol, 1.5 eq) was added dropwise under nitrogen flow. After stirring for 10 min, a solution of cycloheptenone (7.5 ml, 66 mmol, 1.0 eq) in dry toluene (60 ml) was added over 8 h by syringe pump and the resulting mixture was stirred for 24 hours at -25 °C. Ethyl iodide (54 ml, 660 mmol, 10.0 eq) and HMPA (115 ml, 660 mmol, 10.0 eq) were added, the mixture was warmed up to 0 °C and stirred for 60 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with Et_2O (3x), washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 49:1) to give **3** as a clear oil. Due to the volatile nature of the product it was used in the next reaction without further analysis.

(8*R*)-ethyl-(7*S*)-methyloxocan-2-one (4)

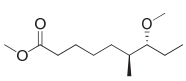
Compound **3** (10.2 g, 66 mmol, 1.0 eq) was dissolved in DCM (250 mL, 0.26 M) and mCPBA (81.4 g, 330 mmol, 5.0 eq) was added to the solution. The mixture was refluxed for 3 days after which it was cooled to rt. The mixture was washed with sat. aq. $NaHCO_3$, sat. aq. NaS_2O_3 and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 49:1) to give the **4** as a clear oil. Due to the volatile nature of the product it was used in the next reaction without further analysis.

Methyl (7*R*)-hydroxy-(6*S*)-methylnonanoate (24)



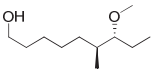
Compound **4** (11.2 g, 18.5 mmol, 1.0 eq) was dissolved in MeOH (250 mL, 0.26 M), this solution was cooled to 0 °C and K_2CO_3 (3.48 g, 27.8 mmol, 1.5 eq) was added. The reaction was allowed to stir overnight while slowly warming to rt. The reaction was quenched with sat. aq. NH_4Cl, extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) to give **25** (5.72 g, 28.3 mmol, 43% over 3 steps) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[33]

Methyl (7*R*)-methoxy-(6*S*)-methylnonanoate (25)



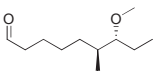
Compound **24** (1.59 g, 7.84 mmol, 1.0 eq) was dissolved in dry DMF (78 mL, 0.1 M) and MeI (1.46 mL, 23.5 mmol, 3.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.63 g, 15.7 mmol, 2.0 eq) was added. The reaction mixture was warmed to rt while stirring for 6 hours. The reaction was quenched by addition of MeOH, partitioned between water and Et_2O and extracted with Et_2O (2x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 6:4) gave the title compound (1.42 g, 6.57 mmol, 84%) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[33]

(7*R*)-methoxy-(6*S*)-methylnonan-1-ol (26)



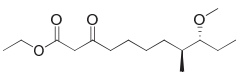
Compound **25** (1.42 g, 6.57 mmol, 1.0 eq) was dissolved in Et_2O (50 mL, 0.13 M), and the solution was cooled to 0 °C. $LiAlH_4$ (4.0 M in Et_2O, 1.7 mL, 6.9 mmol, 1.05 eq) was added and the reaction was allowed to stir for 2 hours. The reaction was quenched by addition of MeOH and washed with 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*, giving the product as a clear oil (1.22 g, 6.46 mmol, 98%). The product was used in the next reaction without further purification. Spectroscopic data were in accordance with those previously reported in the literature.[21]

(7*R*)-methoxy-(6*S*)-methylnonanal (5)



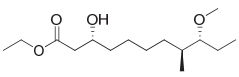
Compound **26** (1.22 g, 6.46 mmol, 1.0 eq) was dissolved in DCM (32 mL, 0.2 M) and DMP (3.02 g, 7.11 mmol, 1.1 eq) was added to the solution. The reaction was allowed to stir for 4 hours after which it was quenched by addition of a 1:1 mixture of sat. aq. $NaHCO_3$ and sat. aq. NaS_2O_3. The layers were separated and the organic layer was washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) to give **5** (1.01 g, 5.41 mmol, 84%) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[33]

(8*S*,9*R*)-ethyl-9-methoxy-8-methyl-3-oxoundecanoate (11)



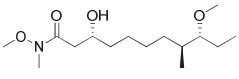
Compound **5** (0.613 g, 3.29 mmol, 1.0 eq) was dissolved in DCM (35 mL, 0.1 M) and a catalytic amount [the amount was not weighed due to tendency for hydrolysis] of $NbCl_5$ was added to the solution and it was cooled to 0 °C. EDAA (87%, 0.6 mL, 4.94 mmol, 1.5 eq) was slowly added and the reaction was allowed to stir for 4 hours after which it was diluted with H_2O and extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) to give **11** (0.735 g, 2.7 mmol, 86%) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[33]

(3*R*,8*S*,9*R*)-ethyl-3-hydroxy-9-methoxy-8-methyl-oxoundecanoate (27)



Compound **11** (1.13 g, 4.15 mmol, 1.0 eq) was dissolved in EtOH (20 mL, 0.2 M) and (*R*)-[(RuCl(tol-BINAP))$_2$(μ-Cl)]$_3$[NH_2Me_2] (74 mg, 42 μmol, 0.01 eq) was added to the solution. The mixture was purged with N_2 after which it was stirred under 22 bar of H_2 atmosphere for 24 hours. The mixture was then diluted with toluene, concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 6:4) to give **28** (0.99 g, 3.61 mmol, 87%) as a slightly green oil. Spectroscopic data were in accordance with those previously reported in the literature.[33]

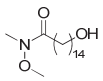
(3*R*,8*S*,9*R*)-3-hydroxy-*N*,9-dimethoxy-*N*,8-dimethylundecanamide (12)



N,O-dimethylhydroxylamine hydrochloride (1.06 g, 10.8 mmol, 3.0 eq) was dissolved in dry THF (36 mL) and the solution was cooled to 0 °C. $AlMe_3$ (2 M in toluene, 5.4 mL, 10.8 mmol, 3.0 eq) was added. This mixture was allowed to stir for 1 hour after which compound **27** (0.99 g, 3.61 mmol, 1.0 eq) was dissolved in THF (3.6

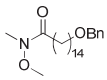
mL, 1 M) and added to the solution. The reaction was allowed to stir overnight while slowly warming to rt. The reaction was then quenched by addition of MeOH and the resulting mixture was diluted with Et_2O. The organic layer was washed with 1 M HCl and the resulting aqueous layer was extracted with Et_2O (2x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (Et_2O) to give **12** (935 mg, 3.23 mmol, 89%) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[33]

15-hydroxy-*N*-methoxy-*N*-methylpentadecanamide (18)



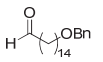
Pentadecanolide (62.74 g, 261 mmol, 1.0 eq) was dissolved in dry THF (1.0 L, 0.26 M) after which *N,O*-dimethylhydroxylamine hydrochloride (38.24 g, 392 mmol, 1.5 eq) was added to the solution. The mixture was then cooled to 0 °C after which isopropylmagnesium chloride (2.0 M in THF, 392 mL, 783 mmol, 3.0 eq) was added. After stirring for three hours the reaction was quenched by addition of sat. aq. NH_4Cl, and extracted with Et_2O (3x). The combined organic layers were then washed with brine, dried with $MgSO_4$ and concentrated *in vacuo* to give the title compound (77.3 g, 256 mmol, 98%) as a white waxy solid. The compound was used in the next step without further purification.

15-((benzyl(oxy)-*N*-methoxy-*N*-methylpentadecanamide (19)



Weinreb amide **18** (30.24 g, 100 mmol, 1.0 eq) was dissolved in dry DMF (0.5 L, 0.2 M) after which BnBr (23.8 mL, 200 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C and NaH (60% dispersion in mineral oil, 8.00 g, 200 mmol, 2.0 eq) was added. The reaction was stirred for 40 hours while warming to RT after which the reaction was quenched by addition of H_2O and extracted with Et_2O (3x). The combined organic layers were then washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 6:4) gave the title compound (29.98 g, 76.6 mmol, 77%) as a white waxy solid. ^{1}H-NMR (500 MHz) δ: 7.33-7.28 (m, 4H, C*H*$_{arom}$); 7.26-7.21 (m, 1H, C*H*$_{arom}$); 4.48 (s, 2H, PhC*H*$_2$); 3.65 (s, 3H, OC*H*$_3$); 3.46 (t, 2H, *J* = 5.2 Hz, OC*H*$_2$); 3.15 (s, 3H, NC*H*$_3$); 2.39 (t, 2H, *J* = 6.0 Hz, C*H*$_2$); 1.66-1.58 (m, 4H, C*H*$_2$); 1.37-1.26 (m, 20H, C*H*$_2$). ^{13}C-BBD NMR (125 MHz) δ: 174.9 (RN*C*O); 138.8 (C$_{q,arom}$); 128.4, 127.6, 127.5 (*C*H$_{arom}$); 72.9 (Ph*C*H$_2$); 70.6 (O*C*H$_2$); 61.2 (O*C*H$_3$); 32.2 (N*C*H$_3$); 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 26.3, 24.7 (*C*H$_2$). IR (thin film, cm^{-1}): 1102, 1384, 1454, 1668, 2853, 2925. HRMS calculated for $C_{24}H_{42}NO_3$ 392.3165 $[M+H]^+$; found 392.3156.

15-((benzyl(oxy)pentadecanal (20)



Compound **19** (21.4 g, 50.7 mmol, 1.0 eq) was dissolved in Et_2O (500 mL, 0.1 M) and the reaction was cooled to 0 °C. After stirring for a few minutes $LiAlH_4$ (4.0 M in Et_2O, 6.58 mL, 26.3 mmol, 0.5 eq) was slowly added to the solution. After TLC-analysis (*n*-pentane-Et_2O 7:3) indicated complete conversion of the starting material the reaction was quenched with MeOH. The organic layer was washed with 1 M HCl, sat. aq. $NaHCO_3$ and brine, after which it was dried with $MgSO_4$ and concentrated *in vacuo* to give the title compound (25.3 g, 76.2 mmol, 100%) as a white waxy solid. ^{1}H-NMR (400 MHz) δ: 9.76 (t, 1H, *J* = 1.8 Hz, C*H*O); 7.37-7.30 (m, 5H, C*H*$_{arom}$); 4.50 (s, 2H, PhC*H*$_2$); 3.46 (t, 2H, *J* = 6.6 Hz); 2.42 (dt, 2H, *J* = 1.8, 7.4 Hz); 1.66-1.58 (m, 4H); 1.37-1.25 (m, 20H). ^{13}C-APT NMR (101 MHz) δ: 203.2 (*C*HO); 138.9 (C$_{q,arom}$); 128.5, 127.8, 127.6 (*C*H$_{arom}$); 73.0, 70.7, 44.1, 29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5,

29.3, 26.3, 22.2 (CH_2). IR (thin film, cm^{-1}): 1029, 1043, 1100, 1235, 1262, 1362, 1455, 1497, 1507, 1747, 2853, 2925. HRMS calculated for $C_{22}H_{37}O_2$ 333.2794 $[M+H]^+$; found 333.2785.

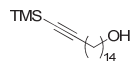
1,1-dibromo-16-((benzyl(oxy)hexadec-1-ene (21)

CBr_4 (1.62 g, 4.88 mmol, 2.0 eq) was dissolved in DCM (6.1 mL, 0.81 M) and the solution was cooled to 0 °C after which PPh_3 (2.63 g, 9.76 mmol, 4.0 eq) was added. The mixture was stirred for 40 minutes after which a solution of aldehyde **20** (0.812 g, 2.44 mmol, 1.0 eq) in DCM (5.0 mL, 0.5 M) was added. After stirring for 45 minutes the reaction mixture was diluted with hexane and Et_2O after which it was filtered over celite. The filtrate was concentrated *in vacuo*, diluted with Et_2O, and filtered again. The filtrate was then concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 49:1) gave the title compound (1.08 g, 2.22 mmol, 91%) as a clear oil. ^{1}H-NMR (400 MHz) δ: 7.37-7.30 (m, 5H, CH_{arom}); 6.38 (t, 1H, *J* = 7.2 Hz, CBr_2CH); 4.50 (s, 2H, PhCH_2); 3.46 (t, 2H, *J* = 6.6 Hz); 2.08 (dt, 2H, 7.2, 7.6 Hz); 1.65-1.59 (m, 2H); 1.43-1.26 (m, 22H). ^{13}C-APT NMR (101 MHz) δ: 139.1 (CBr_2CH); 138.9 ($C_{q,arom}$); 128.5, 127.8, 127.6 (CH_{arom}); 88.5 (CBr_2); 73.0, 70.7, 33.2, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.2, 27.9, 26.3 (CH_2). IR (thin film, cm^{-1}): 1029, 1102, 1362, 1454, 2853, 2925. HRMS calculated for $C_{23}H_{37}Br_2O$ 489.1180 $[M+H]^+$; found 489.1185.

1-trimethylsilyl-16-((benzyl(oxy)hexadec-1-yne (22)

Compound **21** (23.6 g, 48.3 mmol, 1.0 eq) was dissolved in Et_2O (500 mL, 0.1 M) and the solution was cooled to 0 °C. After stirring for a few minutes *n*-BuLi (2.5 M in hexanes, 48.3 mL, 121 mmol, 2.5 eq) was slowly added to the solution. After stirring for 1.5 hours TMSCl (24.5 mL, 193 mmol, 4.0 eq) was added. The reaction was allowed to stir for 2 hours while warming to RT. The reaction was then quenched by addition of sat. aq. NH_4Cl and extracted with Et_2O (3x). The combined organic layers were then washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 49:1) gave the title compound (18.2 g, 45.3 mmol, 94%) as a clear liquid. ^{1}H-NMR (400 MHz) δ: 7.31-7.27 (m, 5H, CH_{arom}); 4.51 (s, 2H, PhCH_2); 3.47 (t, 2H, *J* = 6.6 Hz); 2.21 (t, 2H, *J* = 7.2 Hz); 1.65-1.58 (m, 2H); 1.55-1.48 (m, 2H); 1.36-1.26 (m, 22H). ^{13}C-APT NMR (101 MHz) δ: 138.9 ($C_{q,arom}$); 128.5, 127.8, 127.6 (CH_{arom}); 108.0, 84.4 ($C_{q,alkyne}$); 73.0, 70.7, 29.9, 29.8, 29.8, 29.6, 29.2, 29.0, 28.8, 26.3, 20.0 (CH_2); 0.3 ($CH_{3,TMS}$). IR (thin film, cm^{-1}): 1029, 1102, 1202, 1249, 1362, 1455, 1497, 2175, 2853, 2924. HRMS calculated for $C_{26}H_{48}NOSi$ 418.3505 $[M+NH_4]^+$; found 418.3499.

1-trimethylsilylhexadec-1-yn-16-ol (14)



Compound **22** (18.16 g, 45.3 mmol, 1.0 eq) was dissolved in DCM/H_2O (20:1, 440 mL, 0.1 M) and the solution was cooled to 0 °C. After stirring for a few minutes DDQ (15.42 g, 68.0 mmol, 1.5 eq) was added to the solution. The reaction was stirred vigorously overnight after which it was quenched by addition of sat. aq. $NaHCO_3$. The organic layer was then washed sat. aq. $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (12.1 g, 39.0 mmol, 86%) as a white waxy solid. The spectroscopic data were in accordance with those previously reported in the literature.[33]

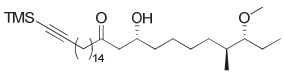
16-(trimethylsilyl)hexadec-15-yn-1-yl 4-toluenesulfonate (23)

Compound **14** (1.77 g, 5.7 mmol, 1.0 eq) was dissolved in $CHCl_3$ (30 mL, 0.2 M) together with *p*-TsCl (2.17 g, 11.4 mmol, 2.0 eq) and pyridine (1.38 mL, 17.1 mmol, 3.0 eq) was added to the solution. The reaction was left to stir overnight and was then diluted with Et_2O. The organic layer was then washed with H_2O, 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 19:1) gave the title compound (2.52 g, 5.42 mmol, 95%) as a white waxy solid. The spectroscopic data were in accordance with those previously reported in the literature.[33]

(16-iodohexadec-1-yn-1-yl)trimethylsilane (15)

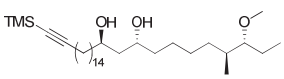
Compound **23** (11.1 g, 23.9 mmol, 1.0 eq) was dissolved in acetone (250 mL, 0.1 M) and NaI (14.3 g, 95.6 mmol, 4.0 eq) was added to the solution. The reaction was left to stir overnight after which it was diluted with EtOAc and concentrated *in vacuo*. The residue was then diluted with EtOAc and washed with sat. aq. $Na_2S_2O_3$, H_2O and brine. The organic layer was then dried with $MgSO_4$ and concentrated *in vacuo* after which the product was purified by means of column chromatography (*n*-pentane-Et_2O 49:1) gave the title compound (9.70 g, 23.1 mmol, 96%) as a clear oil. The spectroscopic data were in accordance with those previously reported in the literature.[33]

(3*R*,4*S*,9*R*)-9-hydroxy-3-methoxy-4-methyl-27-(trimethylsilyl)heptacos-26-yn-11-one (16)



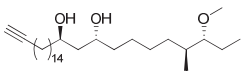
Compound **15** (3.19 g, 7.58 mmol, 3.0 eq) was dissolved in Et_2O (76 mL, 0.1 M) and the solution was cooled to -78 °C. *t*-BuLi (1.6 M in hexane, 7.9 mL, 12.6 mmol, 5.0 eq) was added to the solution and the mixture was allowed to stir for 30 minutes. After this time a solution of compound **12** (0.731 g, 2.53 mmol, 1.0 eq) in Et_2O (5.1 mL, 0.5 M) was slowly added and the reaction was allowed to stir for 1 hour. The reaction was then quenched by the addition of a 4:1 mixture of MeOH/sat. aq. NH_4Cl and allowed to warm to rt. The layers were then separated and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification of the product by means of column chromatography (*n*-pentane-Et_2O 3:2) gave the title compound (0.798 g, 1.53 mmol, 60%) as a white waxy solid. The spectroscopic data were in accordance with those previously reported in the literature. [33]

(3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methyl-27-(trimethylsilyl)heptacos-26-yne-9,11-diol (28)



Compound **16** (304 mg, 0.581 mmol, 1.0 eq) was dissolved in a 12:12:1 mixture of MeCN, AcOH and THF (194 mL, 0.003 M) and this solution was cooled to 0 °C. $Me_4NBH(OAc)_3$ (0.92 g, 3.49 mmol, 6.0 eq) was added in 5 portions over 60 minutes and the reaction was allowed to stir for 90 more minutes. The reaction was quenched by the addition of H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (3×) and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification of the product by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (245 mg, 0.467 mmol, 80%) as a white waxy solid. The spectroscopic data were in accordance with those previously reported in the literature.[33]

(3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol (17)



Compound **28** (0.491 g, 0.935 mmol, 1.0 eq) was dissolved in MeOH (20 mL, 0.05 M) and K_2CO_3 (0.65 g, 4.68 mmol, 5.0 eq) was added solution and the reaction was allowed to stir overnight. The mixture was then diluted with Et_2O and H_2O, the layers were separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (0.41 g, 0.91 mmol, 97%) as a white waxy solid. The spectroscopic data were in accordance with those previously reported in the literature.[33]

References

1. Stodola, F. H. & Anderson, R. J. The Chemistry of the Lipids of Tubercle Bacilli. *J. Biol. Chem.* **114**, 467–472 (1936).
2. Stendal, N. Sur la présence d'un glycol dans la cire du Bacille tuberculeux. *C R Hebd Séanc Acad Sci Paris* **198**, 1549–1551 (1934).
3. Drayson, F. K., Lewis, J. W. & Polgar, N. 76. Experiments relating to phthiocerol. Part III. Degradative studies of a C11 oxidation product of phthiocerol. *J. Chem. Soc.* 430 (1958).
4. Demarteau-Ginsburg, H. & Lederer, E. Sur la structure chimique du mycoside B. *Biochim. Biophys. Acta - Spec. Sect. Lipids Relat. Subj.* **70**, 442–451 (1963).
5. Ryhage, R. & Stenhagen, E. Mass spectrometry in lipid research. *J. Lipid Res.* **1**, 361–390 (1960).
6. Randall, H. M. & Smith, D. W. Characterization of mycobacteria by infrared spectroscopic examination of their lipid fractions. *Zentr. Bacteriol., I., Ref.* 190–201 (1964).
7. Maskens, K., Minnikin, D. E. & Polgar, N. Studies relating to phthiocerol. Part VI. Stereochemical studies. *J. Chem. Soc. C Org.* **3552**, 2113 (1966).
8. Minnikin, D. E. & Polgar, N. Phthiocerol B, a constituent of the lipids of tubercle bacilli. *Chem. Commun.* **43**, 495 (1965).
9. Minnikin, D. E. & Polgar, N. Studies relating to phthiocerol. Part V. Phthiocerol A and B. *J. Chem. Soc. C Org.* 2107 (1966) doi:10.1039/j39660002107.
10. Minnikin, D. E. & Polgar, N. Studies relating to phthiocerol. Part VII. Phthiodiolone A. *J. Chem. Soc. C Org.* 803 (1967).
11. Huet, G. *et al.* A Lipid Profile Typifies the Beijing Strains of Mycobacterium tuberculosis. *J. Biol. Chem.* **284**, 27101–27113 (2009).
12. Noll, H. The chemistry of some native constituents of the purified wax of Mycobacterium tuberculosis. *J. Biol. Chem.* **224**, 149–164 (1957).
13. Gastambide-Odier, M., Sarda, P. & Lederer, E. Structure des aglycones des mycosides A et B. *Tetrahedron Lett.* **6**, 3135–3143 (1965).
14. Onwueme, K. C., Vos, C. J., Zurita, J., Ferreras, J. A. & Quadri, L. E. N. The dimycocerosate ester polyketide virulence factors of mycobacteria. *Prog. Lipid Res.* **44**, 259–302 (2005).
15. Minnikin, D. E. *et al.* Ancient mycobacterial lipids: Key reference biomarkers in charting the evolution of tuberculosis. *Tuberculosis* **95**, S133–S139 (2015).
16. Minnikin, D. E., Kremer, L., Dover, L. G. & Besra, G. S. The Methyl-Branched Fortifications of Mycobacterium tuberculosis. *Chem. Biol.* **9**, 545–553 (2002).
17. Daffe, M. & Laneelle, M. A. Distribution of phthiocerol diester, phenolic mycosides and related compounds in mycobacteria. *J. Gen. Microbiol.* **134**, 2049–2055 (1988).
18. Daffé, M., Lanéelle, M. A., Roussel, J. & Asselineau, C. Lipides spécifiques de Mycobacterium ulcerans. *Ann. l'Institut Pasteur / Microbiol.* **135**, 191–201 (1984).
19. Besra, G. S., Mallet, A. I., Minnikin, D. E. & Ridell, M. New members of the phthiocerol and phenolphthiocerol families from Mycobacterium marinum. *J. Chem. Soc. Chem. Commun.* 1451 (1989).
20. Besra, G. S., Minnikin, D. E., Sharif, A. & Stanford, J. L. Characteristic new members of the phthiocerol and phenolphtiocerol families from Mycarbacterium ulcerans. *FEMS Microbiol. Lett.* **66**, 11–13 (1990).
21. Casas-Arce, E., Ter Horst, B., Feringa, B. L. & Minnaard, A. J. Asymmetric total synthesis of PDIM A: A virulence factor of Mycobacterium tuberculosis. *Chem. - A Eur. J.* **14**, 4157–4159 (2008).

22. ter Horst, B., Feringa, B. L. & Minnaard, A. J. Catalytic asymmetric synthesis of mycocerosic acid. *Chem. Commun.* 489–491 (2007) doi:10.1039/B612593J.

23. Guo, H. C. & Ma, J. A. Catalytic asymmetric tandem transformations triggered by conjugate additions. *Angew. Chemie - Int. Ed.* **45**, 354–366 (2006).

24. Arnold, L. A. *et al.* Enantioselective catalytic conjugate addition of dialkylzinc reagents using copper-phosphoramidite complexes; ligand variation and non-linear effects. *Tetrahedron* **56**, 2865–2878 (2000).

25. Feringa, B. L. Phosphoramidites: Marvellous Ligands in Catalytic Asymmetric Conjugate Addition. *Acc. Chem. Res.* **33**, 346–353 (2000).

26. Boyall, D., López, F., Sasaki, H., Frantz, D. & Carreira, E. M. Enantioselective Addition of 2-Methyl-3-butyn-2-ol to Aldehydes: Preparation of 3-Hydroxy-1-butynes. *Org. Lett.* **2**, 4233–4236 (2000).

27. Trost, B. M., Ball, Z. T. & Laemmerhold, K. M. An Alkyne Hydrosilylation-Oxidation Strategy for the Selective Installation of Oxygen Functionality. *J. Am. Chem. Soc.* **127**, 10028–10038 (2005).

28. Fürstner, A. *et al.* Total Synthesis of Myxovirescin A1. *Chem. - A Eur. J.* **13**, 8762–8783 (2007).

29. Marshall, J. A. & Yanik, M. M. Synthesis of a C1–C21 Subunit of the Protein Phosphatase Inhibitor Tautomycin: A Formal Total Synthesis. *J. Org. Chem.* **66**, 1373–1379 (2001).

30. Evans, D. A., Chapman, K. T. & Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **110**, 3560–3578 (1988).

31. Colby, E. A., O'Brie, K. C. & Jamison, T. F. Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective, Reductive Macrocyclizations. *J. Am. Chem. Soc.* **127**, 4297–4307 (2005).

32. Casas-Arce, E., Ter Horst, B., Feringa, B. L. & Minnaard, A. J. Asymmetric total synthesis of PDIM A: A virulence factor of Mycobacterium tuberculosis. *Chem. - A Eur. J.* **14**, 4157–4159 (2008).

33. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie Int. Ed.* **51**, 11774–11777 (2012).

34. Yadav, J. S., Subba Reddy, B. V., Eeshwaraiah, B. & Reddy, P. N. Niobium(V) chloride-catalyzed C–H insertion reactions of α-diazoesters: synthesis of β-keto esters. *Tetrahedron* **61**, 875–878 (2005).

35. Mashima, K. *et al.* Cationic BINAP-Ru(II) Halide Complexes: Highly Efficient Catalysts for Stereoselective Asymmetric Hydrogenation of .alpha.- and .beta.-Functionalized Ketones. *J. Org. Chem.* **59**, 3064–3076 (1994).

36. Noyori, R. *et al.* Stereoselective hydrogenation via dynamic kinetic resolution. *J. Am. Chem. Soc.* **111**, 9134–9135 (1989).

37. Macaulay, S. R. Isomerization of internal triple bonds of alkyn-1-ols with sodium hydride in 1,3-diaminopropane. *J. Org. Chem.* **45**, 734–735 (1980).

38. Buck, M. & Chong, J. M. Alkylation of 1-alkynes in THF. *Tetrahedron Lett.* **42**, 5825–5827 (2001).

39. Gilbert, J. C. & Weerasooriya, U. Diazoethenes: their attempted synthesis from aldehydes and aromatic ketones by way of the Horner-Emmons modification of the Wittig reaction. A facile synthesis of alkynes. *J. Org. Chem.* **47**, 1837–1845 (1982).

40. Ohira, S. Methanolysis of Dimethyl (1-Diazo-2-oxopropyl) Phosphonate: Generation of Dimethyl (Diazomethyl) Phosphonate and Reaction with Carbonyl Compounds. *Synth. Commun.* **19**, 561–564 (1989).

41. Müller, S., Liepold, B., Roth, G. J. & Bestmann, H. J. An Improved One-pot Procedure for the Synthesis of Alkynes from Aldehydes. *Synlett* 521–522 (1996) doi:10.1055/s-1996-5474.

42. Corey, E. J. & Fuchs, P. L. A Synthetic Method for Formyl-Ethynyl Conversion. *Tetrahedron Lett.* **36**, 3769–3772 (1972).

43. Sahu, B., Muruganantham, R. & Namboothiri, I. N. N. Synthetic and Mechanistic Investigations on the Rearrangement of 2,3-Unsaturated 1,4-Bis(alkylidene)carbenes to Enediynes. *European J. Org. Chem.* **2007**, 2477–2489 (2007).

44. Fritsch, P. IV. Ueber die Darstellung von Diphenylacetaldehyd und eine neue Synthese von Tolanderivaten. *Justus Liebig's Ann. der Chemie* **279**, 319–323 (1894).

45. Buttenberg, W. P. Condensation des Dichloracetals mit Phenol und Toluol. *Justus Liebig's Ann. der Chemie* **279**, 324–337 (1894).

46. Wiechell, H. Condensation des Dichloracetals mit Anisol und Phenetol. *Justus Liebig's Ann. der Chemie* **279**, 337–344 (1894).

47. Volbeda, A. G. *et al.* Chemoselective Cleavage of p-Methoxybenzyl and 2-Naphthylmethyl Ethers Using a Catalytic Amount of HCl in Hexafluoro-2-propanol. *J. Org. Chem.* **80**, 8796–8806 (2015).

48. Cavedon, C. *et al.* Visible-Light-Mediated Oxidative Debenzylation Enables the Use of Benzyl Ethers as Temporary Protecting Groups. *Org. Lett.* **23**, 514–518 (2021).

49. Bissember, A. C., Levina, A. & Fu, G. C. A Mild, Palladium-Catalyzed Method for the Dehydrohalogenation of Alkyl Bromides: Synthetic and Mechanistic Studies. *J. Am. Chem. Soc.* **134**, 14232–14237 (2012).

Chapter 4

Synthesis of PGLs originating from the *Mycobacterium tuberculosis* complex

Introduction

The *Mycobacterium tuberculosis* complex (MTBC) is a group of slow-growing species of mycobacteria which are genetically very similar to *Mycobacterium tuberculosis*.[1] Most of these species can cause tuberculosis in humans, which still is one of the most deadly infectious diseases worldwide, especially in countries which are heavily impacted by HIV/AIDS.[2] Approximately one third of the world population is thought to harbor a latent tuberculosis infection,[3] and these individuals are at risk to develop the active disease. Phenolic glycolipids are thought to play a major role in the virulence of many mycobacteria belonging to the MTBC.[4–8] While most strains of *M. tuberculosis* do not produce phenolic glycolipids, some isolates belonging to the W-Beijing family do and these show "hyperlethality" in murine disease models.[9–11] These strains produce a triglycosyl phenolic glycolipid, PGL-tb1, carrying a 2,3,4,-tri-*O*-methyl-α-L-fucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-2-*O*-methyl-α-L-rhamnopyranosyl trisaccharide on the phthiocerol lipid (Figure 1).[12] This PGL is also produced by some isolates of *M. africanum*[13] and the *M. canetti* strain.* The strains of *M. tuberculosis* that do not produce PGLs do produce *p*-hydroxybenzoic acid derivative II (*p*-HBAD-II), a biosynthetically closely related glycosylated phenol, bearing the same trisaccharide, as well as phthiocerol

* There is an ongoing discussion regarding whether or not *M. canetti* belongs to the MTBC as it is genetically closely related and can cause tuberculosis but there are contrasting specific phenotypic and genomic characteristics.[38]

dimycocerosate (PDIM), which resembles the lipid part of PGLs.[14–17] Other species of the MTBC, such as *M. bovis*, *M. microti*, *M. africanum* and *M. pinnipedii* almost exclusively produce a monoglycosylated PGL, also referred to as mycoside B, carrying a 2-*O*-methyl-α-L-rhamnopyranose. Some strains of *M. bovis* also produce a PGL having an α-L-rhamnopyranosyl-(1→3)-2-*O*-methyl-α-L-rhamnopyranose disaccharide,[18] and PGLs with variations in the methylation pattern, that arise from mutations in genes related to methyltransferases, have also been isolated.[19–21] Several syntheses of truncated and simplified versions of PGLs and related molecules have been reported (see Chapter 1).[8,15,22–26] However, in order to fully understand the interactions between PGLs and the host immune system, pure synthetic complete PGLs are required. Therefore, this chapter describes the synthesis of all known PGLs originating from the MTBC.

The general strategy for the synthesis of these phenolic glycolipids is based on the total synthesis of PGL-tb1 as published by Barroso et al. (Figure 1).[26,27] Fully protected iodoaryl glycans are to be synthesized starting from the 'reducing end', after which they can be attached to a phthiocerol alkyne derivative in a Sonogashira cross coupling. The resulting diol can then be esterified with two mycocerosic acids under Steglich conditions and hydrogenation finally leads to the global deprotection and concomitant reduction of the conjugated internal alkyne which is formed in the Sonogashira reaction.

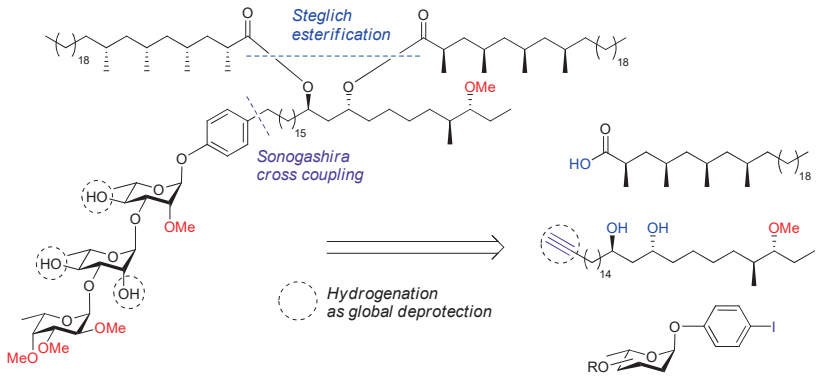


Figure 1. General synthetic strategy for phenolic glycolipids with PGL-tb1 as an example.

This synthetic strategy requires the oligosaccharides to be protected with protecting groups that can be removed under hydrogenation conditions. If 1,2-*trans* linkages were to be formed with ester based participating protecting groups these would

have to be removed and replaced with for example benzyl ethers before the Sonogashira cross coupling. To circumvent these extra protecting group manipulations, the carboxybenzyl (Cbz) protecting group will be probed, as this carbonate may provide anchimeric assistance, directing the formation the desired 1,2-*trans* linkages, while it is susceptible to hydrogenation.[28] Of note, the Cbz-group has found only very little application in the assembly of oligosaccharides. The retrosynthetic analysis of the MTBC glycans and the required building blocks are depicted in Figure 2.

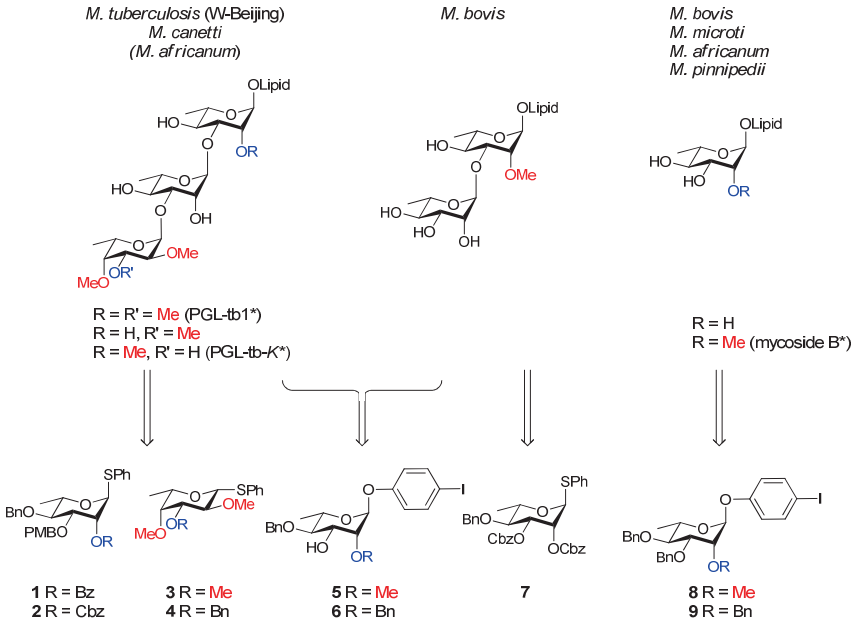
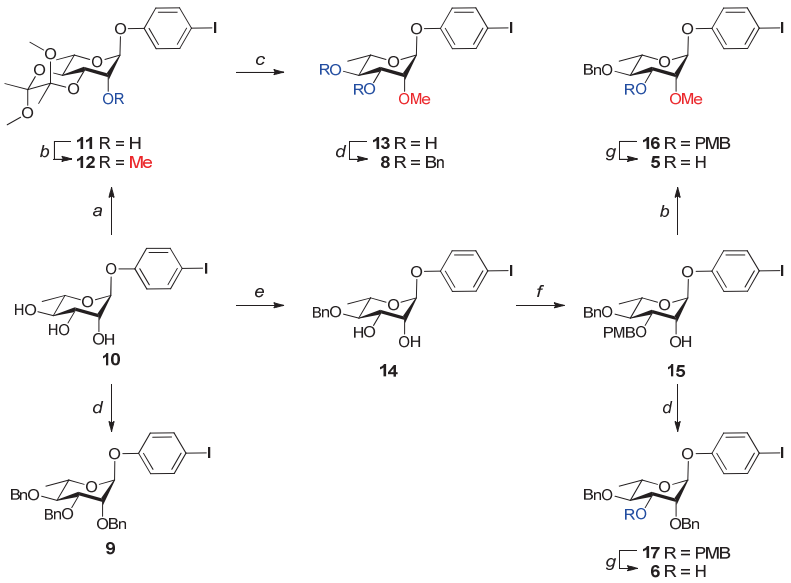


Figure 2. Retrosynthetic analysis of the glycans of MTBC PGLs. (* = trivial name)

The triglycosyl PGLs are to be synthesized from acceptors **5** and **6** and rhamnose donor **2**. In order to establish the efficacy of the Cbz group in PGL assembly, a route using the C-2 benzoyl bearing rhamnose donor **1** will be followed for comparison. The terminal fucose has to be fused to the disaccharide through a 1,2-*cis* linkage, and building blocks **3** and **4** will be probed for this purpose. This will require the conception of effective glycosylation chemistry that does not build on neighboring group participation. Acceptor **5** can also be used for the synthesis of the *M. bovis* disaccharide in combination with 2,3-di-*O*-Cbz donor **7**. The monoglycosylated PGLs are to be synthesized from **8** and **9**.

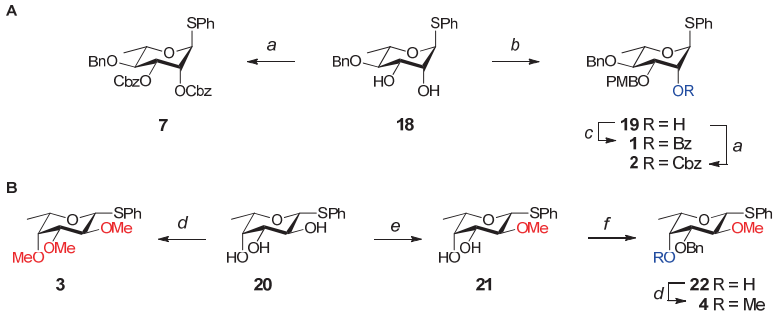
Results and discussion

All requisite iodoaryl bearing rhamnoses were synthesized from intermediate **10** as depicted in Scheme 1.[26] To generate mycoside B, the 3,4-diol in **10** was selectively protected with a butane 2,3-bisacetal (BDA) under mild conditions[29] to avoid hydrolysis of the anomeric phenol. After methylation of the C-2 alcohol in **11**, the BDA was hydrolyzed using acetic acid, after which the resulting diol **13** was benzylated to give iodophenyl rhamnose **8** in 37% yield over 4 steps. Perbenzylation of **10** gave **9** in 98% yield. Acceptors **5** and **6** were synthesized by selectively protecting the C-3 position of **14**, obtained from **10** by acetonide formation, benzylation and acetonide removal, with a *para*-methoxybenzyl ether by treatment of the diol with Bu_2SnO, followed by TBABr and PMBCl.[30] After methylation (to give **16**) or benzylation (providing **17**), the PMB ether was removed using a catalytic amount of HCl in HFIP[31] to give monosaccharide acceptors **5** and **6** in 79% and 63% over 3 steps, respectively.



Scheme 1. Reagents and conditions: (a) 2,3-butanedione, trimethyl orthoformate, $BF_3{\cdot}OEt_2$, MeOH, 0 °C → RT, 77%, (b) Na, MeI, DMF, 0 °C → RT, 87% (**8**), 80% (**16**), (c) $AcOH/H_2O$, 4:1, 80 °C, 65%, (d) NaH, BnBr, DMF, 0 °C → RT, 84% (**8**), 98% (**9**), 77% (**17**), (e) 1. DMP, CSA, acetone, 2. NaH, BnBr, DMF, 3. $AcOH/H_2O$, 4:1, 80 °C, 86% over 3 steps, (f) 1. Bu_2SnO, toluene reflux, 2. PMBCl, TBABr, toluene reflux, 99% (8:1), (g) HCl/HFIP, HFIP/DCM, 100% (**5**), 82% (**6**).

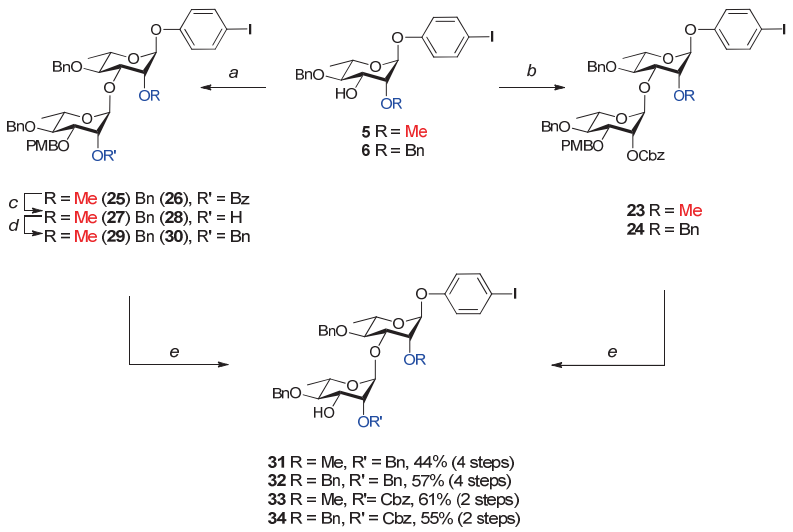
The synthesis of the required donors is depicted in Scheme 2. Donor **7** was synthesized from **18** in near quantitative yield by reacting the diol with CbzCl and DMAP in DCM.[32] Selective protection of the C-3 alcohol of **18** with a PMB ether provided **19** in 77% yield, from which benzoyl donor **1** and Cbz donor **2** were synthesized in 100% and 76% yield, respectively. Permethylation of triol **20** gave **3** in 87% yield. The synthesis of fucose donor **4** was accomplished by masking the 3,4-diol in **20** with an isopropylidene ketal, installation of the C-2 methyl ether and removal of the isopropylidene to provide intermediate **21** in 88% yield over 3 steps. A benzyl ether was then selectively installed on the C-3 position by using a catalytic amount of Bu_2SnCl_2 in acetonitrile,[33] after which the remaining free alcohol was methylated in 83% yield. Alternatively, this building block could be synthesized from triol **20** in 2 steps by directly benzylating the C-3 alcohol using organotin chemistry. However, this resulted in a lower overall yield because of the decreased selectivity of the benzylation reaction.



Scheme 2. Reagents and conditions: (a) CbzCl, DMAP, DCM, 0 °C → RT, 99% (**7**), 76% (**2**), (b) 1. Bu_2SnO, toluene, reflux, 2. PMBCl, TBABr, toluene, reflux, 77% (c) BzCl, pyridine, DCM, 0 °C → RT, 100%, (d) NaH, MeI, DMF, 0 °C → RT, 87% (**3**), 83% (**4**), (e) 1. DMP, CSA, acetone, 2. NaH, MeI, DMF, 0 °C → RT, 3. $AcOH/H_2O$, 4:1, 80 °C, 88% over 3 steps, (f) BnBr, TBABr, Bu_2SnCl_2, K_2CO_3, MeCN, 80 °C, 97%.

Scheme 3 depicts the synthesis of the disaccharide acceptors needed for the MTBC trisaccharide PGLs using either a benzoyl donor (left) or a Cbz donor (right). Benzoyl donor **1** was combined with C-2 methyl acceptor **5** or C-2 benzyl acceptor **6** to provide disaccharides **25** and **26** in 64% and 75% yield, respectively. Thereafter the benzoyl esters were removed and replaced with benzyl ethers to offer **29** and **30** in 81% and 77% yield over 2 steps, respectively. Then the C-3' PMB ethers were removed to give disaccharide acceptors **31** and **32** in 84% and 98% yield, respectively. In the alternative

route, Cbz donor **2** was used in combination with **5** and **6** to produce disaccharides **23** and **24** in 68% and 64% yield, respectively, whereafter only the PMB ether had to be removed. Although it was anticipated that the Cbz could migrate to the C-3' position or form a 2,3-carbonate under the acidic conditions needed for the removal of the PMB ether, neither of these byproducts were detected in significant amounts, possibly due to the very short reaction time (<2 minutes). The removal of the PMB ether gave disaccharide acceptors **33** and **34** in 89% and 86% yield, respectively. It was observed that prolonged reaction times led to the hydrolysis of the iodophenol on the reducing end. When DDQ was used instead of HCl in HFIP the disaccharide acceptors were produced in a slightly lower yield and removal of the C-4 benzyl ether was detected as a side reaction.



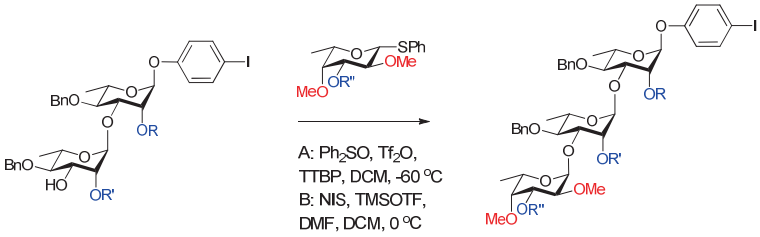
Scheme 3. Reagents and conditions: (a) Donor **1**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 64% (**25**), 75% (**26**), (b) Donor **2**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 68% (**23**), 64% (**24**), (c) Na, MeOH/THF, 81% (**27**), 86% (**28**), (d) NaH, BnBr, TBAI, DMF, 0 °C → RT, 100% (**29**), 90% (**30**), (e) HCl/HFIP, HFIP/DCM, 84% (**31**), 98% (**32**), 89% (**33**), 86% (**34**).

Overall, it can be concluded that the implementation of the Cbz group in the synthetic routes increases the efficiency. The disaccharides **31** and **33**, carrying a C-2 methyl ether were generated in 44% over four steps and 61% yield over two steps, respectively. Although the overall yield for disaccharide acceptors **32** and **34** did not differ much

between the Cbz and Bz routes, the Cbz route required only two steps, where the route with the Bz ester needed four steps.

The disaccharide acceptors could then be fucosylated to generate the PGL trisaccharides. For the fucosylation several reaction conditions were screened as summarized in Table 1 below. First the 1,2-*cis* glycosylation was attempted using Ph_2SO pre-activation conditions (method A). When acceptors **31** and **33** were combined with donor **3** trisaccharides **35** and **36** were produced in good yield with moderate stereoselectivity (5:1 and 4:1, respectively). Coupling of acceptors **32** and **34** to the same donor under the same conditions provided trisaccharides **37** and **38** in a 2:1 α/β ratio. Coupling of donor **4** to acceptor **33** produced trisaccharide **39** as a 3:2 α/β mixture. An alternative method was then applied using DMF as a stereodirecting additive.[34] First the donor was activated using stoichiometric amounts of both NIS and TMSOTf after which DMF was added (method B). This method improved the selectivity of the coupling of donor **3** to acceptor **33** from 4:1 to 10:1. In addition, coupling of donor **3** to acceptors **32** and **34** improved the selectivity of these couplings to 4:1 and 7:1, respectively. The use of method B improved the selectivity of the coupling of donor **4** to acceptor **33** from 3:2 to 5:1. From these results it appears that the stereoselectivity of the condensation reactions improves most when an acceptor is used that carries electron withdrawing protecting groups (*i.e.* the Cbz carbonate). It is hypothesized that upon activation of the glycosyl donor, the DMF additive generates a mixture of α- and β-glycosyl imidinium ion intermediates that are in rapid equilibrium. The β-imidinium ion is less stable and therefore more reactive than its α-counterpart.

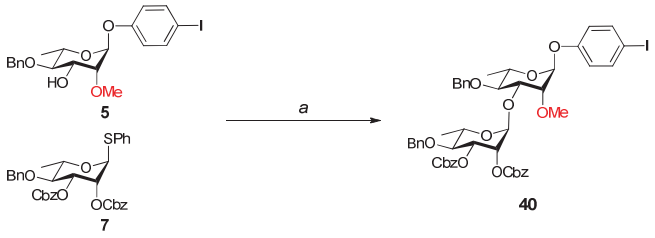
Table 1. Yields and selectivities of glycosylations using either Ph_2SO/Tf_2O (A) or NIS/TMSOTf (B).



Acceptor	Donor	Product	R	R'	R''	Method	Yield	Selectivity (α:β)
31	**3**	**35**	Me	Bn	Me	A	70%	5:1
33	**3**	**36**	Me	Cbz	Me	A	79%	4:1
33	**3**	**36**				B	73%	10:1
32	**3**	**37**	Bn	Bn	Me	A	85%	2:1
32	**3**	**37**				B	89%	4:1
34	**3**	**38**	Bn	Cbz	Me	A	78%	2:1
34	**3**	**38**				B	73%	7:1
33	**4**	**39**	Me	Cbz	Bn	A	88%	3:2
33	**4**	**39**				B	82%	5:1

Even though it is the minor component in the anomeric mixture, it represents the most important product forming intermediate as weak nucleophiles do not readily displace the more stable α-imidinium ion and weaker nucleophiles will react with better stereoselectivity.[35] It was noted that application of method B did lead to the formation of a minor side product resulting from silylation of the C-3' alcohol of the acceptor. Switching from TMSOTf to TfOH could circumvent this problem but this led to partial hydrolysis of the iodophenol on the reducing end.

The last glycan to be prepared was the *M. bovis* disaccharide, which was synthesized by coupling **5** and **7**. Donor **7**, carrying two Cbz carbonates was activated using the Ph_2SO/Tf_2O couple after which addition of acceptor **5** led to the formation of disaccharide **40** in 65% yield (Scheme 3).

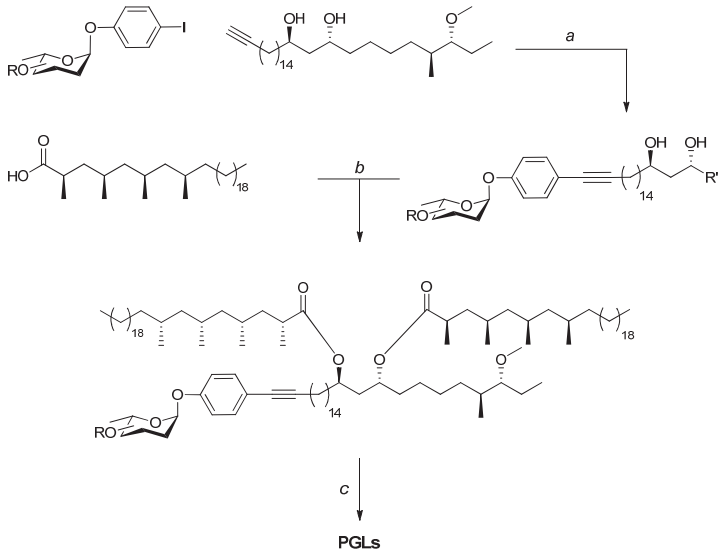


Scheme 4. Reagents and conditions: (a) Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 65%

With all glycans in hand the stage was set for the connection of the lipids and complete the syntheses of the PGLs. The yields of the final steps of the assembly of PGLs is summarized in Table 2. First the glycans were coupled to the phthiocerol alkyne derivative using a Sonogashira cross coupling in excellent yields. For these reactions it

proved crucial to use triethylamine that was freshly was distilled from KOH (less than 24 hours before the reaction). A slight excess (1.2 equivalents) of alkyne was used. It was observed that a minor amount of the diyne byproduct, generated by coupling of two alkynes, was formed, the amount of which increased if more alkyne was used. The diols that resulted from the Sonogashira reaction could then be coupled to mycocerosic acid[36] under Steglich esterification conditions using di-*iso*-propylcarbodiimide. The best results were obtained if these reactions were started at 0 °C to minimize the amount of *N*-acyl di-*iso*-propylurea rearrangement product formed. While the low reaction temperature was required at the start of the reaction, it was observed that warming the reaction to 40 °C was required to achieve full conversion and the use of ambient temperature led to the generation of the mono- mycocerosic acid ester compounds. With these conditions the diols were esterified in good yields with the exception of the *M. bovis* disaccharide. In this case the retention time of the *N*-acyl urea rearrangement products during column chromatography was very similar to the retention time of the product and multiple rounds of purification were needed. After the esterification reaction the products were hydrogenated and this uneventfully completed the syntheses of all PGLs originating from the MTBC.

Table 2. Yields of the final stages of PGL assembly. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, 40 °C, (b) DIC, DMAP, DCM, 0 °C → RT → 40 °C, (c) Pd/C, H_2, THF/EtOH.



Starting glycan	Sonogashira	Esterification	Hydrogenation	Overall yield
36	90%	94%	82%	69%
38	87%	75%	80%	52%
39	100%	74%	82%	61%
8	100%	84%	62%	52%
9	99%	75%	31%	23%
40	96%	51%	60%	29%

Conclusion

This chapter has described the synthesis of all phenolic glycolipids originating from the *Mycobacterium tuberculosis* complex. The presence of the two mycocerosic esters in the final products necessitated a strategy using a hydrogenation step for global deprotection. Therefore, in order to reduce the amount of steps required to assemble the oligosaccharides, the carboxybenzyl (Cbz) group has been probed as a participating

protecting group. Although there is relatively little precedent for the use of the Cbz-carbonate in oligosaccharide synthesis the group performed well and the Cbz protected donors selectively produced the desired α products in good yield. In the synthesis of the Mtb PGL trisaccharides, the stereoselective introduction of the 1,2-*cis* fucosyl linkages was achieved using an additive (DMF) based glycosylation method to provide the desired trisaccharides in good yields and selectivities. The iodoaryl-bearing glycans were then coupled to the phthiocerol alkyne derivative using a Sonogashira coupling, which was followed by a Steglich esterification of the resulting diol with mycocerosic acid. Finally, global deprotection with H_2 and Pd/C resulted in all the phenolic glycolipids originating from the *Mycobacterium tuberculosis* complex and these are at present being investigated for their immunomodulatory capabilities.

EXPERIMENTAL:

General procedures

All reactions were carried out in oven-dried glassware (80 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under N_2 atmosphere (balloon). Commercially available reagents and solvents (Aldrich Chemistry, Honeywell, Merck, Fischer Scientific, Biosolve, Fluka, VWR Chemicals, Acros Organics, Fluorochem, Brunschwig, Carbosynth) were used as received unless stated otherwise.

Solvents for reactions were reagent grade and dried by storage over flame dried 4 Å molecular sieves when needed. Tf_2O used in glycosylations was dried by distillation over P_2O_5 and stored under N_2 atmosphere in a Schlenk flask at -20 °C. Et_2O used for column chromatography was distilled before use and stored over iron filings. EtOAc used for column chromatography was distilled before use. NEt_3 used for Sonogashira couplings was distilled from KOH, degassed with N_2, and stored over KOH for a maximum of 24 hours. DMAP used for Steglich esterifications was recrystallized from toluene before use.

Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, F254); visualization was carried out by irradiation with UV light (254 nm), and spraying with 20% H_2SO_4 in EtOH (w/v) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% H_2SO_4 or $KMnO_4$ (7.5 g/L) and K_2CO_3 (50 g/L) in H_2O, followed by charring. Additional analysis with TLC-MS was used when needed.

Column chromatography was carried out using silica gel (Fluka, 40-63 μm mesh). The column was prepared using the apolar component mentioned in the corresponding experimental. If the apolar component was pentane the product was brought up in toluene. If the apolar component was DCM the product was brought up in DCM, possibly with a few drops of methanol if needed. Colum chromatography was performed using a gradient ranging from 0% polar component up to the ratio mentioned in the corresponding experimental in 2 to 5 steps depending on the ease of separation.

NMR spectra were recorded at ambient temperature on a Bruker AV-400LIQ spectrometer. Samples were prepared in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) in $CDCl_3$ are reported in ppm relative to Me_4Si (δ: 0.00 ppm) for ^{1}H-NMR and $CDCl_3$ (δ: 77.16 ppm) for ^{13}C-NMR. Chemical shifts in CD_3OD are reported in ppm relative to H_2O (δ: 4.87 ppm) for ^{1}H-NMR and CD_3OD (δ: 49.00 ppm) for ^{13}C-NMR. ^{13}C-APT spectra are ^{1}H decoupled and structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants (J) are given in Hz. Coupling constants of anomeric carbon atoms ($J_{H1,C1}$) were determined using HMBC-GATED experiments. Optical rotations were measured on an Anton Paar Modular Circular Polarimeter MCP 100/150. High resolution mass spectra were recorded on a Synapt G2-Si or a Q Exactive HF Orbitrap equipped with an electron spray ion source positive mode. Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR.

General procedure A: Pre-activation glycosylation:

Donor (1.5 eq), Ph_2SO (2.0 eq) and TTBP (3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -60 °C after which Tf_2O (2.0 eq) was added to the solution. After stirring for 30 minutes, the acceptor (1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (1-4 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography.

General procedure B: NIS mediated glycosylation:

Donor (1.5 eq) was dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, and then dissolved in dry DCM (0.05 M) and flame-dried 3Å molecular sieves were added. DMF (24 eq) was added and the solution was cooled to 0 °C. NIS (1.5 eq) and TMSOTf (1.5 eq) were then added to the solution and the mixture was left to stir for 45 minutes. Acceptor (1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (1-4 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with NaS_2O_3 and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography.

General procedure C: Sonogashira cross coupling

Iodoaryl glycoside (1.0 eq) was dissolved in freshly distilled NEt_3 (0.05 M) together with phthiocerol (1.2 eq). A mixture of $Pd(PPh_3)_2Cl_2$, PPh_3 and CuI (ratio 1:1:2) was dissolved in freshly distilled NEt_3 and was stirred for 15 minutes at 40 °C. Of this cocktail, enough was added to the sugar/alkyne mixture to amount to 0.05 eq $Pd(PPh_3)_2Cl_2$, 0.05 eq PPh_3 and 0.1 eq CuI. The reaction was allowed to stir at 40 °C until the complete consumption of the starting material as indicated by TLC (2-16 h). The solvent was then removed under a stream of N_2. The crude was transferred to a silica column in toluene and the column was flushed with toluene. Thereafter the product was purified by means of column chromatography.

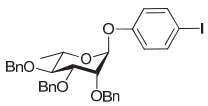
General procedure D: Esterification with mycocerosic acid

Starting material (1.0 eq) was dissolved in dry DCM (0.05 M) together with mycocerosic acid (3.0 eq) and DMAP (9 eq). The resulting mixture was cooled to 0 °C after which DIC (6.0 eq) was added. The reaction was allowed to stir for 16 hours while warming to rT, after which it was warmed to 40 °C and stirred for a further 5 hours. The reaction mixture was then diluted with Et_2O and the organic layer was washed 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography. Note: In order to detect the most prevalent byproducts, staining with $KMnO_4$ is required.

General procedure E: Hydrogenation

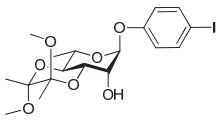
Starting material (1.0 eq) was dissolved in a mixture of THF and EtOH (1:1, 0.007 M) ans the solution was purged with N_2. Pd/C (10%, 1.0 eq) was then added to the solution and the resulting mixture was purged with H_2. The reaction was left to stir under H_2 atmosphere until TLC complete conversion of the starting material and reaction intermediates to a single low running spot (DCM-MeOH 19:1). The reaction mixture was then purged with N_2 and filtered over celite. Purification by means of column chromatography.

4-iodophenyl 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranoside (9)



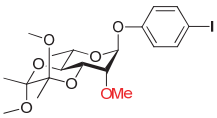
Compound **10** (0.73 g, 2.0 mmol, 1.0 eq) was dissolved in dry DMF (20 mL, 0.1 M) and BnBr (1.42 mL, 12 mmol, 6.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.29 g, 7.2 mmol, 3.6 eq) was then added. The reaction mixture was warmed to rt while stirring for 16 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 19:1) gave the title compound (1.24 g, 1.96 mmol, 98 %) as a pale oil. $[\alpha]_D^{25}$ = -62.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.54-7.50 (m, 2H, C*H*$_{arom}$); 7.39-7.24 (m, 15H, C*H*$_{arom}$); 6.75-6.72 (m, 2H, C*H*$_{arom}$); 5.41 (d, 1H, *J* = 2.0 Hz, H-1); 4.95 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.78 (dd, 2H, *J* = 12.4, 28.8 Hz, PhC*H*$_2$); 4.73-4.64 (m, 3H, PhCH*H*, PhC*H*$_2$); 4.02 (dd, 1H, *J* = 2.8, 8.8 Hz, H-3); 3.93 (d, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.77-3.66 (m, 2H, H-4, H-5); 1.29 (d, 3H, *J* = 5.2 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.1, 138.5 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 138.1 (C$_{q,arom}$); 128.6, 128.5, 128.5, 128.1, 128.1, 128.0, 127.8, 127.8, 118.7 (*C*H$_{arom}$); 96.3 (C-1); 84.8 (*C*I$_{arom}$); 80.4 (C-4); 79.8 (C-3); 75.6 (Ph*C*H$_2$); 74.6 (C-2); 73.2, 72.5 (Ph*C*H$_2$); 69.0 (C-5); 18.1 (C-6). IR (thin film, cm^{-1}): 1028, 1050, 1098, 1115, 1137, 1232, 1454, 1484. HRMS calculated for $C_{33}H_{33}IO_5Na$ 659.1270 [M+Na]$^+$; found 659.1274.

4-iodophenyl 3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α-L-rhamnopyranoside (11)



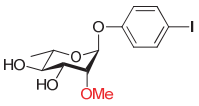
Compound **10** (0.366 g, 1.0 mmol, 1.0 eq) was dissolved in MeOH (10 mL, 0.1 M) and trimethyl orthoformate (0.44 mL, 4.0 mmol, 4.0 eq) and 2,3-butanedione (0.1 mL, 1.1 mmol, 1.1 eq) were added to the solution. The mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (12 µL, 0.1 mmol, 0.1 eq) was added to the solution. The mixture was stirred for 72 hours after which the reaction was quenched by addition of NEt_3 (2.5 mL). The resulting mixture was concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 3:2) gave the title compound (0.37 g, 0.77 mmol, 77%) as a pale oil. $[\alpha]_D^{25}$ = -136.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.54 (m, 2H, C*H*$_{arom}$); 6.84-6.80 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.2 Hz, H-1); 4.15-4.10 (m, 2H, H-2, H-3); 3.88-3.76 (m, 2H, H-4, H-5); 3.34 (s, 3H, OC*H*$_{3,BDA}$); 3.25 (s, 3H, OC*H*$_{3,BDA}$); 2.95 (bs, 1H, 2-O*H*); 1.36 (s, 3H, CC*H*$_{3,BDA}$); 1.31 (s, 3H, CC*H*$_{3,BDA}$); 1.22 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.0 (C$_{q,arom}$); 138.4, 118.7 (*C*H$_{arom}$); 100.4, 100.0 (*C*CH$_{3,BDA}$); 97.7 (C-1); 84.8 (*C*I$_{arom}$); 69.7 (C-2); 68.2 (C-4); 68.1 (C-3); 67.7 (C-5); 48.3, 47.8 (O*C*H$_{3,BDA}$); 17.9, 17.8 (C*C*H$_{3,BDA}$); 16.6 (C-6). IR (thin film, cm^{-1}): 1002, 1017, 1037, 1053, 1076, 1115, 1143, 1233, 1378, 1485, 2932, 3470. HRMS calculated for $C_{18}H_{25}IO_7Na$ 503.0543 [M+Na]$^+$; found 503.05388.

4-iodophenyl 2-*O*-methyl-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α-L-rhamnopyranoside (12)



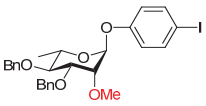
Compound **11** (2.95 g, 6.15 mmol, 1.0 eq) was dissolved in dry DMF (50 mL, 0.12 M) and MeI (0.57 mL, 9.23 mmol, 1.5 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.49 g, 12.3 mmol, 2.0 eq) was then added. The reaction mixture was warmed to rt while stirring for 4 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (2.64 g, 5.34 mmol, 87%) as a pale oil. $[\alpha]_D^{25}$ = -181.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.55 (m, 2H, C*H*$_{arom}$); 6.84-6.80 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 4.17 (dd, 1H, *J* = 3.0, 9.8 Hz, H-3); 3.83-3.74 (m, 2H, H-4, H-5); 3.63 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.56 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.25 (s, 3H, OC*H*$_3$); 1.36 (s, 3H, OC*H*$_3$); 1.30 (s, 3H, OC*H*$_3$); 1.22 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 138.5, 118.7 (*C*H$_{arom}$); 100.2, 99.8 (*C*CH$_{3,BDA}$); 96.1 (C-1); 84.9 (*C*I$_{arom}$); 78.5 (C-2); 68.6 (C-4); 68.3 (C-3); 68.0 (C-5); 59.6 (O*C*H$_3$); 48.2, 47.8 (O*C*H$_{3,BDA}$); 18.0 (*C*H$_{3,BDA}$); 16.8 (C-6). IR (thin film, cm^{-1}): 1037, 1055, 1080, 1115, 1142, 1232, 1484. HRMS calculated for $C_{19}H_{27}IO_7Na$ 517.0699 $[M+Na]^+$; found 517.0695.

4-iodophenyl 2-*O*-methyl-α-L-rhamnopyranoside (13)



Compound **12** (0.216 g, 0.44 mmol, 1.0 eq) was dissolved in a mixture of AcOH and H_2O (4:1, 50 mL, 0.01 M) and the solution was warmed to 80 °C. The reaction was allowed to stir for 4 hours after which it was concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-EtOAc 3:7) gave the title compound (0.108 g, 0.28 mmol, 65%) as a clear oil. $[\alpha]_D^{25}$ = -68.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.56 (m, 2H, C*H*$_{arom}$); 6.89-6.83 (m, 2H, C*H*$_{arom}$); 5.53 (d, 1H, *J* = 1.6 Hz, H-1); 3.93 (dd, 1H, *J* = 2.8, 8.8 Hz, H-3); 3.70-3.63 (m, 2H, H-2, H-5); 3.53 (s, 3H, OC*H*$_3$); 3.46 (t, 1H, *J* = 9.4 Hz, H-4); 1.26 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.3 (C$_{q,arom}$); 138.5, 118.7 (*C*H$_{arom}$); 94.6 (C-1); 85.0 (*C*I$_{arom}$); 80.1 (C-2); 73.7 (C-4); 71.4 (C-3); 68.8 (C-5); 59.2 (O*C*H$_3$); 17.7 (C-6). IR (thin film, cm^{-1}): 1022, 1067, 1112, 1232, 1484, 3410. HRMS calculated for $C_{13}H_{17}IO_5Na$ 403.0018 $[M+Na]^+$; found 403.0013.

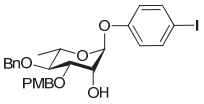
4-iodophenyl 2-*O*-methyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (8)



Compound **13** (74 mg, 0.2 mmol, 1.0 eq) was dissolved in dry DMF (2 mL, 0.1 M) after which BnBr (71 μL, 0.6 mmol, 3.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 32 mg, 0.8 mmol, 4.0 eq) was added. The mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (94 mg, 0.17 mmol, 84%) as a pale oil. $[\alpha]_D^{25}$ = -92.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.53 (m, 2H, C*H*$_{arom}$); 7.44-7.40 (m, 2H, C*H*$_{arom}$); 7.37-7.26 (m, 8H, C*H*$_{arom}$); 6.82-6.78 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 4.95 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.81-4.75 (m, 2H, PhC*H*$_2$); 4.63 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.02 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 3.73-3.68 (m, 2H, H-2, H-5); 3.60-3.56 (m, 4H, H-4, OC*H*$_3$); 1.26 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2,

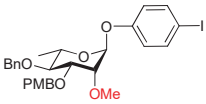
138.5 ($C_{q,arom}$); 138.5 (CH_{arom}); 138.4 ($C_{q,arom}$); 138.4, 128.6, 128.5, 128.1, 128.0, 127.9, 127.9, 118.7 (CH_{arom}); 95.6 (C-1); 84.3 (CI_{arom}); 80.3 (C-4); 79.6 (C-3); 78.0 (C-2); 75.7, 72.7 (PhCH_2); 69.0 (C-5); 59.8 (OCH_3); 18.1 (C-6). IR (thin film, cm^{-1}): 1047, 1138, 1178, 1232, 1454, 1484. HRMS calculated for $C_{27}H_{29}IO_5Na$ 583.0957 $[M+Na]^+$; found 583.0950.

4-iodophenyl 3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranoside (15)



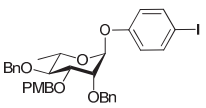
Compound **14**[26] (6.05 g, 13.3 mmol, 1.0 eq) was dissolved in toluene (500 mL, 0.03 M) and Bu_2SnO (3.63 g, 14.6 mmol, 1.1 eq) was added to the solution. The mixture was refluxed for 2 hours and then cooled to 80 °C. PMBCl (2.35 mL, 17.2 mmol, 1.3 eq) and TBAB (5.13 g, 15.9 mmol, 1.2 eq) were added to the mixture and it was refluxed for 2 hours. The reaction mixture was then concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 1:1) to give the tite compound (7.62 g, 13.2 mmol, 100%, 8:1 mixture of regioisomers) as a slightly yellow oil. $[\alpha]_D^{25}$ = -54.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.53-7.49 (m, 2H, CH_{arom}); 7.34-7.18 (m, 7H, CH_{arom}); 6.87-6.76 (m, 4H, CH_{arom}); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 4.87 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.65-4.60 (m, 3H, PhC*H*H, PhCH_2); 4.09 (s, 1H, H-2); 3.97 (dd, 1H, *J* = 3.2, 8.8 Hz, H-3); 3.77-3.71 (m, 4H, $CH_{3,PMB}$, H-5); 3.51 (t, 1H, *J* = 9.2 Hz, H-4); 3.16 (bs, 1H, 2-O*H*); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.4, 155.9 ($C_{q,arom}$); 138.3, 138.2 (CH_{arom}); 138.2, 129.8 ($C_{q,arom}$); 128.4, 127.9, 127.8, 118.6, 113.9 (CH_{arom}); 97.0 (C-1); 84.7 (CI_{arom}); 81.7 (C-4); 79.7 (C-3); 75.4 (PhCH_2); 72.0 (PhCH_2); 68.3 (C-5); 64.7 (C-2); 55.2 ($CH_{3,PMB}$); 17.9 (C-6). IR (thin film, cm^{-1}): 1028, 1072, 1234, 1249, 1484, 1513, 2925, 3483. HRMS calculated for $C_{27}H_{29}IO_6Na$ 599.0907 $[M+Na]^+$; found 599.0909.

4-iodophenyl 2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranoside (16)



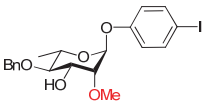
Compound **15** (6.22 g, 11.8 mmol, 1.0 eq) was dissolved in dry DMF (60 mL, 0.2 M) and MeI (1.47 mL, 23.7 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.71 g, 17.8 mmol, 1.5 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (5.56 g, 9.4 mmol, 80%) as a pale oil. $[\alpha]_D^{25}$ = -103.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.61-7.57 (m, 2H, CH_{arom}); 7.38-7.26 (m, 7H, CH_{arom}); 6.90-6.86 (m, 2H, CH_{arom}); 6.82-6.78 (m, 2H, CH_{arom}); 5.46 (d, 1H, *J* = 1.6 Hz, H-1); 4.94 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.71-4.70 (m, 2H, PhCH_2); 4.62 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.00 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.81 (s, 3H, $CH_{3,PMB}$); 3.72-3.67 (m, 1H, H-5); 3.64-3.63 (m, 1H, H-2); 3.58-3.53 (m, 4H, H-4, OCH_3); 1.26 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2, 138.6 ($C_{q,arom}$); 138.5 (CH_{arom}); 130.6 ($C_{q,arom}$); 129.7, 128.5, 128.1, 127.9, 118.7, 114.0 (CH_{arom}); 95.6 (C-1); 84.8 (CI_{arom}); 80.3 (C-4); 79.3 (C-3); 78.0 (C-2); 75.7, 72.4 (PhCH_2); 69.0 (C-5); 59.8 (OCH_3); 55.4 ($CH_{3,PMB}$); 18.1 (C-6). IR (thin film, cm^{-1}): 1098, 1139, 1233, 1249, 1484, 1513, 2924, 3462. HRMS calculated for $C_{28}H_{31}IO_6Na$ 613.1063 $[M+Na]^+$; found 613.1068.

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-L-rhamnopyranoside (17)



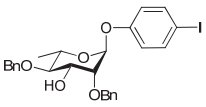
Compound **15** (7.37 g, 12.8 mmol, 1.0 eq) was dissolved in dry DMF (64 mL, 0.2 M) after which BnBr (3.0 mL, 25.6 mmol, 2 eq) and TBAI (0.47 g, 1.28 mmol, 0.1 eq) were added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.77 g, 19.2 mmol, 1.2 eq) was added. The mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) gave the title compound (6.58 g, 9.82 mmol, 77%) as a pale oil. $[\alpha]_D^{25}$ = -50.1 ° (c = 0.8, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.56-7.51 (m, 2H, C*H*$_{arom}$); 7.41-7.26 (m, 12H, C*H*$_{arom}$); 6.90-6.85 (m, 2H, C*H*$_{arom}$); 6.75-6.71 (m, 2H, C*H*$_{arom}$); 5.39 (d, 1H, *J* = 2.0 Hz, H-1); 4.95 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.78 (dd, 2H, *J* = 12.4, 34.4 Hz, PhCH_2); 4.66 (m, 3H, PhCH*H*, PhCH_2); 4.00 (dd, 1H, *J* = 3.0, 9.0 Hz, H-3); 3.90-3.88 (m, 1H, H-2); 3.82 (s, 3H, C$H_{3,PMB}$); 3.70-3.63 (m, 2H, H-4, H-5); 1.27 (d, 3H, *J* = 6.0 Hz). ^{13}C-APT NMR (101 MHz) δ: 156.2, 138.6 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 138.2, 130.6 (C$_{q,arom}$); 129.5, 128.6, 128.5, 128.1, 128.0, 127.9, 118.7, 113.9 (*C*H$_{arom}$); 96.4 (C-1); 84.7 (*C*I$_{arom}$); 80.4 (C-4); 79.6 (C-3); 75.6 (Ph*C*H$_2$); 74.7 (C-2); 73.2, 72.3 (Ph*C*H$_2$); 69.1 (C-5); 55.4 (*C*H$_{3,PMB}$); 18.2 (C-6). IR (thin film, cm^{-1}): 1029, 1137, 1233, 1248, 1484, 1513, 2921. HRMS calculated for $C_{34}H_{35}IO_6Na$ 689.1376 [M+Na]$^+$; found 689.1387.

4-iodophenyl 2-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (5)



Compound **16** (2.48 g, 2.5 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 25 mL, 0.1 M) after which a solution of HCl in HFIP (1.25 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (1.17 g, 2.48 mmol, 100%) as a pale oil. Spectroscopic data were in accordance with those previously reported in the literature.[26]

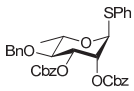
4-iodophenyl 2,4-di-*O*-benzyl-α-L-rhamnopyranoside (6)



Compound **17** (6.58 g, 9.8 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 98 mL, 0.1 M) after which a solution of HCl in HFIP (4.9 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (4.38 g, 8.0 mmol, 82%) as a pale oil. $[\alpha]_D^{25}$ = -51.5 ° (c =1.1, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.53 (m, 2H, C*H*$_{arom}$); 7.41-7.26 (m, 10H, C*H*$_{arom}$); 6.79-6.74 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 4.90 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.79 (d,1H, *J* = 11.6 Hz, PhC*H*H); 4.49-4.65 (m, 2H, PhCH*H*, PhCH*H*); 4.14-4.09 (m, 1H, H-3); 3.91-3.90 (m, 1H, H-2); 3.81-3.68 (m, 1H, H-5); 3.39 (t, 1H, *J* = 9.4 Hz, H-4); 2.33 (bs, 1H, 3-O*H*); 1.28 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2, 138.5 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 128.8, 128.6, 128.4, 128.2,

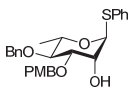
128.1, 128.0, 118.7 (*C*H$_{arom}$); 95.3 (C-1); 84.7 (*C*I$_{arom}$); 82.1 (C-4); 78.3 (C-2); 75.3, 73.5 (PhCH$_2$); 71.6 (C-3); 68.3 (C-5); 18.2 (C-6). IR (thin film, cm^{-1}): 1020, 1027, 1040, 1075, 1130, 1232, 1455, 1484, 2931, 3534. HRMS calculated for $C_{26}H_{27}IO_5Na$ 569.0801 [M+Na]$^+$; found 569.0806.

Phenyl 2,3-di-*O*-benzyloxycarbonyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (7)



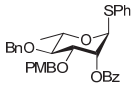
Compound **18** (376 mg, 1.09 mmol, 1.0 eq) was dissolved in DCM (11 mL, 0.1 M) and DMAP (0.66 g, 5.43 mmol, 5.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (0.61 mL, 4.34 mmol, 4.0 eq) was slowly added. The reaction was allowed to stir for 4 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (0.66 g, 1.07 mmol, 99%) as a clear oil. $[\alpha]_D^{25}$ = -48.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47-7.44 (m, 2H, C*H*$_{arom}$); 7.40-7.24 (m, 18H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.2 Hz, H-1); 5.46 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 5.22-5.14 (m, 5H, H-3, PhC*H*$_2$, PhC*H*$_2$); 4.65 (dd, 2H, *J* = 11.0, 56.2 Hz, PhC*H*$_2$); 4.28 (dq, 1H, *J* = 3.2, 6.4 Hz, H-5); 3.63 (t, 1H, *J* = 9.6 Hz, H-4); 1.33 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 154.5, 154.3 (*C*O$_{Cbz}$); 137.9, 135.1, 134.8, 133.5 (C$_{q,arom}$); 132.1, 129.3, 128.8, 128.7, 128.6, 128.5, 128.0, 128.0, 128.0 (*C*H$_{arom}$); 85.5 (C-1); 78.7 (C-4); 76.3 (C-3); 75.6 (Ph*C*H$_2$); 75.5 (C-2); 70.4, 70.2 (Ph*C*H$_2$); 69.3 (C-5); 17.8 (C-6). IR (thin film, cm^{-1}): 1029, 1036, 1100, 1241, 1275, 1384, 1455, 1751. HRMS calculated for $C_{35}H_{34}O_8SNa$ 637.18666 [M+Na]$^+$; found 637.18633.

Phenyl 3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (19)



Compound **18** (16.3 g, 47 mmol, 1.0 eq) was dissolved in toluene (500 mL, 0.09 M) and Bu_2SnO (12.9 g, 51.7 mmol, 1.1 eq) was added to the solution. The mixture was refluxed for 2 hours and then cooled to 80 °C. PMBCl (8.31 mL, 61.1 mmol, 1.3 eq) and TBAB (18.2 g, 56.4 mmol, 1.2 eq) were added to the mixture and it was refluxed for 2 hours. The reaction mixture was then concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (16.8 g, 36.1 mmol, 77%) as a slightly yellow oil. The product was used in the next step without further analysis.

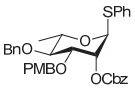
Phenyl 2-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (1)



Compound **19** (8.52 g, 18.3 mmol, 1.0 eq) was dissolved in DCM (50 mL, 0.4 M) and pyridine (2.95 mL, 36.5 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C and BzCl (4.24 mL, 36.5 mmol, 2.0 eq) was added. The reaction was allowed to stir for 4 hours while slowly warming to RT. The reaction was quenched by addition of H_2O, and the product was extracted with Et_2O (3x). The combined organic layers were washed with 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (10.4 g, 18.3 mmol, 100%) as a clear oil. $[\alpha]_D^{25}$ = -39.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.08-8.06 (m, 2H, C*H*$_{arom}$); 7.50-7.11 (m, 16H, C*H*$_{arom}$); 6.81 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.83 (d, 1H, *J* = 1.6 Hz, H-2); 5.54 (s, 1H, H-1); 4.93 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.73 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.65 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.52 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.30-4.27 (m, 1H, H-5); 4.00 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.76 (s, 3H, C*H*$_{3,PMB}$); 3.60 (t, 1H, *J* = 9.4 Hz, H-4); 1.38 (d, 3H, *J* = 6.0 Hz, H-6).

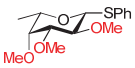
^{13}C-APT NMR (101 MHz) δ: 165.8 (CO_{Bz}); 159.4, 138.4, 134.0 ($C_{q,arom}$); 133.3, 131.8, 130.0, 129.9 (CH_{arom}); 129.8 ($C_{q,arom}$); 129.1, 128.5, 128.4, 128.2, 127.8, 127.7, 113.8 (CH_{arom}); 86.3 (C-1); 80.2 (C-4); 78.1 (C-3); 75.6, 71.4 (PhCH_2); 71.2 (C-2); 69.2 (C-5); 18.2 (C-6). IR (thin film, cm^{-1}): 1035, 1070, 1096, 1251, 1268, 1515, 1722. HRMS calculated for $C_{34}H_{34}O_6SNa$ 593.1974 [M+Na]$^+$; found 593.1976.

Phenyl 2-*O*-benzyloxycarbonyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (2)



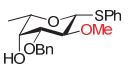
Compound **19** (8.16 g, 17.5 mmol, 1.0 eq) was dissolved in DCM (125 mL, 0.14 M) and DMAP (4.28 g, 35 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (5.0 mL, 35 mmol, 2.0 eq) was slowly added. The reaction was allowed to stir for 4 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (7.96 g, 13.3 mmol, 76%) as a clear oil. $[\alpha]_D^{25}$ = -61.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.46-7.42 (m, 2H, C*H*$_{arom}$); 7.39-7.24 (m, 15H, C*H*$_{arom}$); 6.85-6.82 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.40 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 5.17 (s, 2H, C$H_{2,Cbz}$); 4.91 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.68 (d, 1H, *J* = 11.0 Hz, PhC*H*H); 4.60 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.52 (d, 1H, *J* = 11.0 Hz, PhCH*H*); 4.21-4.17 (m, 1H, H-5); 3.88 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 3.80 (s, 3H, C$H_{3,PMB}$); 3.52 (t, 1H, *J* = 9.6 Hz, H-4); 1.32 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.4 ($C_{q,arom}$); 154.8 (CO_{Cbz}); 138.5, 135.1, 133.9 ($C_{q,arom}$); 131.9 (CH_{arom}); 129.9 ($C_{q,arom}$); 129.9, 129.2, 128.7, 128.7, 128.5, 128.5, 128.1, 127.9, 127.8 (CH_{arom}); 86.0 (C-1); 80.0 (C-4); 78.0 (C-3); 75.7 (PhCH_2); 74.8 (C-2); 71.7, 70.1 (PhCH_2); 69.3 (C-5); 55.4 ($CH_{3,PMB}$); 17.9 (C-6). IR (thin film, cm^{-1}): 1027, 1086, 1103, 1251, 1382, 1514, 1747. HRMS calculated for $C_{35}H_{36}O_7SNa$ 623.2079 [M+Na]$^+$; found 623.2074.

Phenyl 2,3,4-tri-*O*-methyl-1-thio-α-L-fucopyranoside (3)



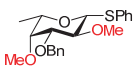
Compound **20** (0.55 g, 2.15 mmol, 1.0 eq) was dissolved in dry DMF (21.5 mL, 0.1 M) and MeI (0.8 mL, 12.9 mmol, 6.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.31 g, 7.74 mmol, 3.6 eq) was then added. The reaction mixture was warmed to rt while stirring for 2 hours after which it was quenched by addition of H_2O. The aqueous layer was extracted with Et_2O (3x) and the organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (0.56 g, 1.88 mmol, 87%) as a white amorphous solid. Spectroscopic data were in accordance with those previously reported in the literature.[37]

Phenyl 2-*O*-methyl-3-*O*-benzyl-1-thio-α-L-fucopyranoside (22)



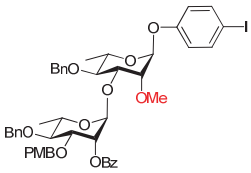
Compound **21** (1.18 g, 4.36 mmol, 1.0 eq) was dissolved in MeCN (44 mL, 0.1 M). To this solution Bu_2SnCl_2 (0.134 g, 0.44 mmol, 0.1 eq), TBABr (0.142 g, 0.44 mmol, 0.1 eq), BnBr (1.03 mL, 8.72 mmol, 2 eq) and K_2CO_3 (0.90 g, 6.54 mmol, 1.5 eq) were added and the resulting mixture was stirred for 16 hours at 80 °C. The mixture was then filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 6:4) gave the title compound (1.54 g, 4.22 mmol, 97%) as a pale oil. The product was used in the next step without further analysis.

Phenyl 2,4-di-*O*-methyl-3-*O*-benzyl-1-thio-α-L-fucopyranoside (4)



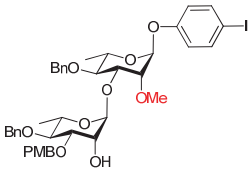
Compound **22** (1.54 g, 4.22 mmol, 1.0 eq) was dissolved in dry DMF (30 mL, 0.14 M) and MeI (0.54 mL, 8.72 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.26 g, 6.54 mmol, 1.5 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours after which it was quenched by addition of H_2O. The aqueous layer was extracted with Et_2O (3x) and the organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) gave the title compound (1.36 g, 3.63 mmol, 86%) as a white amorphous solid. $[\alpha]_D^{25}$ = -17.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.53 (m, 2H, C*H*$_{arom}$); 7.41-7.18 (m, 6H, C*H*$_{arom}$); 4.78-4.69 (m, 2H, PhC*H*$_2$); 4.47 (d, 1H, *J* = 9.2 Hz, H-1); 3.62-3.60 (m, 6H, OC*H*$_3$); 3.53-3.42 (m, 3H, H-2, H-3, H-5); 3.31 (d, 1H, *J* = 2.8 Hz, H-4); 1.29 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 138.4, 134.5 (C$_{q,arom}$); 131.6, 128.8, 128.5, 127.8, 127.7, 127.1 (*C*H$_{arom}$); 87.7 (C-1); 83.9 (C-3); 79.6 (C-4); 79.3 (C-2); 74.5 (C-5); 72.7 (PhCH$_2$); 61.8, 61.2 (OCH$_3$); 16.9 (C-6). IR (thin film, cm^{-1}): 1027, 1045, 1085, 1102, 1128, 1164, 1194, 1440, 1455, 1480. HRMS calculated for $C_{21}H_{26}O_4SNa$ 397.1495 $[M+Na]^+$; found 397.1445.

4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (25)



Prepared according to general procedure A using donor **1** (856 mg, 1.5 mmol, 1.5 eq) and acceptor **5** (470 mg, 1.0 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 4:1) as a slightly yellow oil (894 mg, 0.64 mmol, 64%). $[\alpha]_D^{25}$ = -38.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.08-8.06 (m, 2H, C*H*$_{arom}$); 7.61-7.53 (m, 3H, C*H*$_{arom}$); 7.47 (t, 2H, *J* = 7.6 Hz, C*H*$_{arom}$); 7.37-7.17 (m, 13H, C*H*$_{arom}$); 6.83-6.79 (m, 2H, C*H*$_{arom}$); 6.75-6.72 (m, 2H, C*H*$_{arom}$); 5.75 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.24 (d, 1H, *J* = 1.6 Hz, H-1'); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.85 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.69-4.58 (m, 3H, PhC*H*H, PhCH*H*, PhCH*H*); 4.45 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.23 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 4.10-4.03 (m, 2H, H-3', H-5'); 3.74-3.66 (m, 5H, H-2, H-5, C*H*$_{3,PMB}$); 3.58-3.52 (m, 5H, H-4, H-4', OC*H*$_3$); 1.30 (d, 3H, *J* = 6.0 Hz, H-6'); 1.23 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.7 (*C*O$_{Bz}$); 159.2, 156.2, 138.6 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.0 (C$_{q,arom}$); 133.3 (*C*H$_{arom}$); 130.2, 130.1 (C$_{q,arom}$); 130.0, 129.7, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.8, 118.7, 113.8 (*C*H$_{arom}$); 100.0 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 80.1 (C-4); 80.1 (C-4'); 80.0 (C-3); 78.9 (C-3'); 75.7, 75.5, 71.3 (PhCH$_2$); 69.7 (C-2); 69.1 (C-5); 68.6 (C-5'); 59.1, 55.3 (OCH$_3$); 18.5 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1027, 1044, 1098, 1139, 1178, 1234, 1249, 1269, 1484, 1513, 1722. HRMS calculated for $C_{48}H_{51}IO_{11}Na$ 953.2374 $[M+Na]^+$; found 953.2390.

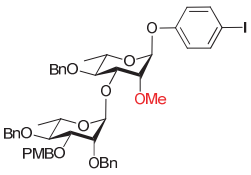
4-iodophenyl 2-*O*-methyl-3-*O*-(3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (27)



Compound **25** (0.55 g, 0.59 mmol, 1.0 eq) was dissolved in THF (3 mL, 0.2 M). A small piece of sodium was dissolved in MeOH and 3 mL of this solution was added. The reaction was stirred for 2 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic

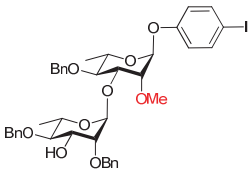
layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (394 mg, 0.48 mmol, 81%) as a pale oil. $[\alpha]_D^{25}$ = -87.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.53 (m 2H, C*H*$_{arom}$); 7.37-7.22 (m, 12H, C*H*$_{arom}$); 6.85-6.80 (m, 4H, C*H*$_{arom}$); 5.47 (s, 1H, H-1); 5.15 (s, 1H, H-1'); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.65 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.58-4.53 (m, 3H, PhCH*H*, PhC*H*$_2$); 4.17 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.03 (s, 1H, H-2'); 3.98-3.94 (m, 1H, H-5'); 3.88 (dd, 1H, *J* = 3.0, 9.0 Hz, H-3'); 3.71-3.68 (m, 5H, H-2, H-5, C*H*$_{3,PMB}$); 3.55-3.45 (m, 5H, H-4, H-4', OC*H*$_3$); 2.47 (bs, 1H, 2-O*H*); 1.34 (d, 3H, *J* = 6.4 Hz, H-6'); 1.22 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.5, 156.2, 138.5 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 138.1, 130.1 (C$_{q,arom}$); 129.6, 128.6, 128.5, 128.1, 128.0, 128.0, 127.9, 118.7, 114.0 (*C*H$_{arom}$); 101.5 (C-1'); 99.4 (C-1); 84.9 (*C*I$_{arom}$); 80.2 (C-4); 80.0 (C-2); 80.0 (C-4'); 79.6 (C-3'); 79.0 (C-3); 75.5, 75.5 (Ph*C*H$_2$); 71.9 (Ph*C*H$_2$); 69.1 (C-2'); 69.0 (C-5); 68.2 (C-5'); 59.0 (O*C*H$_3$); 55.3 (*C*H$_{3,PMB}$); 18.2 (C-6'); 18.0 (C-6). IR (thin film, cm^{-1}): 1029, 1042, 1080, 1099, 1138, 1234, 1249, 1269, 1484, 1515, 3503. HRMS calculated for $C_{41}H_{47}IO_{10}Na$ 849.2112 $[M+Na]^+$; found 849.2128.

4-iodophenyl 2-*O*-methyl-3-*O*-(2,4-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (29)



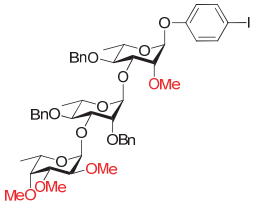
Compound **27** (0.34 g, 0.41 mmol, 1.0 eq) was dissolved in DMF (2 mL, 0.2 M) after which BnBr (0.1 mL, 0.82 mmol, 2.0 eq) and TBAI (15 mg, 0.04 mmol, 0.1 eq) were added to the solution. The mixture was cooled to 0 °C and NaH (60%, 33 mg, 0.82 mmol, 2.0 eq) was added. After stirring for 90 minutes the reaction was quenched by addition of H_2O. The aqueous layer was extracted with Et_2O (3x) and the organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (0.39 g, 0.41 mmol, 100%) as a pale oil. $[\alpha]_D^{25}$ = -63.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.53 (m, 2H, C*H*$_{arom}$); 7.45-7.16 (m, 17H, C*H*$_{arom}$); 6.84-6.79 (m, 4H, C*H*$_{arom}$); 5.46 (s, 1H, H-1); 5.14 (s, 1H, H-1'); 4.96 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.67-4.64 (m, 2H, PhCH*H*, PhC*H*H); 4.57-4.48 (m, 5H, PhCH*H*, PhC*H*$_2$); 4.18-4.15 (m, 1H, H-3); 3.95-3.90 (m, 2H, H-3', H-5'); 3.79 (s, 1H, H-2'); 3.75-3.62 (m, 6H, C*H*$_{3,PMB}$, H-2, H-5, H-4'); 3.50-3.46 (m, 4H, H-4, OC*H*$_3$); 1.37 (d, 3H, *J* = 6.0 Hz, H-6'); 1.20 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.2, 156.3, 138.8 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$) 138.4, 138.3, 130.7 (C$_{q,arom}$); 129.3, 128.6, 128.4, 128.4, 128.4, 128.1, 127.8, 127.7, 127.6, 127.6, 127.3, 118.7, 113.8 (*C*H$_{arom}$); 100.5 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 80.5 (C-4'); 80.1 (C-2, C-4); 79.6 (C-3'); 78.8 (C-3); 75.9 (C-2'); 75.4, 75.1, 72.7, 71.9 (Ph*C*H$_2$); 69.0 (C-5); 68.9 (C-5'); 59.1 (O*C*H$_3$); 55.3 (*C*H$_{3,PMB}$); 18.3 (C-6'); 18.0 (C-6). IR (thin film, cm^{-1}): 1030, 1058, 1099, 1233, 1248, 1454, 1484, 1513. HRMS calculated for $C_{48}H_{53}IO_{10}Na$ 939.2581 $[M+Na]^+$; found 939.2593.

4-iodophenyl 2-*O*-methyl-3-*O*-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (31)



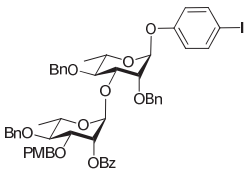
Compound **29** (0.39 g, 0.42 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 4.2 mL, 0.1 M) after which a solution of HCl in HFIP (0.21 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (0.28 g, 0.35 mmol, 84%) as a pale oil. Spectroscopic data were in accordance with those previously reported in the literature.[26]

4-iodophenyl 2-*O*-methyl-3-*O*-(2,4-di-*O*-benzyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (35)



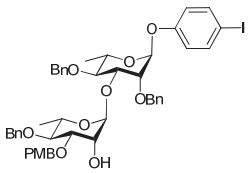
Prepared according to glycosylation procedure A using donor **3** (78 mg, 0.263 mmol, 1.5 eq) and acceptor **31** (139 mg, 0.175 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 1:1) as a pale oil (120 mg, 0.122 mmol, 70%, α/ß 5:1). Spectroscopic data were in accordance with those previously reported in the literature.[26]

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (26)



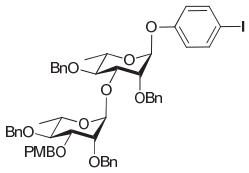
Prepared according to glycosylation procedure A using donor **1** (0.67 g, 1.17 mmol) and acceptor **6** (0.43 g, 0.78 mmol) the title compound was obtained after column chromatography (*n*-pentane-Et_2O 4:1) as a slightly yellow oil (0.60 g, 0.60 mmol, 77%). $[\alpha]_D^{25}$ = -26.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 8.06 (d, 2H, *J* = 7.2 Hz, C*H*$_{arom}$); 7.61-7.45 (m, 6H, C*H*$_{arom}$); 7.39-7.17 (m, 16H, C*H*$_{arom}$); 6.76-6.70 (m, 4H, C*H*$_{arom}$); 5.75 (d, 1H, *J* = 2.0 Hz, H-2'); 5.40 (d, 1H, *J* = 1.6 Hz, H-1); 5.28 (s, 1H, H-1'); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.86 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.79-4.61 (m, 5H, PhCH*H*, PhCH*H*, PhC*H*H, PhC*H*$_2$); 4.45 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.28 (dd, 1H, *J* = 2.8, 8.8 Hz, H-3); 4.06 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3'); 3.95-3.89 (m, 2H, H-2, H-5'); 3.74-3.66 (m, 5H, H-4, H-5, C*H*$_{3,PMB}$); 3.53 (t, 1H, *J* = 9.4 Hz, H-4'); 1.33 (d, 3H, *J* = 6.4 Hz, H-6'); 1.26 (d, 3H, *J* = 5.2 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 165.7 (*C*O$_{Bz}$); 159.3, 156.1, 138.8 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 137.9 (C$_{q,arom}$); 133.3 (*C*H$_{arom}$); 130.1 (C$_{q,arom}$); 130.1, 130.0, 129.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.7, 118.7, 113.8 (*C*H$_{arom}$); 99.6 (C-1'); 95.9 (C-1); 84.8 (*C*I$_{arom}$); 80.7 (C-4); 80.1 (C-4'); 77.6 (C-3'); 77.4 (C-2); 77.3 (C-3); 75.6, 75.3, 73.2, 71.3 (Ph*C*H$_2$); 69.5 (C-2'); 69.3 (C-5); 68.7 (C-5'); 55.3 (*C*H$_{3,PMB}$); 18.4 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1028, 1097, 1139, 1233, 1249, 1269, 1484, 1722. HRMS calculated for $C_{54}H_{55}IO_{11}Na$ 1029.2687 $[M+Na]^+$; found 1029.2698.

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (28)



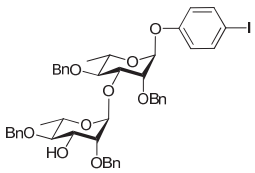
Compound **26** (0.60 g, 0.60 mmol, 1.0 eq) was dissolved in THF (3 mL, 0.2 M). A small piece of sodium was dissolved in MeOH and 3 mL of this solution was added. The reaction was stirred for 2 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (465 mg, 0.52 mmol, 86%) as a pale oil. $[\alpha]_D^{25}$ = -76.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.51 (m, 2H, C*H*$_{arom}$); 7.39-7.22 (m, 17H, C*H*$_{arom}$); 6.82-6.75 (m, 4H, C*H*$_{arom}$); 5.40 (d, 1H, *J* = 1.6 Hz, H-1); 5.20 (s, 1H, H-1'); 4.90 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.78-4.70 (m, 3H, PhC*H*H, PhC*H*$_2$); 4.65-4.55 (m, 4H, PhCH*H*, PhCH*H*, PhC*H*$_2$); 4.23 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 4.00 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2'); 3.90-3.83 (m, 3H, H-2, H-3', H-5'); 3.74-3.71 (m, 4H, H-5, C*H*$_{3,PMB}$); 3.64 (t, 1H, *J* = 9.4 Hz, H-4); 3.46 (t, 1H, *J* = 9.2 Hz, H-4'); 2.65 (bs, 1H, 2-O*H*); 1.28-1.25 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 159.5, 156.1, 138.7 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 138.0, 137.9, 130.0 (C$_{q,arom}$); 129.7, 128.7, 128.6, 128.4, 128.0, 128.0, 127.8, 127.7, 127.5, 118.8, 114.0 (*C*H$_{arom}$); 101.0 (C-1'); 95.9 (C-1); 84.9 (*C*I$_{arom}$); 80.8 (C-4); 79.9 (C-4'); 79.5 (C-3'); 77.5 (C-2, C-3); 75.5, 75.3, 73.2, 71.8 (Ph*C*H$_2$); 69.2 (C-5); 69.0 (C-2'); 68.2 (C-5'); 55.3 (*C*H$_{3,PMB}$); 18.1 (C-6); 18.1 (C-6'). IR (thin film, cm^{-1}): 1028, 1098, 1139, 1233, 1249, 1268, 1454, 1484, 1513, 3482. HRMS calculated for $C_{47}H_{51}IO_{10}Na$ 925.2425 $[M+Na]^+$; found 925.2437.

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (30)



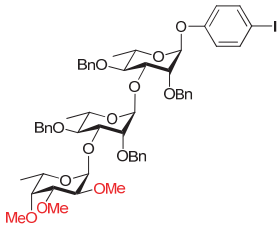
Compound **28** (0.50 g, 0.55 mmol, 1.0 eq) was dissolved in dry DMF (5.5 mL, 0.1 M) and BnBr (0.13 mL, 1.1 mmol, 2.0 eq) and TBAI (22 mg, 0.06 mmol, 0.1 eq) were added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 44 mg, 1.1 mmol, 2.0 eq) was then added. The reaction mixture was warmed to rt while stirring for 2 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (0.407 g, 0.50 mmol, 90%) as a pale oil. $[\alpha]_D^{25}$ = -54.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.52 (m, 2H, C*H*$_{arom}$); 7.39-7.20 (m, 22H, C*H*$_{arom}$); 6.78-6.75 (m, 4H, C*H*$_{arom}$); 5.38 (d, 1H, *J* = 2.0 Hz, H-1); 5.19 (s, 1H, H-1'); 4.97 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.77-4.46 (m, 9H, PhCH*H*, PhC*H*$_2$); 4.23 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.92-3.83 (m, 3H, H-2', H-3', H-5'); 3.75-3.70 (5H, H-2, H-5, C*H*$_{3,PMB}$); 3.64-3.61 (m, 2H, H-4, H-4'); 1.31 (d, 3H, *J* = 6.4 Hz, H-6'); 1.21 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.2, 156.1, 139.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.4, 138.3, 137.9, 130.7 (C$_{q,arom}$); 129.4, 128.6, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 118.7, 113.8 (*C*H$_{arom}$); 100.0 (C-1'); 96.0 (C-1); 84.8 (*C*I$_{arom}$); 80.6 (C-4'); 80.5 (C-4); 79.5 (C-3'); 77.6 (C-2', C-3); 75.8 (C-2); 75.2, 74.9, 73.2, 72.7, 72.0 (Ph*C*H$_2$); 69.2 (C-5); 68.9 (C-5'); 55.3 (*C*H$_{3,PMB}$); 18.3 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1029, 1041, 1097, 1174, 1233, 1247, 1454, 1484, 1513. HRMS calculated for $C_{54}H_{57}IO_{10}Na$ 1015.2894 $[M+Na]^+$; found 1015.2900.

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (32)



Compound **30** (0.50 g, 0.50 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 5 mL, 0.1 M) after which a solution of HCl in HFIP (0.25 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (0.40 g, 0.46 mmol, 91%) as a pale oil. $[\alpha]_D^{25}$ = -51.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.53 (m, 2H, CH_{arom}); 7.40-7.22 (m, 18H, CH_{arom}); 7.16-7.14 (m, 2H, CH_{arom}); 6.79-6.77 (m, 2H, CH_{arom}); 5.41 (d, 1H, *J* = 2.0 Hz, H-1); 5.24 (s, 1H, H-1'); 4.91 (d, 1H, *J* = 11.4 Hz, PhC*H*H); 4.81-4.71 (m, 4H, PhCH_2); 4.64 (d, 1H, *J* = 11.4 Hz, PhCH*H*); 4.33 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.28 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 4.12 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.00-3.88 (m 1H, H-3'); 3.83-3.68 (m, 5H, H-2, H-2', H-5, H-5', H-4); 3.33 (t, 1H, *J* = 9.2 Hz, H-4'); 2.31 (bs, 1H, 3-O*H*); 1.30 (d, 3H, *J* = 6.0 Hz, H-6'); 1.26 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.1, 138.8, 138.4 ($C_{q,arom}$); 138.4 (*C*H$_{arom}$); 137.8 ($C_{q,arom}$); 128.6, 128.6, 128.5, 128.4, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 126.9, 118.7 (*C*H$_{arom}$); 99.0 (C-1'); 96.0 (C-1); 84.9 (*C*I$_{arom}$); 82.2 (C-4'); 80.8 (C-4); 79.1 (C-2'); 77.5 (C-2, C-3); 75.0, 74.9, 73.2, 72.6 (Ph*C*H$_2$); 71.7 (C-3'); 69.3 (C-5); 68.0 (C-5'); 18.2 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1028, 1043, 1097, 1136, 1231, 1454, 1484, 3564. HRMS calculated for $C_{46}H_{49}IO_9Na$ 895.2319 $[M+Na]^+$; found 895.2335.

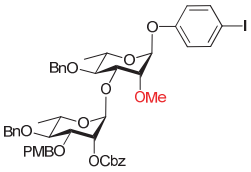
4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (37)



Prepared according to glycosylation procedure B using donor **3** (52 mg, 0.17 mmol, 1.5 eq) and acceptor **32** (0.10 g, 0.12 mmol, 1.0 eq). The title compound was obtained after column chromatography (DCM-EtOAc 19:1) as a slightly yellow oil (0.11 g, 0.10 mmol, 89%, α:ß 4:1). $[\alpha]_D^{25}$ = -86.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.56-7.53 (m, 2H, CH_{arom}); 7.41 (d, 2H, *J* = 7.2 Hz, CH_{arom}); 7.34-7.20 (m, 18H, CH_{arom}); 6.80-6.78 (m, 2H, CH_{arom}); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.29 (H-1'); 5.20 (s, 1H, H-1''); 5.19 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.85 (d, 1H, *J* = 11.8 Hz, PhC*H*H); 4.78 (s, 2H, PhCH_2); 4.72 (d, 1H, *J* = 11.8 Hz, PhCH*H*); 4.58 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.47 (d, 1H, *J* = 12.2 Hz, PhC*H*H); 4.30 (dd, 1H, *J* = 2.8, 9.2 Hz, H-3); 4.15 (d, 1H, *J* = 12.2 Hz, PhCH*H*); 4.10 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3'); 3.93 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.88-3.84 (m, 1H, H-5'); 3.80-3.67 (m, 4H, H-2', H-5, H-4, H-5''); 3.61 (t, 1H, *J* = 9.2 Hz, H-4'); 3.55-3.50 (m, 8H, H-2'', H-4'', OCH_3); 3.28 (s, 3H, OCH_3); 3.21 (s, 1H, H-3''); 1.29 (d, 3H, *J* = 6.0 Hz, H-6'); 1.24 (d, 3H, *J* = 6.0 Hz, H-6); 1.02 (d, 3H, *J* = 6.4 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.1, 139.3, 138.5, 138.5 ($C_{q,arom}$); 138.4 (*C*H$_{arom}$); 137.8 ($C_{q,arom}$); 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, 127.3, 127.3, 126.9, 118.7 (*C*H$_{arom}$); 99.6 (C-1''); 99.0 (C-1'); 95.9 (C-1); 84.8 (*C*I$_{arom}$); 80.5 (C-4''); 80.4 (C-4); 80.0 (C-4'); 79.2 (C-3'); 78.8 (C-2'); 78.0 (C-3, C-3''); 77.9 (C-2''); 77.8 (C-2); 74.8, 74.6, 73.2, 71.4 (Ph*C*H$_2$); 69.3 (C-5); 68.9 (C-5'); 66.4 (C-5''); 61.8, 59.1, 58.1 (O*C*H$_3$); 18.2 (C-6'); 18.0 (C-6); 16.7 (C-6''). IR (thin film, cm^{-1}): 1030, 1043,

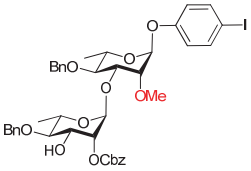
1095, 1129, 1233, 1455, 1484, 1497. HRMS calculated for $C_{55}H_{65}IO_{13}Na$ 1083.3368 $[M+Na]^+$; found 1083.3385.

4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (23)



Prepared according to glycosylation procedure A using donor **2** (0.41 g, 0.68 mmol, 1.5 eq) and acceptor **5** (214 mg, 0.46 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 4:1) as a slightly yellow oil (299 mg, 0.311 mmol, 68%). $[\alpha]_D^{25}$ = -21.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.38-7.19 (m, 17H, C*H*$_{arom}$); 6.81 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 6.77 (dd, 2H, *J* = 2.0, 6.4 Hz, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 2.0 Hz, H-1); 5.31 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 5.19 (d, 1H, *J* = 1.6 Hz, H-1'); 5.15 (d, 2H, *J* = 2.0 Hz, PhC*H*$_2$); 4.91 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.80 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.64-4.55 (m, 3H, PhCH*H*, PhC*H*H, PhC*H*$_2$); 4.45 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.20 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 3.99-3.94 (m, 2H, H-3', H-5'); 3.72-3.65 (m, 5H, H-2, H-5, C*H*$_{3,PMB}$); 3.55-3.46 (m, 5H, H-4, H-4', OC*H*$_3$); 1.34 (d, 3H, *J* = 6.0 Hz, H-6'); 1.22 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.3, 156.2 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.6 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.0, 135.2, 130.2, 129.7 (C$_{q,arom}$); 128.7, 128.7, 128.6, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.6, 118.7, 113.8 (*C*H$_{arom}$); 99.6 (C-1'); 94.8 (C-1); 84.9 (*C*I$_{arom}$); 80.1 (C-4); 79.9 (C-4'); 79.9 (C-2); 78.8 (C-3); 77.5 (C-3'); 75.6 (Ph*C*H$_2$); 73.3 (C-2'); 71.6, 70.0 (Ph*C*H$_2$); 69.0 (C-5); 68.7 (C-5'); 59.1 (O*C*H$_3$); 55.3 (*C*H$_{3,PMB}$); 18.2 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1029, 1099, 1175, 1251, 1384, 1444, 1455, 1482, 1514, 1747. HRMS calculated for $C_{49}H_{53}IO_{12}Na$ 983.2479 $[M+Na]^+$; found 983.2474.

4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (33)

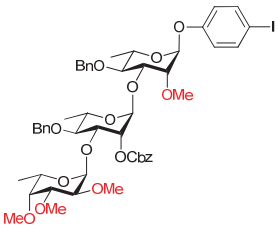


Compound **23** (0.25 g, 0.26 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 2.6 mL, 0.1 M) after which a solution of HCl in HFIP (0.13 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (194 mg, 0.23 mmol, 89%) as a pale oil. $[\alpha]_D^{25}$ = -97.5 ° (c =1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.54 (m, 2H, C*H*$_{arom}$); 7.39-7.24 (m, 15H, C*H*$_{arom}$); 6.83-6.80 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.22 (d, 1H, *J* = 1.2 Hz, H-1'); 5.14 (s, 2H, PhC*H*$_2$); 5.08 (dd, *J* = 1.6, 3.2 Hz, H-2'); 4.87-4.84 (m, 2H, PhC*H*H, PhC*H*H); 4.70 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.58 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.22-4.16 (m, 2H, H-3, H-3'); 3.97-3.93 (m, 1H, H-5'); 3.71-3.68 (m, 2H, H-2, H-5); 3.57-3.52 (m, 4H, H-4, OC*H*$_3$); 3.41 (t, 1H, *J* = 9.4 Hz, H-4'); 2.18 (bs, 1H, 3'-O*H*); 1.38 (d, 3H, *J* = 6.4 Hz, H-6'); 1.22 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.3, 138.1, 134.9 (C$_{q,arom}$); 128.8, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 118.7 (*C*H$_{arom}$); 99.2 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 81.7 (C-4'); 80.3 (C-4); 80.0 (C-2); 78.6 (C-3); 76.6 (C-2'); 75.6, 75.5, 70.3 (Ph*C*H$_2$); 70.3 (C-3'); 69.1 (C-5); 68.3 (C-5'); 59.1 (O*C*H$_3$); 18.2 (C-6'); 18.1 (C-6).

IR (thin film, cm^{-1}): 1020, 1043, 1098, 1138, 1233, 1262, 1484, 1747, 3444. HRMS calculated for $C_{41}H_{45}IO_{11}Na$ 863.1904 $[M+Na]^+$; found 863.1889.

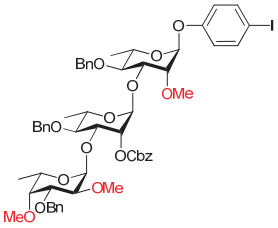
4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (36)

Prepared according to glycosylation procedure B using donor **3** (48 mg, 0.16 mmol) and acceptor **33** (89 mg, 0.11 mmol) the title compound was obtained after column chromatography (DCM-EtOAc 9:1) as a pale oil (80 mg, 78µmol, 73%, α/ß 10:1). $[\alpha]_D^{25}$ = -99.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.54 (m, 2H, C*H*$_{arom}$); 7.42-7.26 (m, 15H, C*H*$_{arom}$); 6.82-6.80 (m, 2H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.10 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.19 (dd, 2H, *J* = 2.8, 9.6 Hz, H-3, H-3'); 4.04-3.97 (m, 1H, H-5); 3.81 (q, 1H, *J* = 6.8 Hz, H-5''); 3.73 (dd, 1H, *J* = 2.0, 6.4 Hz, H-2); 3.71-3.61 (m, 1H, H-5'); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.27 (d, 1H, *J* = 2.0 Hz, H-4''); 1.34 (d, 3H, *J* = 6.0 Hz, H-6); 1.19 (d, 3H, *J* = 6.4 Hz, H-6'); 0.97 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.1, 135.2 (*C*H$_{arom}$); 128.9, 128.9, 128.8, 128.5, 12.4, 127.9, 127.6, 127.5, 118.7 (*C*H$_{arom}$); 100.0 (C-1''); 99.5 (C-1'); 94.5 (C-1); 84.9 (*C*I$_{arom}$); 80.3 (C-4'); 80.1 (C-4); 80.0 (C-2); 79.8 (C-3''); 79.6 (C-3'); 79.3 (C-4'); 78.3 (C-3); 77.7 (C-2''); 76.8 (C-2'); 75.7, 75.1, 70.1 (Ph*C*H$_2$); 69.0 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2 (O*C*H$_3$); 18.2 (C-6); 18.1 (C-6'); 16.3 (C-6''). IR (thin film, cm^{-1}): 1045, 1099, 1138, 1178, 1196, 1233, 1262, 1358, 1384, 1454, 1484, 1747. HRMS calculated for $C_{50}H_{61}IO_{15}Na$ 1051.2953 $[M+Na]^+$; found 1051.2947.



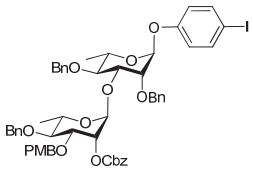
4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,4-di-*O*-methyl-3-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (39)

Prepared according to glycosylation procedure B using donor **4** (72 mg, 0.19 mmol, 1.5 eq) and acceptor **33** (107 mg, 0.127 mmol, 1.0 eq). The title compound was obtained after column chromatography (DCM-EtOAc 19:1) as a slightly yellow oil (115 mg, 0.104 mmol, 82%, α/ß 5:1). $[\alpha]_D^{25}$ = -80.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.54 (m, 2H, C*H*$_{arom}$); 7.39-7.24 (m, 20H, C*H*$_{arom}$); 6.81 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.48 (s, 1H, H-1); 5.22-5.08 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.92 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.72 (dd, 2H, *J* = 12.4, 28.8 Hz, PhC*H*$_2$); 4.58-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.21-4.17 (m, 2H, H-3, H-3'); 4.03-3.96 (m, 1H, H-5); 3.83 (q, 1H, *J* = 6.4 Hz, H-5''); 3.79-3.63 (m, 4H, H-2, H-2'', H-3'', H-5'); 3.55-3.51 (m, 8H, H-4, H-4', OC*H*$_3$); 3.36 (s, 3H, OC*H*$_3$); 3.24 (d, 1H, *J* = 1.6 Hz, H-4''); 1.35 (d, 3H, *J* = 6.0 Hz, H-6); 1.21 (d, 3H, *J* = 6.4 Hz, H-6'); 0.95 (d, 3H, *J* = 6.4 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 139.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.1, 135.2 (C$_{q,arom}$); 128.8, 128.8, 128.7, 128.7, 128.5, 128.5, 128.5, 128.4, 127.9, 127.8, 127.6, 127.4, 118.7 (*C*H$_{arom}$); 100.1 (C-1''); 99.5 (C-1'); 94.5 (C-1); 84.9 (*C*I$_{arom}$); 80.5 (C-4''); 80.0 (C-3'); 79.8 (C-2); 79.6 (C-4 and C-4'); 78.6 (C-3); 78.4 (C-3''); 78.2 (C-2''); 76.7 (C-2'); 75.7, 75.2, 72.7, 70.1 (Ph*C*H$_2$); 69.0 (C-5'); 68.7 (C-5); 67.2 (C-5''); 61.9, 59.4,



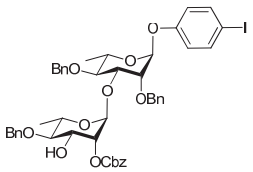
58.8 (O*C*H$_3$); 18.2 (C-6); 18.1 (C-6'); 16.2 (C-6''). IR (thin film, cm^{-1}): 1046, 1099, 1178, 1232, 1264, 1455, 1484, 1747. HRMS calculated for $C_{56}H_{65}IO_{15}Na$ 1127.3266 [M+Na]$^+$; found 1127.3263.

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (24)



Prepared according to glycosylation procedure A using donor **2** (0.46 g, 0.75 mmol, 1.5 eq) and acceptor **6** (273 mg, 0.5 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et$_2$O 4:1) as a slightly yellow oil (333mg, 0.32 mmol, 64%). $[\alpha]_D^{25}$ = -40.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.51 (m, 2H, C*H*$_{arom}$); 7.39-7.19 (m, 22H, C*H*$_{arom}$); 6.77-6.72 (m, 4H, C*H*$_{arom}$); 5.38 (d, 1H, *J* = 1.6 Hz, H-1); 5.30 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 5.24 (d, 1H, *J* = 1.6 Hz, H-1'); 5.17-5.10 (m, 2H, PhC*H*$_2$); 4.92 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.82 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.71 (dd, 2H, *J* = 12.0, 22.0 Hz, PhC*H*$_2$); 4.64-4.58 (m, 3H, PhCH*H*, PhCH*H*, PhC*H*H); 4.44 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.25 (dd, 1H, *J* = 3.0, 9.0 Hz, H-3); 3.95 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3'); 3.87-3.83 (m, 2H, H-2, H-5'); 3.73-3.64 (m, 5H, H-4, H-5, C*H*$_{3,PMB}$); 3.46 (t, 1H, *J* = 9.4 Hz, H-4'); 1.28-1.24 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 159.3, 156.1 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.4 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 138.0, 137.8, 135.2, 130.1 (C$_{q,arom}$); 129.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.9, 127.9, 127.7, 118.7, 113.8 (*C*H$_{arom}$); 99.2 (C-1'); 95.9 (C-1); 84.9 (*C*I$_{arom}$); 80.7 (C-4); 79.8 (C-4'); 77.4, 77.3 (C-2, C-3, and C-3'); 75.5, 75.4, 73.2 (Ph*C*H$_2$); 73.1 (C-2'); 71.6, 70.0 (Ph*C*H$_2$); 69.2 (C-5); 68.7 (C-5'); 55.3 (*C*H$_{3,PMB}$); 18.1 (C-6 and C-6'). IR (thin film, cm^{-1}): 1029, 1050, 1073, 1093, 1140, 1233, 1262, 1455, 1484, 1749, 2932. HRMS calculated for $C_{55}H_{57}IO_{12}Na$ 1059.2792 [M+Na]$^+$; found 1059.2778.

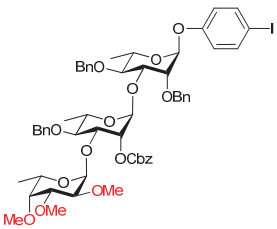
4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyloxycarbonyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (34)



Compound **24** (113 mg, 0.109 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 1.08 mL, 0.1 M) after which a solution of HCl in HFIP (54 µL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et$_2$O 7:3) gave the title compound (86 mg, 94 µmol, 86%) as a pale oil. $[\alpha]_D^{25}$ = -57.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.56-7.52 (m, 2H, C*H*$_{arom}$); 7.39-7.23 (m, 20H, C*H*$_{arom}$); 6.78-6.74 (m, 2H, C*H*$_{arom}$); 5.41 (d, 1H, *J* = 2.0 Hz, H-1); 5.25 (s, 1H, H-1'); 5.13 (s, 2H, PhC*H*$_2$); 5.10 (dd, 1H, *J* = 2.0, 3.6 Hz, H-2'); 4.87 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.81 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.74 (s, 2H, PhC*H*$_2$); 4.68 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.61 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.25 (dd, 1H, *J* = 2.8, 8.8 Hz, H-3); 4.13 (dd, 1H, *J* = 2.8, 9.2 Hz, H-3'); 3.88-3.83 (m, 2H, H-2, H-5'); 3.74-3.66 (m, 2H, H-4, H-5); 3.39 (t, 1H, *J* = 9.0 Hz, H-4'); 2.15 (bs, 1H, O*H*); 1.30 (d, 3H, *J* = 6.4 Hz, H-6'); 1.26 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.1 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.1, 137.8, 134.9 (C$_{q,arom}$); 128.8, 128.8, 128.7, 128.7, 128.6, 128.5, 128.1, 128.0, 128.0, 127.9, 127.8, 118.7 (*C*H$_{arom}$); 98.9 (C-1'); 95.8 (C-1); 84.9 (*C*I$_{arom}$); 81.7 (C-4'); 80.8 (C-4); 77.5 (C-2 and C-3); 76.4 (C-2'); 75.5, 75.3, 73.1 (Ph*C*H$_2$); 70.4 (C-3); 70.3 (Ph*C*H$_2$); 69.2 (C-5);

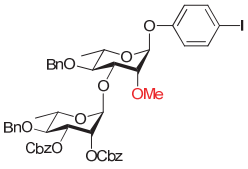
68.3 (C-5'); 18.1 (C-6 and C-6'). IR (thin film, cm^{-1}): 1000, 1029, 1043, 1096, 1136, 1232, 1264, 1454, 1484, 1749, 2931, 3504. HRMS calculated for $C_{47}H_{49}IO_{11}Na$ 939.2217 $[M+Na]^+$; found 939.2212.

4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (38)



Prepared according to glycosylation procedure B using donor **3** (40 mg, 0.14 mmol) and acceptor **34** (81 mg, 0.09 mmol) the title compound was obtained after column chromatography (DCM-EtOAc 15:1) as a pale oil (73 mg, 66 µmol, 73%, α/ß 7:1). $[\alpha]_D^{25}$ = -78.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.52 (m, 2H, CH_{arom}); 7.40-7.22 (m, 20H, CH_{arom}); 6.76 (d, 2H, *J* = 8.8 Hz, CH_{arom}); 5.43 (s, 1H, H-1); 5.27 (s, 1H, H-1'); 5.20-5.09 (m, 5H, H-1'', H-2', PhC*H*H, PhCH_2); 4.94 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.74 (dd, 2H, *J* = 12.0, 16.4 Hz, PhCH_2); 4.59-4.55 (m, 2H, PhCH*H*, PhCH*H*); 4.25 (dd, 1H, *J* = 2.8, 8.4 Hz, H-3); 4.18 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3'); 3.92-3.85 (m, 3H, H-2, H-5', H-5''); 3.72-3.62 (m, 2H, H-4, H-5); 3.57-3.44 (m, 9H, H-2'', H-4', H-4'', OCH_3); 3.29 (s, 1H, H-3''); 3.28 (s, 3H, OCH_3); 1.28 (d, 3H, *J* = 6.4 Hz, H-6); 1.21 (d, 3H, *J* = 5.2 Hz, H-6'); 1.03 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.1 ($C_{q,arom}$); 154.8 (CO_{Cbz}); 139.1 ($C_{q,arom}$); 138.4 (CH_{arom}); 138.2, 137.8, 135.2 ($C_{q,arom}$); 128.8, 128.8, 128.7, 128.4, 128.4, 128.4, 128.3, 128.0, 127.8, 127.4, 127.4, 118.7 (CH_{arom}); 99.8 (C-1''); 99.0 (C-1'); 95.6 (C-1); 84.8 (CI_{arom}); 80.4 (C-4); 80.3 (C-4'); 79.7 (C-4''); 79.3 (C-3''); 78.3 (C-3); 77.8 (C-2 and C-3'); 77.7 (C-2''); 76.6 (C-2'); 75.5, 74.9, 73.1, 70.0 (PhCH_2); 69.2 (C-5); 68.7 (C-5'); 67.1 (C-5''); 61.9, 59.1, 58.1 (OCH_3); 18.1 (C-6 and C-6'); 16.4 (C-6''). IR (thin film, cm^{-1}): 1042, 1098, 1130, 1233, 1262, 1455, 1484, 1747. HRMS calculated for $C_{56}H_{65}IO_{15}Na$ 1127.3266 $[M+Na]^+$; found 1127.3255.

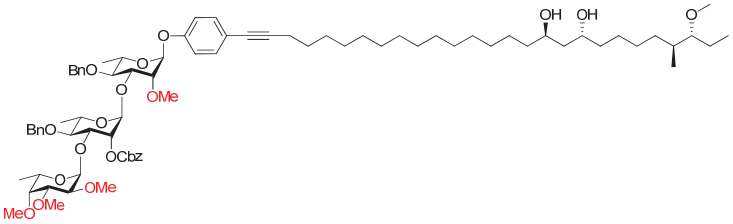
4-iodophenyl 2,4-di-*O*-benzyl-3-*O*-(2,3-di-*O*-benzyloxycarbonyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (40)



Prepared according to glycosylation procedure A using donor **7** (90 mg, 0.146 mmol, 1.5 eq) and acceptor **5** (46 mg, 98 µmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 3:1) as a pale oil (62 mg, 64 µmol, 65%). $[\alpha]_D^{25}$ = -46.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.53 (m, 2H, CH_{arom}); 7.38-7.22 (m, 20H, CH_{arom}); 6.84-6.79 (m, 2H, CH_{arom}); 5.46 (d, 1H, *J* = 1.6 Hz, H-1); 5.34-5.29 (m, 2H, H-2', H-3'); 5.19 (d, 1H, *J* = 1.6 Hz, H-1'); 5.16 (d, 2H, *J* = 1.2 Hz, PhCH_2); 5.12 (s, 2H, PhCH_2); 4.90 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.73 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.62-4.57 (m, 2H, PhCH*H*, PhCH*H*); 4.19 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 4.06 (dq, 1H, *J* = 3.6, 6.4 Hz, H-5'); 3.72-3.66 (m, 2H, H-2, H-5); 3.62-3.55 (m, 2H, H-4, H-4'); 3.52 (s, 3H, OCH_3); 1.35 (d, 3H, *J* = 6.4 Hz, H-6'); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2 ($C_{q,arom}$); 154.5, 154.4 (CO_{Cbz}); 138.5 (CH_{arom}); 138.2, 138.0, 135.2, 134.9 ($C_{q,arom}$); 128.8, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.8, 118.7 (CH_{arom}); 99.3 (C-1'); 94.8 (C-1); 84.9 (CI_{arom}); 79.9 (C-2 and C-4); 79.6 (C-3); 78.5 (C-4'); 76.0 (C-3'); 75.7, 75.5 (PhCH_2); 74.1 (C-2'); 70.3, 70.1 (PhCH_2); 69.1 (C-5); 68.6 (C-5'); 59.1 (OCH_3); 18.1 (C-6); 18.1 (C-6'). IR (thin film, cm^{-1}): 1029, 1043, 1059, 1063, 1079, 1099,

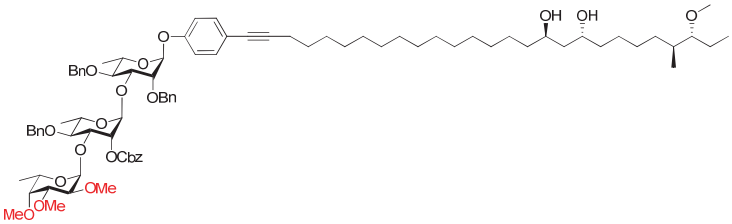
1126, 1236, 1273, 1455, 1484, 1751. HRMS calculated for $C_{49}H_{51}IO_{13}Na$ 997.22666 $[M+Na]^+$; found 997.22558.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (41)



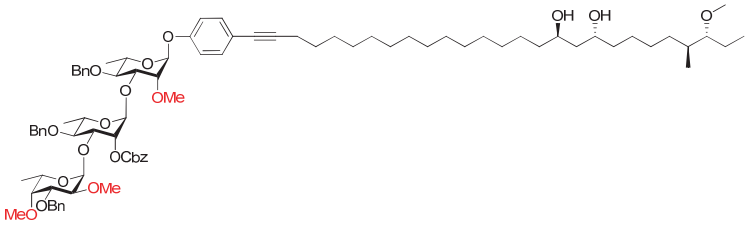
The title compound was synthesized according to general procedure C using **36** (65 mg, 63 µmol, 1.0 eq) and phthiocerol (34 mg, 74 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the title compound (77 mg, 57 µmol, 90%) as a pale oil. $[\alpha]_D^{25}$ = -78.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.41-7.26 (m, 17H, C*H*$_{arom}$); 6.94 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 5.52 (d, 1H, *J* = 1.6 Hz, H-1); 5.23-5.13 (m, 6H, H-1', H-1'', H-2', PhCH_2, PhC*H*H); 4.93 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.21-4.18 (m, 2H, H-3, H-3'); 4.05-3.90 (m, 3H, H-5', C*H*$_{,Phth}$); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.74-3.65 (m, 2H, H-2, H-5); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OCH_3); 3.33 (s, 3H, OCH_3); 3.31 (s, 3H, OCH_3); 3.27 (d, 1H, *J* = 1.6 Hz, H-4''); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.50 (bs, 2H, O*H*); 2.37 (t, 2H, *J* = 7.2 Hz, C$H_{2,Phth}$); 1.70-1.18 (m, 53H, C$H_{2,Phth}$, H-6, H-6'); 1.15-1.05 (m, 2H, C*H*$_{Phth}$); 0.97 (d, 3H, *J* = 6.4 Hz, H-6''); 0.91 (t, 3H, *J* = 7.6 Hz, C$H_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C$H_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.6 ($C_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 138.1, 135.2 ($C_{q,arom}$); 132.9, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.8, 127.6, 127.5 (*C*H$_{arom}$); 118.0 ($C_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 ($C_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.3 (C-3); 80.1 ($C_{q,alkyne}$); 80.1 (C-2 and C-3''); 79.8, 79.6 (C-4 and C-4'); 79.3 (C-4''); 78.3 (C-3'); 77.7 (C-2''); 76.8 (C-2'); 75.7, 75.1, 70.1 (Ph*C*H$_2$); 69.6, 69.5 (*C*H$_{Phth}$); 68.9 (C-5'); 68.6 (C-5); 67.1 (C-5''); 61.8, 59.0, 58.8, 58.1, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.7, 29.8, 29.7, 29.7, 29.3, 29.0, 28.9, 27.7, 26.2, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.2 (C-6); 18.0 (C-6'); 16.3 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1099, 1130, 1138, 1235, 1262, 1384, 1457, 1507, 1747, 2855, 2926, 3430. HRMS calculated for $C_{79}H_{116}O_{18}Na$ 1375.8059 $[M+Na]^+$; found 1375.8055.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (42)



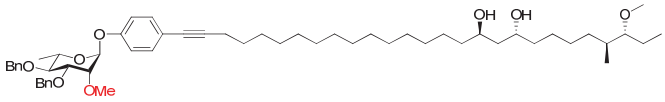
The title compound was synthesized according to general procedure C using **38** (33 mg, 30 µmol, 1.0 eq) and phthiocerol (16 mg, 36 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the title compound (37 mg, 26 µmol, 87%) as a yellow oil. $[\alpha]_D^{25}$ = -71.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.41-7.23 (m, 22H, C*H*$_{arom}$); 6.89 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.27 (d, 1H, *J* = 1.2 Hz, H-1'); 5.19-5.11 (m, 5H, H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (dd, 2H, *J* = 11.8, 21.0 Hz, PhC*H*$_2$); 4.59-4.55 (m, 2H, PhCH*H*, PhCH*H*); 4.27 (dd, 1H, *J* = 3.2, 8.8 Hz, H-3); 4.18 (dd, 1H, *J* = 3.4, 9.4 Hz, H-3'); 3.95-3.84 (m, 5H, H-2, H-5', H-5'', C*H*$_{Phth}$); 3.74-3.65 (m, 2H, H-4, H-5); 3.57-3.44 (m, 9H, H-2'', H-3'', H-4', OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.29 (d, 1H, *J* = 1.6 Hz, H-4''); 3.28 (s, 3H, OC*H*$_3$); 2.89-2.85 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.75-1.17 (m, 54H, H-6, H-6', C*H*$_{2,Phth}$); 1.03 (d, 3H, *J* = 6.4 Hz, H-6''); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.6 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.1, 138.2, 137.8, 135.2 (C$_{q,arom}$); 132.9, 128.8, 128.8, 128.7, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.4, 127.4 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.3 (*C*H$_{arom}$); 99.8 (C-1''); 99.0 (C-1'); 95.5 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.5 (C-4); 80.4 (C-4'); 80.1 (C$_{q,alkyne}$); 79.8 (C-3''); 79.3 (C-4''); 78.3 (C-3); 77.9 (C-2); 77.8 (C-3'); 77.7 (C-2''); 76.6 (C-2'); 75.6, 74.9, 73.0, 70.1 (PhC*H*$_2$); 69.7, 69.6 (*C*H$_{Phth}$); 69.1 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.2, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.1 (C-6 and C-6'); 16.4 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1099, 1132, 1175, 1235, 1264, 1384, 1455, 1507, 1747, 2926, 3396. HRMS calculated for $C_{85}H_{120}O_{18}Na$ 1451.8372 $[M+Na]^+$; found 1451.8371.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,4-di-*O*-methyl-3-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (43)



The title compound was synthesized according to general procedure C using **39** (57 mg, 52 µmol, 1.0 eq) and phthiocerol (28 mg, 62 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 4:1) yielded the title compound (74 mg, 52 µmol, 100%) as a yellow oil. $[\alpha]_D^{25}$ = -75.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.38-7.26 (m, 22H, C*H*$_{arom}$); 6.93 (d, 2H *J* = 8.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.21-5.10 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.92 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.71 (dd, 2H, *J* = 10.8. 27.6 Hz, PhC*H*$_2$); 4.58-4.52 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (dd, 2H, *J* = 3.2, 9.6 Hz, H-3, H-3'); 4.02-3.90 (m, 3H, H-5', C*H*$_{Phth}$); 3.83 (q, 1H, *J* = 6.4 Hz, H-5''); 3.79-3.62 (m, 4H, H-2, H-2'', H-3'', H-5); 3.55-3.51 (m, 8H, H-4, H-4', OC*H*$_3$); 3.35 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.24 (d, 1H, *J* = 2.0 Hz, H-4''); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.62-1.26 (m, 51H, H-6', C*H*$_{2,Phth}$); 1.19 (d, 3H, *J* = 6.0 Hz, H-6); 1.15-1.05 (m, 2H, C*H*$_{2,Phth}$); 0.95-0.89 (m, 6H, H-6'', C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.6 (C$_{q,arom}$); 154.7 (*C*O$_{Cbz}$); 139.0, 139.0, 138.1, 135.2 (C$_{q,arom}$); 133.0, 128.8, 128.8, 128.5, 128.5, 128.5, 128.4, 128.3, 127.8, 127.8, 127.6, 127.4 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.1 (C-1''); 99.4 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.5 (C-4''); 80.1 (C$_{q,alkyne}$); 80.1 (C-2); 80.0 (C-3); 79.9 (C-4'), 79.6 (C-4); 78.6 (C-3''); 78.3 (C-3'); 78.2 (C-2''); 76.7 (C-2'); 75.7, 75.2, 72.7, 70.0 (PhC*H*$_2$); 69.6, 69.5 (*C*H$_{Phth}$); 68.9 (C-5); 68.6 (C-5'); 67.2 (C-5''); 61.9, 59.4, 58.8, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.7, 29.8, 29.8, 29.7, 29.3, 29.1, 28.9, 27.7, 26.2, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.2 (C-6'); 18.0 (C-6); 16.2 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1100, 1137, 1263, 1455, 1507, 1748, 2926, 3408. HRMS calculated for $C_{85}H_{120}O_{18}Na$ 1451.8372 $[M+Na]^+$; found 1451.8367.

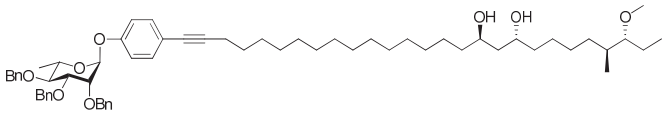
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-methyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (44)



The title compound was synthesized according to general procedure C using **8** (29 mg, 52 µmol, 1.0 eq) and phthiocerol (28 mg, 62 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 4:1) yielded the title compound (46 mg, 52 µmol, 100%) as a yellow oil. $[\alpha]_D^{25}$ = -74.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.42 (d, 2H, *J* = 6.8 Hz, C*H*$_{arom}$); 7.38-7.28 (m, 10H, C*H*$_{arom}$); 6.93 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 2.0 Hz, H-1); 4.95 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.83-4.74 (m, 2H, PhC*H*$_2$); 4.63 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.04 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 3.99-3.89 (m, 2H, C*H*$_{Phth}$); 3.75-3.68 (m, 2H, H-2, H-5); 3.60-3.55 (m, 4H, H-4,

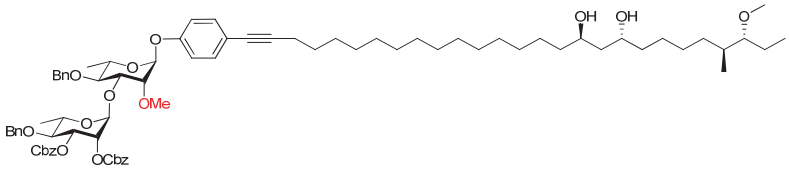
OCH_3); 3.34 (s, 3H, OCH_3); 2.90-2.83 (m, 1H, CH_{Phth}); 2.37 (t, 2H, *J* = 7.0 Hz, C$H_{2,Phth}$); 1.75-1.17 (m, 45H, H-6, C$H_{2,Phth}$); 1.16-1.03 (m, 2H, C$H_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C$H_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C$H_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.6, 138.6, 138.5 ($C_{q,arom}$); 133.0, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8 (*C*H$_{arom}$); 118.0 ($C_{q,arom}$); 116.2 (*C*H$_{arom}$); 95.4 (C-1); 89.5 ($C_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.4 (C-4); 80.1 ($C_{q,alkyne}$); 79.7 (C-3); 78.1 (C-2); 75.7, 72.7 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 68.9 (C-5); 59.7, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.7, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.1 (C-6); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1047, 1098, 1139, 1233, 1454, 1507, 2853, 3400. HRMS calculated for $C_{56}H_{84}O_8Na$ 907.6064 [M+Na]$^+$; found 907.6058.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranoside (45)



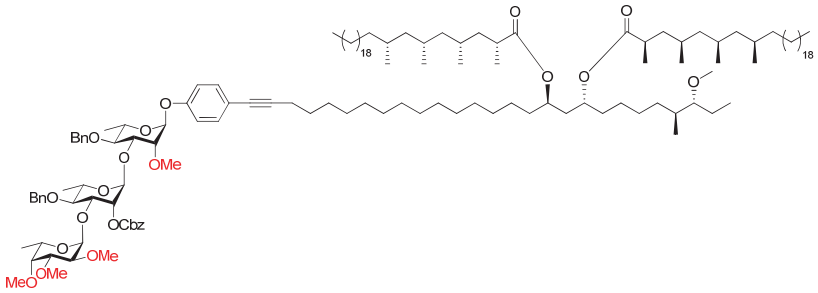
The title compound was synthesized according to general procedure C using **9** (32 mg, 50 µmol, 1.0 eq) and phthiocerol (27 mg, 60 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 4:1) yielded the title compound (48 mg, 50 µmol, 99%) as a yellow oil. $[\alpha]_D^{25}$ = -38.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.26 (m, 17H, C*H*$_{arom}$); 6.86 (dd, 2H, *J* = 2.0, 7.2 Hz, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 2.0 Hz, H-1); 4.94 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.68 (dd, 2H, *J* = 12.4, 25.2 Hz, PhC*H*$_2$); 4.70-4.64 (m, 3H, PhC*H*$_2$, PhCH*H*); 4.04 (dd, 1H, *J* = 3.0, 9.0 Hz, H-3); 3.96-3.90 (m, 3H, H-2, C*H*$_{Phth}$); 3.74-3.68 (m, 2H, H-4, H-5); 3.34 (s, 3H, OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 1H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.00 (bs, 2H, O*H*$_{Phth}$); 1.62-1.09 (m, 63H, C*H*$_{Phth}$, C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.6 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.6, 138.6, 138.2 ($C_{q,arom}$); 133.0, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.8 (*C*H$_{arom}$); 117.9 ($C_{q,arom}$); 116.2 (*C*H$_{arom}$); 96.2 (C-1); 89.5 ($C_{q,alkyne}$); 80.5 (C-4); 80.1 ($C_{q,alkyne}$); 80.0 (C-3); 75.6 (Ph*C*H$_2$); 74.7 (C-2); 73.2, 72.6 (Ph*C*H$_2$); 69.7, 69.6 (*C*H$_{Phth}$) 69.0 (C-5); 57.6 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.1 (C-6); 15.0, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1029, 1046, 1098, 1126, 1233, 1455, 1507, 2855, 2926, 3418. HRMS calculated for $C_{62}H_{89}O_8$ 961.6557 [M+H]$^+$; found 961.6546.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-benzyl-3-*O*-(2,3-di-*O*-benzyloxycarbonyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (46)



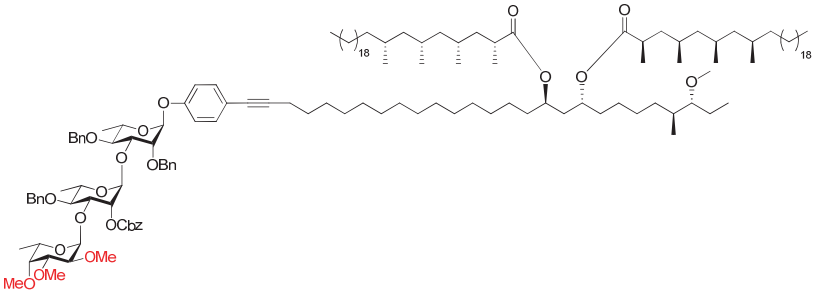
The title compound was synthesized according to general procedure C using **40** (34 mg, 34 µmol, 1.0 eq) and phthiocerol (19 mg, 41 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 4:1) yielded the title compound (43 mg, 33 µmol, 96%) as a yellow oil. $[\alpha]_D^{25}$ = -40.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.38-7.22 (m, 22H, C*H*$_{arom}$); 6.95-6.92 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.34-5.29 (m, 2H, H-2', H-3'); 5.19 (d, 1H, *J* = 2.0 Hz, H-1'); 5.16 (s, 2H, PhC*H*$_2$); 5.12 (s, 2H, PhC*H*$_2$); 4.90 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.73 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.62-4.57 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.10-4.03 (m, 1H, H-5'); 3.98-3.90 (m, 2H, C*H*$_{Phth}$); 3.73-3.69 (m, 2H, H-2, H-5); 3.62-3.52 (m, 5H, H-4, H-4', OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.70-1.02 (m, 64H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 7.2 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.6 (C$_{q,arom}$); 154.5, 154.4 (*C*O$_{Cbz}$); 138.2, 138.0, 135.2, 135.0 (C$_{q,arom}$); 133.0, 128.8, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.8 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.3 (C-1'); 94.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.1 (C$_{q,alkyne}$); 80.0 (C-2 and C-4); 79.6 (C-3); 78.6 (C-4'); 76.1 (C-3'); 75.7, 75.5 (Ph*C*H$_2$); 74.1 (C-2'); 70.2, 70.1 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.6 (C-5'); 59.1, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.1 (C-6); 18.1 (C-6'); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1047, 1052, 1056, 1078, 1096, 1100, 1120, 1125, 1139, 1236, 1275, 1382, 1484, 1507, 1753, 1753, 2855, 2926, 3411. HRMS calculated for $C_{78}H_{107}O_{16}$ 1299.75536 $[M+H]^+$; found 1299.75560.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (47)



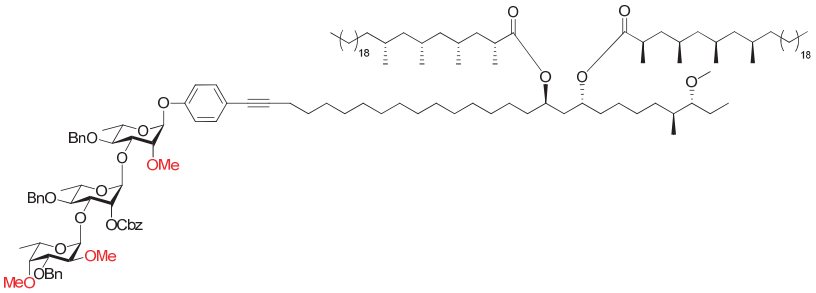
The title compound was synthesized according to general procedure D using **41** (30 mg, 22 µmol, 1.0 eq), mycocerosic acid (32 mg, 66 µmol, 3.0 eq), DIC (21 µL, 133 µmol, 6.0 eq) and DMAP (24 mg, 199 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 3:1) yielded the title compound (48 mg, 21 µmol, 94%) as a waxy solid. $[\alpha]_D^{25}$ = -53.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.44-7.24 (m, 17H, C*H*$_{arom}$); 6.95-6.92 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 2.0 Hz, H-1); 5.22 (d, 1H, *J* = 1.6 Hz, H-1'); 5.20-5.10 (m, 5H, H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.22-4.18 (m, 2H, H-3, H-3'); 4.04-3.97 (m, 1H, H-5'); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.74-3.65 (m, 2H, H-2, H-5); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.27 (d, 1H, *J* = 1.6 Hz, H-4''); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 209H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.7 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 138.2, 135.2 (C$_{q,arom}$); 133.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 127.9, 127.6, 127.5 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.0 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.4 (C-3); 80.1 (C-2 and C-3''); 79.9, 79.7 (C-4 and C-4'); 79.3 (C-4''); 78.3 (C-3'); 77.7 (C-2''); 75.7, 75.1 (Ph*C*H$_2$); 70.4 (*C*H$_{Phth}$); 70.1 (Ph*C*H$_2$); 68.9 (C-5); 68.6 (C-5'); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6'); 18.1 (C-6); 16.4 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1047, 1098, 1130, 1139, 1176, 1261, 1457, 1464, 1472, 1507, 1736, 2849, 2916. HRMS calculated for $C_{143}H_{241}O_{20}$ 2280.79031 $[M+H]^+$; found 2280.80360

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-benzyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (48)



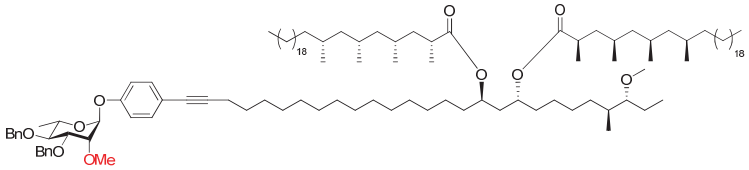
The title compound was synthesized according to general procedure D using **42** (33 mg, 23 µmol, 1.0 eq), mycocerosic acid (33 mg, 69 µmol, 3.0 eq), DIC (21 µL, 138 µmol, 6.0 eq) and DMAP (25 mg, 207 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 7:3) yielded the title compound (41 mg, 17 µmol, 75%) as a waxy solid. $[\alpha]_D^{25}$ = -49.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.41-7.23 (m, 22H, C*H*$_{arom}$); 6.89 (dd, 2H, *J* = 2.0, 7.2 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.27 (d, 1H, *J* = 1.2 Hz, H-1'); 5.20-5.09 (m, 5H, H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.84 (quint, 2H, *J* = 6.2 Hz, C*H*$_{Phth}$); 4.74 (dd, 2H, *J* = 12.0, 21.2 Hz, PhC*H*$_2$); 4.59-4.55 (m, 2H, PhCH*H*, PhCH*H*); 4.27 (dd, 1H, *J* = 3.2, 8.8 Hz, H-3); 4.18 (dd, 1H, *J* = 3.4, 9.2 Hz, H-3'); 3.91-3.84 (m, 3H, H-2, H-5', H-5''); 3.74-3.65 (m, 2H, H-4, H-5); 3.57-3.47 (m, 9H, H-2'', H-3'', H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.29 (d, 1H, *J* = 1.6 Hz, H-4''); 3.28 (s, 3H, OC*H*$_3$); 2.89-2.85 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 243H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.6 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.1, 138.2, 137.8, 135.2 (C$_{q,arom}$); 132.9, 128.9, 128.8, 128.7, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.4, 127.4 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.8 (C-1''); 99.0 (C-1'); 95.5 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.5 (C-4); 80.4 (C-4'); 80.1 (C$_{q,alkyne}$); 79.8 (C-3''); 79.3 (C-4''); 78.4 (C-3); 77.9 (C-2); 77.8 (C-3'); 77.7 (C-2''); 76.6 (C-2'); 75.6, 74.9, 73.0 (Ph*C*H$_2$); 70.4 (*C*H$_{Phth}$); 70.1 (Ph*C*H$_2$); 69.1 (C-5); 68.7 (C-5'); 67.1 (C-5''); 61.9, 59.1, 58.2, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.0 (C-6 and C-6'); 16.4 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1029, 1102, 1130, 1175, 1236, 1261, 1379, 1455, 1464, 1507, 1736, 2850, 2921. HRMS calculated for $C_{149}H_{245}O_{20}$ 2355.81828 $[M+H]^+$; found 2355.82501.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,4-di-*O*-methyl-3-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (49)



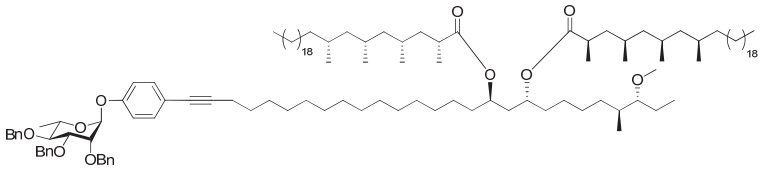
The title compound was synthesized according to general procedure D using **43** (33 mg, 33 µmol, 1.0 eq), mycocerosic acid (33 mg, 69 µmol, 3.0 eq), DIC (21 µL, 138 µmol, 6.0 eq) and DMAP (25 mg, 138 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 2:3) yielded the title compound (40 mg, 17 µmol, 74%) as a waxy solid. $[\alpha]_D^{25}$ = -50.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.24 (m, 22H, C*H*$_{arom}$); 6.95-6.92 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.07 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.92 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.89-4.80 (m, 2H, C*H*$_{Phth}$); 4.71 (dd, 2H, *J* = 12.4, 29.2 Hz, PhC*H*$_2$); 4.58-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (dd, 2H, *J* = 3.2, 9.6 Hz, H-3, H-3'); 4.04-3.95 (m, 1H, H-5'); 3.83 (q, 1H, *J* = 6.4 Hz, H-5''); 3.79-3.63 (m, 4H, H-2, H-2'', H-3'', H-5); 3.55-3.51 (m, 8H, H-4, H-4', OC*H*$_3$); 3.35 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.24 (d, 1H, *J* = 2.0 Hz, H-4''); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 213H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.7 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.1, 139.0, 138.2, 135.2 (C$_{q,arom}$); 128.9, 128.8, 128.5, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.1 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.6 (C-4''); 80.1 (C-2); 80.0 (C-3); 79.9 (C-4'); 79.6 (C-4); 78.6 (C-3''); 78.4 (C-3'); 78.3 (C-2''); 76.7 (C-2'); 75.7, 75.2, 72.7 (Ph*C*H$_2$); 70.4 (*C*H$_{Phth}$); 70.1 (Ph*C*H$_2$); 68.9 (C-5); 68.4 (C-5'); 67.2 (C-5''); 61.9, 59.4, 58.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6'); 18.1 (C-6); 16.2 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1046, 1102, 1139, 1176, 1262, 1379, 1457, 1464, 1507, 1736, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (50)



The title compound was synthesized according to general procedure D using **44** (22 mg, 25 µmol, 1.0 eq), mycocerosic acid (36 mg, 75 µmol, 3.0 eq), DIC (23 µL, 149 µmol, 6.0 eq) and DMAP (27 mg, 224 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 4:1) yielded the title compound (38 mg, 21 µmol, 84%) as a waxy solid. $[\alpha]_D^{25}$ = -33.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.43-7.40 (m, 2H, C*H*$_{arom}$); 7.37-7.26 (m, 10H, C*H*$_{arom}$); 6.94-6.91 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 2.0 Hz, H-1); 4.95 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.89-4.80 (m, 2H, C*H*$_{Phth}$); 4.78 (s, 2H, PhC*H*$_2$); 4.64 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.03 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.76-3.70 (m, 1H, H-5); 3.68 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.60-3.55 (m, 4H, H-4, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 2.89-2.83 (m, 1H, C*H*$_{Phth}$); 2.57-2.48 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 235H, H-6, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc}$, C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 155.7, 138.6, 138.5 (C$_{q,arom}$); 133.0, 128.6, 128.5, 128.1, 128.1, 127.9, 127.8 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 95.4 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.4 (C-4); 80.1 (C$_{q,alkyne}$); 79.7 (C-3); 78.1 (C-2); 75.7, 72.7 (Ph*C*H$_2$); 70.4 (*C*H$_{Phth}$); 68.9 (C-5); 59.7, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.1 (C-6); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1099, 1176, 1378, 1457, 1464, 1507, 1734, 2853, 2923. HRMS calculated for $C_{120}H_{209}O_{10}$ 1810.58403 $[M+H]^+$; found 1810.58417.

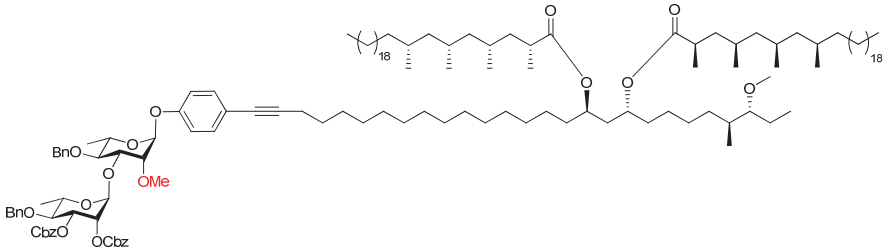
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranoside (51)



The title compound was synthesized according to general procedure D using **45** (23 mg, 24 µmol, 1.0 eq), mycocerosic acid (35 mg, 72 µmol, 3.0 eq), DIC (22 µL, 144 µmol, 6.0 eq) and DMAP (26 mg, 215 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 19:1) yielded the title compound (33 mg, 17 µmol, 73%) as a waxy solid. $[\alpha]_D^{25}$ = -26.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.26 (m, 17H, C*H*$_{arom}$); 6.88-6.85 (m, 2H, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 2.0 Hz, H-1); 4.96 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.87-4.74 (m, 4H, PhC*H*$_2$, C*H*$_{Phth}$); 4.73-4.64 (m, 3H, PhCH*H*, PhC*H*$_2$); 4.04 (dd, 1H, *J* = 3.0, 9.0 Hz, H-3); 3.93 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.78-3.66 (m, 2H, H-4, H-5); 3.33 (s, 3H, OC*H*$_3$); 2.89-2.83 (m, 1H, C*H*$_{Phth}$); 2.57-2.48 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J*

= 7.0 Hz, C$H_{2,Phth}$); 1.77-0.81 (m, 212H, H-6, CH_{Phth}, C$H_{2,Phth}$, C$H_{3,Phth}$, C$H_{Myc,}$ C$H_{2,Myc}$, C$H_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 155.6, 138.6, 138.2 (C$_{q,arom}$); 132.9, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.8 (*C*H$_{arom}$); 117.9 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 96.2 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.5 (C-4); 80.1 (C$_{q,alkyne}$); 80.0 (C-3); 75.6 (PhCH$_2$); 74.7 (C-2); 73.2, 72.6 (PhCH$_2$); 70.4 (*C*H$_{Phth}$); 69.0 (C-5); 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.1 (C-6); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1099, 1175, 1233, 1378, 1457, 1507, 1734, 2853, 2923. HRMS calculated for $C_{126}H_{213}O_{10}$ 1886.61533 [M+H]$^+$; found 1886.61566.

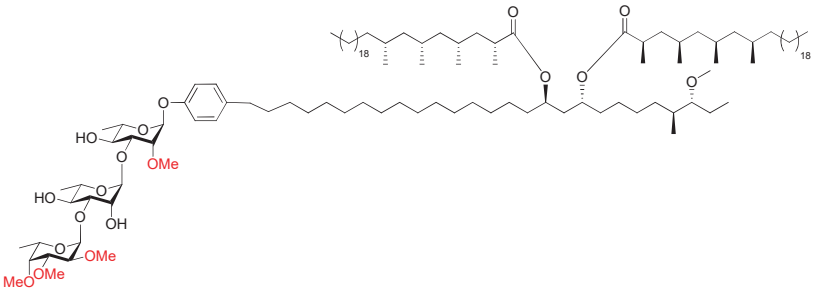
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-benzyl-3-*O*-(2,3-di-*O*-benzyloxycarbonyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (52)



The title compound was synthesized according to general procedure D using **46** (37 mg, 28 μmol, 1.0 eq), mycocerosic acid (41 mg, 85 μmol, 3.0 eq), DIC (26 μL, 171 μmol, 6.0 eq) and DMAP (31 mg, 256 μmol, 9.0 eq). Column chromatography (*n*-pentane-Et$_2$O 17:3) yielded the title compound (32 mg, 14 μmol, 51%) as a waxy solid. [α]$_D^{25}$ = -24.9 ° (c = 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.24 (m, 22H, *C*H$_{arom}$); 6.93 (d, 2H, *J* = 8.8 Hz, *C*H$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.34-5.29 (m, 2H, H-2', H-3'); 5.19 (d, 1H, *J* = 1.6 Hz, H-1'); 5.16 (s, 2H, PhC*H*$_2$); 5.12 (s, 2H, PhC*H*$_2$); 4.91-4.83 (m, 3H, PhC*H*H, C*H*$_{Phth,}$ C*H*$_{Phth}$); 4.73 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.62-4.57 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.10-4.03 (m, 1H, H-5'); 3.73-3.69 (m, 2H, H-2, H-5); 3.62-3.52 (m, 5H, H-4, H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 208H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 155.7 (C$_{q,arom}$); 154.5, 154.4 (*C*O$_{Cbz}$); 138.3, 138.0, 135.3, 135.0 (C$_{q,arom}$); 133.0, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.8 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.3 (C-1'); 94.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.1 (C$_{q,alkyne}$); 80.0 (C-2 and C-4); 79.6 (C-3); 78.6 (C-4'); 76.1 (C-3'); 75.7, 75.5 (PhCH$_2$); 74.1 (C-2'); 70.4 (*C*H$_{Phth}$); 70.2, 70.1 (PhCH$_2$); 69.0 (C-5); 68.6 (C-5'); 59.1, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$);

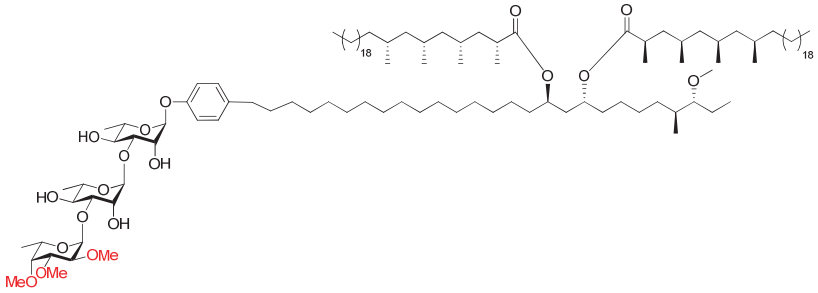
18.1 (C-6); 18.1 (C-6'); 14.8 ($CH_{3,Phth}$); 14.3 ($CH_{3,Myc}$); 10.3 ($CH_{3,Phth}$). IR (thin film, cm^{-1}): 1029, 1047, 1078, 1082, 1100, 1140, 1176, 1236, 1275, 1378, 1457, 1507, 1736, 1753, 2853, 2925. HRMS calculated for $C_{142}H_{231}O_{18}$ 2225.71890 $[M+H]^+$; found 2225.72535.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (53)



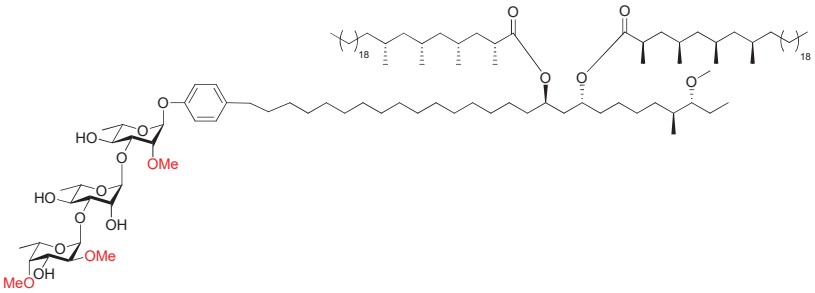
The title compound was synthesized according to general procedure E using **47** (33 mg, 14 µmol, 1.0 eq) and Pd/C (10%, 15 mg, 14 µmol, 1.0 eq). Column chromatography (DCM-MeOH 19:1) yielded the title compound (23 mg, 12 µmol, 82%) as a waxy solid. $[\alpha]_D^{25}$ = -48.4 ° (c = 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, CH_{arom}); 6.99 (d, 2H, *J* = 8.8 Hz, CH_{arom}); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.15-5.14 (m, 2H, H-1', H-1"); 4.84 (quint, 2H, *J* = 6.4 Hz, CH_{Phth}); 4.11 (s, 1H, H-2'); 4.07-4.03 (m, 2H, H-3, H-5"); 3.98-3.91 (m, 1H, H-5'); 3.82-3.74 (m, 3H, H-2, H-3', H-5); 3.70-3.64 (m, 4H, H-2", H-3", H-4, H-4'); 3.61 (s, 3H, OCH_3); 3.58 (s, 3H, OCH_3); 3.52 (s, 3H, OCH_3); 3.49 (s, 3H, OCH_3); 3.48 (d, 1H, *J* = 1.6 Hz, H-4"); 3.33 (s, 3H, OCH_3); 2.88-2.83 (m, 1H, CH_{Phth}); 2.58-2.48 (m, 4H, C$H_{2,Phth}$, CH_{Myc}); 2.27 (bs, 1H, O*H*); 2.16 (bs, 1H, O*H*); 1.77-0.81 (m, 203H, H-6, H-6', H-6", CH_{Phth}, C$H_{2,Phth}$, C$H_{3,Phth}$, C$H_{Myc,}$ C$H_{2,Myc}$, C$H_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.1 (CO_{Myc}); 154.7, 137.0 ($C_{q,arom}$); 129.5, 116.3 (CH_{arom}); 102.3 (C-1"); 100.9 (C-1'); 95.0 (C-1); 86.8 (CH_{Phth}); 83.3 (C-3'); 81.1 (C-3"); 80.2 (C-2); 80.1 (C-3); 79.1 (C-4"); 78.9 (C-2"); 71.9 (C-4'); 71.8 (C-4); 71.3 (C-2'); 70.4 (CH_{Phth}); 69.2 (C-5); 68.8 (C-5'); 67.6 (C-5"); 62.1, 60.4, 58.7, 57.9, 57.5 (OCH_3); 45.6, 45.4 (C$H_{2,Myc}$); 41.1, 38.6 (C$H_{2,Phth}$); 37.9, 37.9 (CH_{Myc}); 36.8 (C$H_{2,Myc}$); 34.9 (CH_{Phth}); 34.8, 32.8 (C$H_{2,Phth}$); 32.1 (C$H_{2,Myc}$); 31.9, 30.2 (C$H_{2,Phth}$); 30.1 (CH_{Myc}); 29.9, 29.9, 29.8, 29.7, 29.5 (CH_2); 28.2 (CH_{Myc}); 27.6 (C$H_{2,Phth}$); 27.3 (CH_{Myc}); 27.1 (C$H_{2,Myc}$); 25.7, 25.3 (C$H_{2,Phth}$); 22.8 (C$H_{2,Myc}$); 22.5 (C$H_{2,Phth}$); 20.9, 20.6, 20.6, 18.6 (C$H_{3,Myc}$); 18.0, 17.9 (C-6 and C-6'); 16.8 (C-6"); 14.8 (C$H_{3,Phth}$); 14.3 (C$H_{3,Myc}$); 10.3 (C$H_{3,Phth}$). IR (thin film, cm^{-1}): 1020, 1043, 1095, 1229, 1259, 1379, 1460, 1508, 1731, 1736, 2853, 2923, 3420. HRMS calculated for $C_{121}H_{227}O_{18}$ 1969.68761 $[M+H]^+$; found 1969.68884.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (54)



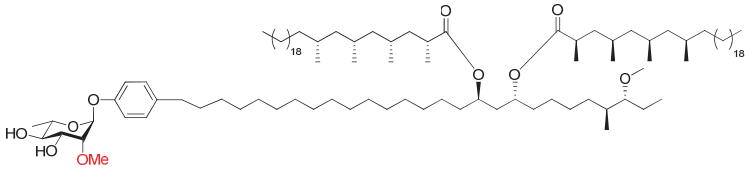
The title compound was synthesized according to general procedure E using **48** (35 mg, 15 µmol, 1.0 eq) and Pd/C (10%, 16 mg, 15 µmol, 1.0 eq). Column chromatography (DCM-acetone 7:3) yielded the title compound (23 mg, 12 µmol, 80%) as a waxy solid. $[\alpha]_D^{25}$ = -47.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.09 (d, 2H, *J* = 8.8 Hz, CH_{arom}); 6.97 (d, 2H, *J* = 8.4 Hz, CH_{arom}); 5.45 (d, 1H, *J* = 1.6 Hz, H-1); 5.20 (d, 1H, *J* = 1.2 Hz, H-1'); 5.16 (d, 1H, *J* = 3.2 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.2 Hz, CH_{Phth}); 4.18 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 4.12 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2'); 4.10-4.02 (m, 2H, H-3, H-5''); 3.92-3.76 (m, 3H, H-3', H-5, H-5'); 3.71-3.64 (m, 4H, H-2'', H-3'', H-4, H-4'); 3.61 (s, 3H, OCH_3); 3.59 (s, 3H, OCH_3); 3.52 (s, 3H, OCH_3); 3.48 (d, 1H, *J* = 1.6 Hz, H-4''); 3.33 (s, 3H, OCH_3); 2.88-2.83 (m, 1H, CH_{Phth}); 2.58-2.48 (m, 4H, C$H_{2,Phth}$, CH_{Myc}); 1.77-0.81 (m, 192H, H-6, H-6', H-6'', CH_{Phth}, C$H_{2,Phth}$, C$H_{3,Phth}$, C$H_{Myc,}$ C$H_{2,Myc}$, C$H_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2 (*C*O$_{Myc}$); 154.3, 137.0 (C$_{q,arom}$); 129.4, 116.3 (*C*H$_{arom}$); 101.8 (C-1''); 101.0 (C-1'); 97.9 (C-1); 86.8 (*C*H$_{Phth}$); 83.2 (C-3'); 81.1 (C-3''); 79.7 (C-3); 79.0 (C-4''); 78.8 (C-2''); 72.2 (C-4); 71.6 (C-4'); 71.2 (C-2'); 70.8 (C-2); 70.4 (*C*H$_{Myc}$); 69.1 (C-5'); 68.8 (C-5); 67.7 (C-5''); 62.1, 60.4, 57.9, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.8, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 18.6 (*C*H$_{3,Myc}$); 17.8 (C-6) 17.8 (C-6'); 16.8 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1090, 1228, 1172, 1229, 1261, 1378, 1457, 1511, 1734, 2853, 2922, 3441. HRMS calculated for $C_{120}H_{225}O_{18}$ 1955.67196 $[M+H]^+$; found 1955.67222.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,4-di-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (55)



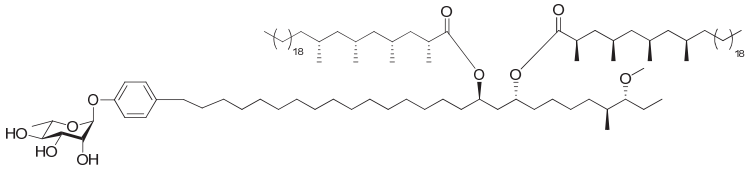
The title compound was synthesized according to general procedure E using **49** (41 mg, 17 µmol, 1.0 eq) and Pd/C (10%, 19 mg, 17.4 µmol, 1.0 eq). Column chromatography (DCM-MeOH 19:1) yielded the title compound (28 mg, 14 µmol, 82%) as a waxy solid. $[\alpha]_D^{25}$ = -44.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.99 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.18 (d, 1H, *J* = 3.6 Hz, H-1''); 5.13 (d, 1H, *J* = 1.2 Hz, H-1'); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.16-4.11 (m, 2H, H-2', H-5''); 4.04 (dd, 2H, *J* = 3.0, 9.4 Hz, H-3, H-3''); 3.98-3.91 (m, 1H, H-5'); 3.81-3.74 (m, 3H, H-2, H-3', H-5); 3.70-3.61 (m, 5H, H-4, H-4', OC*H*$_3$); 3.58 (s, 3H, OC*H*$_3$); 3.50-3.47 (m, 4H, H-2'', OC*H*$_3$); 3.40 (d, 1H, *J* = 2.4 Hz, H-4''); 3.33 (s, 3H, OC*H*$_3$); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.58-2.48 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 1.77-0.81 (m, 191H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 154.7, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 102.3 (C-1''); 99.9 (C-1'); 95.0 (C-1); 86.8 (*C*H$_{Phth}$); 83.0 (C-3'); 82.5 (C-4''); 80.2 (C-3); 80.1 (C-2''); 80.1 (C-2); 71.9 (C-4); 71.6 (C-4'); 71.2 (C-2'); 70.6 (C-3''); 70.4 (*C*H$_{Phth}$); 69.2 (C-5); 68.8 (C-5'); 67.6 (C-5''); 62.6, 59.8, 58.7, 57.7 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.0 (C-6); 17.9 (C-6'); 16.9 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1129, 1150, 1173, 1261, 1378, 1461, 1510, 1734, 2853, 2923, 3414. HRMS calculated for $C_{120}H_{225}O_{18}$ 1955.67196 [M+H]$^+$; found 1955.67295.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-α-L-rhamnopyranoside (56)



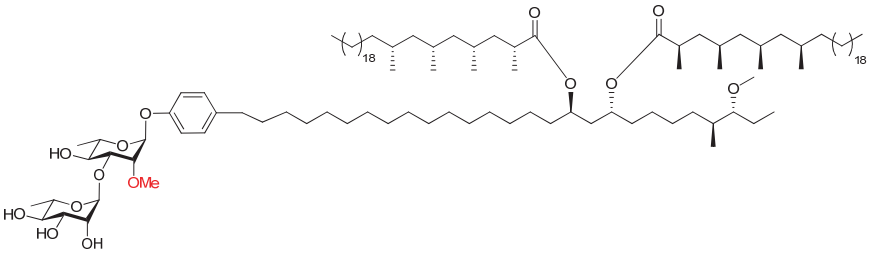
The title compound was synthesized according to general procedure E using **50** (27 mg, 15 µmol, 1.0 eq) and Pd/C (10%, 16 mg, 15 µmol, 1.0 eq). Column chromatography (DCM-acetone 19:1) yielded the title compound (15 mg, 9 µmol, 62%) as a waxy solid. $[\alpha]_D^{25}$ = -7.63 ° (c = 0.8, $CHCl_3$). ^{1}H-NMR (850 MHz) δ: 7.10 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 6.99 (dd, 2H, *J* = 1.7, 6.8 Hz, C*H*$_{arom}$); 5.55 (d, 1H, *J* = 1.7 Hz, H-1); 4.84 (quint, 2H. *J* = 6.4 Hz, C*H*$_{Phth}$); 3.92 (dt, 1H, *J* = 4.0, 9.8 Hz, H-3); 3.76 (dq, 1H, *J* = 6.0, 9.4 Hz, H-5); 3.66 (dd, 1H, *J* = 1.7, 4.3 Hz, H-2); 3.53 (s, 3H, OC*H*$_3$); 3.44 (t, 1H, *J* = 9.4 Hz, H-4); 3.33 (s, 3H, OC*H*$_3$); 2.87-2.85 (m, 1H, C*H*$_{Phth}$); 2.56-2.51 (m, 4H, C*H*$_{Myc}$, C*H*$_{2,Phth}$); 2.37 (d, 1H, *J* = 9.4 Hz, 3-O*H*); 2.34 (bs, 1H, 4-O*H*); 1.77-0.81 (m, 199H, H-6, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (214 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.2 (*C*H$_{arom}$); 94.8 (C-1); 86.8 (*C*H$_{Phth}$); 80.3 (C-2); 74.2 (C-4); 71.5 (C-3); 70.4, 70.4 (*C*H$_{Phth}$); 68.5 (C-5); 59.1, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5, 18.6 (*C*H$_{3,Myc}$); 17.7 (C-6); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1007, 1050, 1096, 1129, 1176, 1231, 1261, 1378, 1511, 1736, 2853, 2923, 3394. HRMS calculated for $C_{106}H_{201}O_{10}$ 1634.52143 $[M+H]^+$; found 1634.52059.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl α-L-rhamnopyranoside (57)



The title compound was synthesized according to general procedure E using **51** (22 mg, 12 µmol, 1.0 eq) and Pd/C (10%, 12 mg, 10 µmol, 1.0 eq). Column chromatography (DCM-MeOH 19:1) yielded the title compound (6 mg, 4 µmol, 32%) as a waxy solid. $[\alpha]_D^{25}$ = -28 ° (c = 0.2, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: δ: 7.09 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.97 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.14 (s, 1H, H-2); 4.01-3.97 (m, 1H, H-3); 3.84-3.77 (m, 1H, H-5); 3.56-3.52 (m, 1H, H-4); 3.33 (s, 3H, OC*H*$_3$); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.56-2.50 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 1.77-0.81 (m, 176H, H-6, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2 (*C*O$_{Myc}$); 154.4, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 98.0 (C-1); 86.8 (*C*H$_{Phth}$); 73.8 (C-4); 71.8 (C-3); 71.0 (C-2); 70.5 (*C*H$_{Phth}$); 68.5 (C-5); 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$);

34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.8, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$);30.0, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 17.7 (C-6); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1100, 1129, 1173, 1261, 1378, 1457, 1511, 1736, 2853, 2923, 3398. HRMS calculated for $C_{105}H_{199}O_{10}$ 1620.50578 $[M+H]^+$; found 1620.50542.



4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(α-L-rhamnopyranoside)-α-L-rhamnopyranoside (58)

The title compound was synthesized according to general procedure E using **52** (23 mg, 10 µmol, 1.0 eq) and Pd/C (10%, 11 mg, 10 µmol, 1.0 eq). Column chromatography (DCM-MeOH 9:1) yielded the title compound (11 mg, 6 µmol, 60%) as a waxy solid. $[\alpha]_D^{25}$ = -23.0 ° (c = 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.98 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 5.49 (s, 1H, H-1); 5.10 (s, 1H, H-1'); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Myc}$); 4.06-4.01 (m, 2H, H-2', H-3); 3.86-3.79 (m, 2H, H-3', H-5'); 3.76-3.72 (m, 2H, H-2, H-5); 3.59 (t, 1H, *J* = 9.6 Hz, H-4); 3.51-3.42 (m, 4H, H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 2.89-2.85 (m, 1H, C*H*$_{Phth}$); 2.56-2.50 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.27 (bs, 1H, O*H*); 1.77-0.81 (m, 195H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.3 (*C*O$_{Myc}$); 154.6, 137.0 (C$_{q,arom}$); 129.4, 116.3 (*C*H$_{arom}$); 102.5 (C-1'); 95.2 (C-1); 86.8 (*C*H$_{Phth}$); 80.3 (C-2); 79.2 (C-3); 73.0 (C-4'); 71.9 (C-4); 71.4 (C-3'); 70.7 (C-2'); 70.5 (*C*H$_{Phth}$); 69.3 (C-5); 68.9 (C-5'); 58.9, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.5 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.7 (*C*H$_{2,Phth}$); 32.0 (*C*H$_{2,Myc}$); 31.8, 30.2 (*C*H$_{2,Phth}$); 30.0 (*C*H$_{Myc}$); 29.9, 29.8, 29.8, 29.7, 29.5 (*C*H$_2$); 28.1 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.4 (*C*H$_{2,Phth}$); 20.8, 20.6, 20.5, 18.5 (*C*H$_{3,Myc}$); 17.8 (C-6 and C-6'); 14.7 (*C*H$_{3,Phth}$); 14.2 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1098, 1130, 1173, 1229, 1261, 1378, 1457, 1511, 1736, 2853, 2923, 3396. HRMS calculated for $C_{112}H_{211}O_{14}$ 1781.58275 $[M+H]^+$; found 1781.58272.

References

1. Forrellad, M. A. *et al.* Virulence factors of the mycobacterium tuberculosis complex. *Virulence* **4**, 3–66 (2013).
2. Glaziou, P., Floyd, K. & Raviglione, M. C. Global Epidemiology of Tuberculosis. *Semin. Respir. Crit. Care Med.* **39**, 271–285 (2018).
3. Parrish, N. M., Dick, J. D. & Bishai, W. R. Mechanisms of latency in Mycobacterium tuberculosis. *Trends Microbiol.* **6**, 107–112 (1998).
4. Cambier, C. J., O'Leary, S. M., O'Sullivan, M. P., Keane, J. & Ramakrishnan, L. Phenolic Glycolipid Facilitates Mycobacterial Escape from Microbicidal Tissue-Resident Macrophages. *Immunity* **47**, 552-565.e4 (2017).
5. Cambier, C. J. *et al.* Mycobacteria manipulate macrophage recruitment through coordinated use of membrane lipids. *Nature* **505**, 218–222 (2014).
6. Elsaidi, H. R. H. & Lowary, T. L. Inhibition of cytokine release by mycobacterium tuberculosis phenolic glycolipid analogues. *ChemBioChem* **15**, 1176–1182 (2014).
7. Arbues, A., Lugo-Villarino, G., Neyrolles, O., Guilhot, C. & Astarie-Dequeker, C. Playing hide-and-seek with host macrophages through the use of mycobacterial cell envelope phthiocerol dimycocerosates and phenolic glycolipids. *Front. Cell. Infect. Microbiol.* **4**, 1–7 (2014).
8. Sato, K. *et al.* Synthesis and Biological Evaluation of O-Methylated Glycolipids Related to PGLs via Direct Stereoselective Glycosidation and Sequential Suzuki–Miyaura Coupling using Boracyclane. *Chem. – A Eur. J.* **23**, 16374–16379 (2017).
9. Puzo, G. The carbohydrate- and lipid-containing cell wall of mycobacteria, phenolic glycolipids: Structure and immunological properties. *Crit. Rev. Microbiol.* **17**, 305–327 (1990).
10. Reed, M. B. *et al.* A glycolipid of hypervirulent tuberculosis strains that inhibits the innate immune response. *Nature* **431**, 84–87 (2004).
11. Bifani, P. J., Mathema, B., Kurepina, N. E. & Kreiswirth, B. N. Global dissemination of the Mycobacterium tuberculosis W-Beijing family strains. *Trends Microbiol.* **10**, 45–52 (2002).
12. Daffé, M., Lacave, C., Lanéelle, M. -A & Lanéelle, G. Structure of the major triglycosyl phenol-phthiocerol of Mycobacterium tuberculosis (strain Canetti). *Eur. J. Biochem.* **167**, 155–160 (1987).
13. Malaga, W. *et al.* Deciphering the genetic bases of the structural diversity of phenolic glycolipids in strains of the Mycobacterium tuberculosis complex. *J. Biol. Chem.* **283**, 15177–15184 (2008).
14. Stadthagen, G. *et al.* Comparative investigation of the pathogenicity of three Mycobacterium tuberculosis mutants defective in the synthesis of p-hydroxybenzoic acid derivatives. *Microbes Infect.* **8**, 2245–2253 (2006).
15. Bourke, J., Brereton, C. F., Gordon, S. V., Lavelle, E. C. & Scanlan, E. M. The synthesis and biological evaluation of mycobacterial p-hydroxybenzoic acid derivatives (p-HBADs). *Org. Biomol. Chem.* **12**, 1114–1123 (2014).
16. Stadthagen, G. *et al.* p-hydroxybenzoic acid synthesis in Mycobacterium tuberculosis. *J. Biol. Chem.* **280**, 40699–40706 (2005).
17. Lundahl, M. *et al.* Mycobacterial para-Hydroxybenzoic Acid-Derivatives (pHBADs) and Related Structures Induce Macrophage Innate Memory. *ACS Chem. Biol.* **15**, 2415–2421 (2020).
18. Vercellone, A. & Puzo, G. New-found phenolic glycolipids in Mycobacterium bovis BCG. Presence of a diglycosylated glycolipid. *J. Biol. Chem.* **264**, 7447–54 (1989).
19. Daffé, M. Further specific triglycosyl phenol phthiocerol diester from Mycobacterium tuberculosis. *Biochim. Biophys. Acta - Lipids Lipid Metab.* **1002**, 257–260 (1989).
20. Watanabe, M., Yamada, Y., Iguchi, K. & Minnikin, D. E. Structural elucidation of new phenolic

glycolipids from Mycobaclerium tuberculosis. *Biochim. Biophys. Acta - Lipids Lipid Metab.* **1210**, 174–180 (1994).

21. Daffe, M. & Servin, P. Scalar, dipolar-correlated and J-resolved 2D-NMR spectroscopy of the specific phenolic mycoside of Mycobacterium tuberculosis. *Eur. J. Biochem.* **185**, 157–162 (1989).

22. Veeneman, G. H., Leeuwen, S. H. V., Zuurmond, H. & Boom, J. H. V. Synthesis of carbohydrate-antegenic structures of mycobacterium tuberculosis using an iodonium ion promoted glycosidation approach. *J. Carbohydr. Chem.* **9**, 783–796 (1990).

23. Fujiwara, T. Synthesis of the Trisaccharide-Protein Conjugate of the Phenolic Glycolipid of Mycobacterium tuberculosis for the Serodiagnosis of Tuberculosis . *Agric. Biol. Chem.* **55**, 2123–2128 (1991).

24. Meng, X. *et al.* Synthesis and immunogenicity of PG-tb1 monovalent glycoconjugate. *Eur. J. Med. Chem.* **134**, 140–146 (2017).

25. Arbués, A. *et al.* Trisaccharides of Phenolic Glycolipids Confer Advantages to Pathogenic Mycobacteria through Manipulation of Host-Cell Pattern-Recognition Receptors. *ACS Chem. Biol.* **11**, 2865–2875 (2016).

26. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie Int. Ed.* **51**, 11774–11777 (2012).

27. Barroso, S., Geerdink, D., Ter Horst, B., Casas-Arce, E. & Minnaard, A. J. Total synthesis of the phenolic glycolipid mycoside B and the glycosylated p-hydroxybenzoic acid methyl ester HBAD-I, virulence markers of mycobacterium tuberculosis. *European J. Org. Chem.* 4642–4654 (2013).

28. Weber, J. *et al.* 2- O -Benzyloxycarbonyl protected glycosyl donors: a revival of carbonate-mediated anchimeric assistance for diastereoselective glycosylation. *Chem. Commun.* **55**, 12543–12546 (2019).

29. Ley, S. V., Owen, D. R. & Wesson, K. E. Rapid access to rare natural pyranosides using 1,2-diacetal protected intermediates. *J. Chem. Soc. Perkin Trans. 1* 2805–2806 (1997).

30. Cheshev, P. E., Khatuntseva, E. A., Tsvetkov, Y. E., Shashkov, A. S. & Nifantiev, N. E. Synthesis of Aminoethyl Glycosides of the Ganglioside GM 1 and Asialo-GM 1 Oligosaccharide Chains. *Russ. J. Bioorganic Chem.* **30**, 60–70 (2004).

31. Volbeda, A. G. *et al.* Chemoselective Cleavage of p-Methoxybenzyl and 2-Naphthylmethyl Ethers Using a Catalytic Amount of HCl in Hexafluoro-2-propanol. *J. Org. Chem.* **80**, 8796–8806 (2015).

32. Nakamura, H. *et al.* Total synthesis of (-)-caprazamycin a. *Angew. Chemie - Int. Ed.* **54**, 3136–3139 (2015).

33. Xu, H. *et al.* Regioselective mono and multiple alkylation of diols and polyols catalyzed by organotin and its applications on the synthesis of value-added carbohydrate intermediates. *Tetrahedron* **72**, 3490–3499 (2016).

34. Wang, L., Overkleeft, H. S., van der Marel, G. A. & Codée, J. D. C. Reagent Controlled Stereoselective Synthesis of α-Glucans. *J. Am. Chem. Soc.* **140**, 4632–4638 (2018).

35. van der Vorm, S., Hansen, T., Overkleeft, H. S., van der Marel, G. A. & Codée, J. D. C. The influence of acceptor nucleophilicity on the glycosylation reaction mechanism. *Chem. Sci.* **8**, 1867–1875 (2017).

36. Provided by Guillaume Le Calvez of Rijksuniversiteit Groningen.

37. Iwasaki, K. *et al.* Total Synthesis of Polycavernosides A and B, Two Lethal Toxins from Red Alga. *J. Org. Chem.* **82**, 13204–13219 (2017).

38. Supply, P. & Brosch, R. The biology and epidemiology of mycobacterium canettii. *Adv. Exp. Med. Biol.* **1019**, 27–41 (2017).

Chapter 5

Synthesis of PGLs originating from *M. leprae* and *M. haemophilum*

L. Melanie Groot contributed to this chapter.

Introduction

Mycobacterium leprae is the etiological agent of leprosy, a chronic disease which often leads to irreversible deformities and lifelong handicaps.[1] The most prevalent PGL of this bacterium (3,6-di-*O*-methyl-ß-D-glucopyranosyl-(1→4)-2,3-di-*O*-methyl-α-L-rhamnopyranosyl-(1→2)-3-*O*-methyl-α-L-rhamnopyranosyl-(1→), PGL-I) constitutes up to 2% of its mass and is thought to play a major role in its pathogenicity (see Chapter 2).[2–11] Two other *M. leprae* triglycosyl PGLs (PGL-II and PGL-III) and a disaccharide PGL have also been detected, all of which are thought to be biosynthetic intermediates of PGL-I.[8,12] Of all known mycobacteria, *Mycobacterium haemophilum* is genetically the most closely associated to *M. leprae*. This "blood-loving" bacterium is a unique species that requires iron supplementation when grown in culture and, like *M. leprae*, prefers lower growth temperatures.[13] *M. haemophilum* also produces a distinct PGL (2,3-di-*O*-methyl-α-L-rhamnopyranosyl-(1→2)-3-*O*-methyl-α-L-rhamnopyranosyl-(1→4)-2,3-di-*O*-methyl-α-L-rhamnopyranosyl-(1→)), which is very similar to PGL-I.[14] A biosynthetic intermediate of this PGL has been found which lacks the C-2'' methyl ether.[15] Many syntheses of truncated *M. leprae* PGLs or variations thereof have been reported (see Chapters 1 & 2). However, in order to fully understand the interactions between PGLs and the host immune system, pure synthetic complete PGLs are required. Therefore, this Chapter describes the synthesis of all known PGLs originating from *M. leprae* and *M. haemophilum*.

The general strategy for the synthesis of these phenolic glycolipids is as described in Chapter 4 (Figure 1).[16,17] Glycans protected with hydrogenation labile groups bearing an iodophenol are to be synthesized from the 'reducing end', after which they can be attached to a phthiocerol alkyne derivative using a Sonogashira cross coupling. The resulting diol can then be esterified with mycocerosic acids using Steglich conditions and finally hydrogenation will lead to the global deprotection and concurrent reduction of the conjugated internal alkyne which is formed in the Sonogashira reaction.

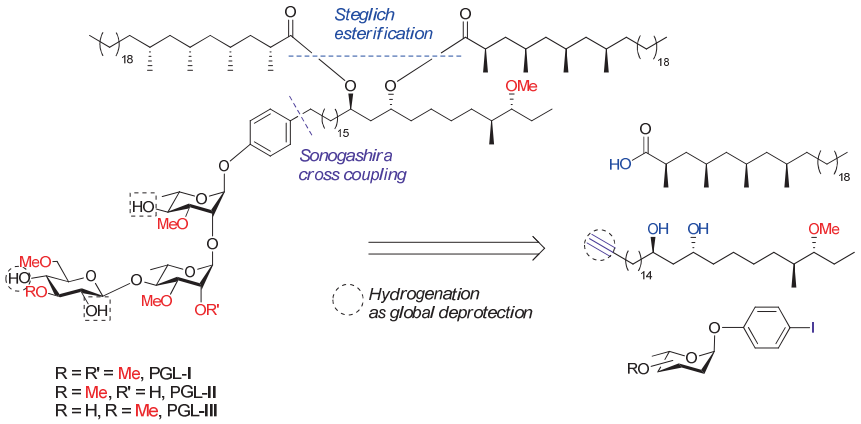


Figure 1. General synthetic strategy of *M. leprae* triglycosyl PGLs.

This synthetic strategy requires the oligosaccharides to be protected only with protecting groups which are susceptible to hydrogenation conditions. In Chapter 4 it was found that a carboxybenzyl (Cbz) protecting group could decrease the amount of synthetic steps required for the synthesis of MTBC PGLs, as it could be used as a hydrogenation labile group capable of selectively forming 1,2-*trans* linkages by means of neighboring group participation.[18] Four out of the six target compounds outlined in this Chapter contain a 1,2-*trans* linked terminal sugar which is not methylated on the C-2 position. Using a C-2 Cbz could therefore benefit the synthesis of these *M. leprae* and *M. haemophilum* PGLs. The retrosynthetic analysis of the target compounds and the resulting building blocks are depicted in Figure 2.

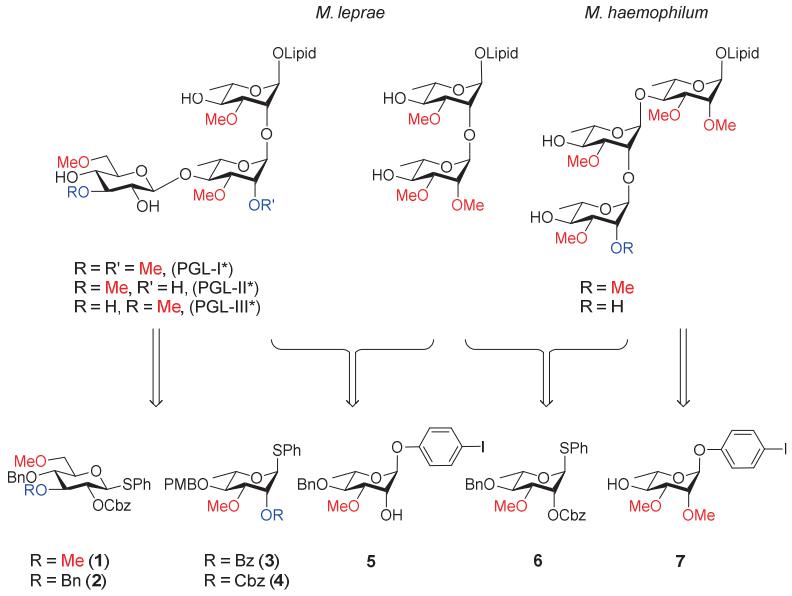
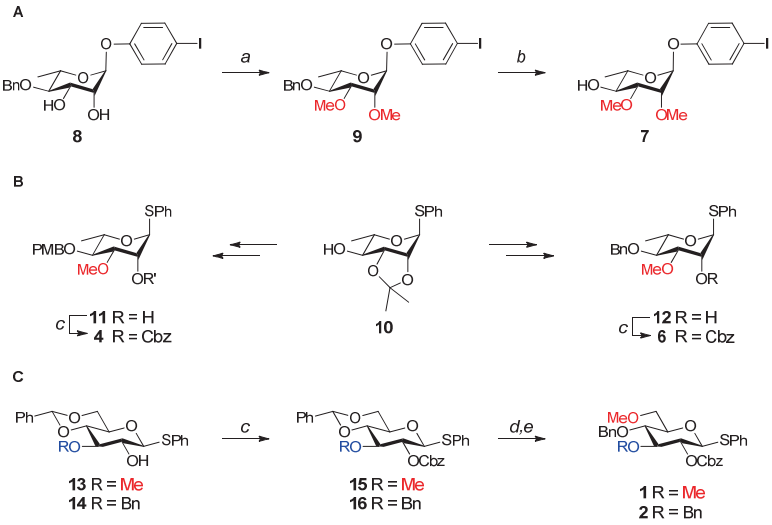


Figure 2. Retrosynthetic analysis of *M. leprae* and *M. haemophilum* glycans. (* = trivial name)

The triglycosyl PGLs of *M. leprae* are to be synthesized starting from acceptor **5** (Chapter 2), which will be coupled to either benzoyl rhamnose donor **3** or Cbz donor **4**. After the necessary protecting group manipulations, the resulting disaccharide acceptors are to be coupled to Cbz glucose donors **1** and **2**. For good measure the results obtained here with the novel Cbz-protected donors, will be compared to those of the corresponding Bz glucose donors used in Chapter 2. The PGLs of *M. haemophilum* are to be synthesized from acceptor **7** and two copies of donor **6**, after which the Cbz of the terminal rhamnose can be either left in place or replaced with a methyl ether. The *M. leprae* disaccharide can be synthesized with acceptor **5** and donor **6**.

Results and Discussion

The synthesis of the previously unreported building blocks is depicted in Scheme 1. The acceptor for the *M. haemophilum* PGLs (**7**) was synthesized by first methylating diol **8** (Scheme 1A) and then removing the C-4 benzyl ether using DDQ.[19]



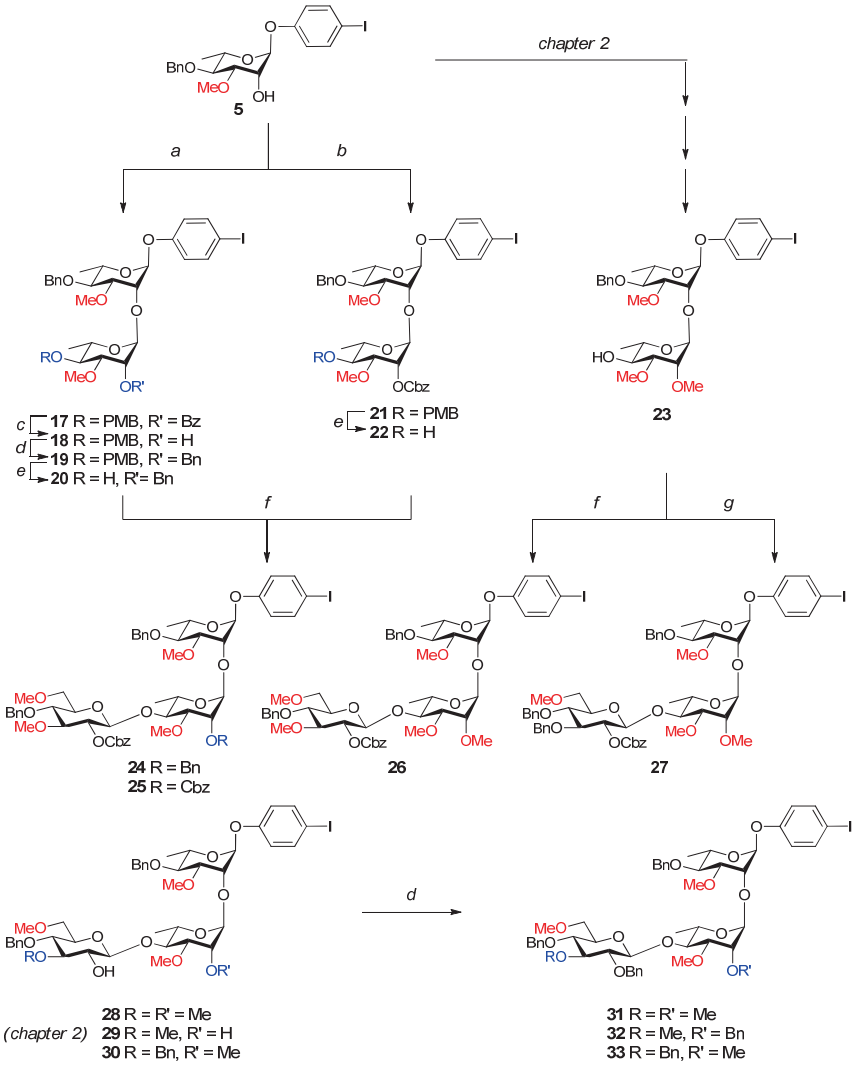
Scheme 1. Building block synthesis. Reagents and conditions: (a) NaH, MeI, DMF, 0 °C → RT, 97%, (b) DDQ, DCM/H_2O (19:1), 97%, (c) CbzCl, DMAP, DCM, 0 °C → RT, 94% (**11**), 68% (**12**), 89% (**13**), 81% (**14**), (d) $BH_3 \cdot THF$, TMSOTf, DCM, 99% (**15**), 91% (**16**), (e) BF_4OMe_3, TTBP, DCM, 78% (**1**), 72% (**2**).

This produced acceptor **7** in 94% yield over 2 steps. Rhamnose donors **4** and **6** (Scheme 1B) were synthesized by protecting the C-2 position of intermediate **11** (Chapter 2) and **12**[20] with a Cbz in 94% and 68% yield, respectively. Glucose donors **1** and **2** could be synthesized from C-3 alkylated benzylidenes **13** and **14** (Scheme 1C). After protection of the C-2 position with a Cbz, a reductive opening of the benzylidene ring with $BH_3 \cdot THF$ and TMSOTf liberated the primary alcohol. This alcohol could be methylated with trimethyloxonium tetrafluoroborate (BF_4OMe_3) and TTBP as a hindered base to prevent migration of the Cbz.† This gave the required glucose donors **1** and **2** in 69% and 53%

† A more detailed investigation of migration-free methylation conditions can be found in Chapter 6

yield over 3 steps, respectively. With the required building blocks in hand the assembly of the oligosaccharides could commence.

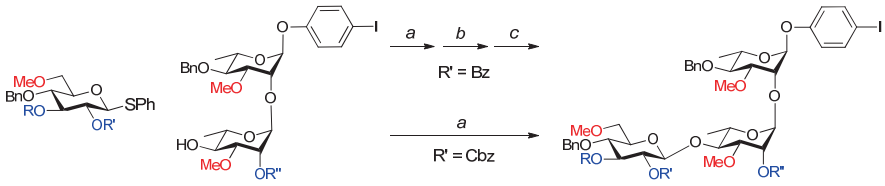
The synthesis of the *M. leprae* trisaccharides is depicted in Scheme 2. In order to fully investigate the potential benefit of using a Cbz group the trisaccharides were made both with benzoyl donors and Cbz donors where applicable. In the route of PGL-I and PGL-III only the glucose donor which is coupled to acceptor **23** (Chapter 2) could benefit from using a Cbz, while PGL-II has two positions which could potentially benefit from a Cbz (C-2' and C-2''). This leaves 3 different options: replacing two benzoyls with benzyls after the final glycosylation (**29** → **32**), replacing the C-2' benzoyl before the final glycosylation (to rule out any effect of the C-2'-*O*-Cbz on the final glycosylation) and coupling of the resulting acceptor to Cbz donor **1** (**20** → **24**) and using a Cbz on both C-2'and C-2'' (**22** → **25**). Coupling of donor **3** to acceptor **5** gave disaccharide **17** in 66% yield. Debenzoylation, subsequent benzylation and removal of the C-4' PMB ether with HCl in HFIP gave disaccharide acceptor **20** in 58% yield over 4 steps. When acceptor **5** was coupled to Cbz donor **4** this produced disaccharide **21** in a modest 47% yield. Multiple attempts were made to improve this yield but to no avail. The C-4' PMB ether was then removed to give disaccharide acceptor **22** in 46% yield over 2 steps. Coupling of disaccharide acceptors **20** and **22** to donor **1** produced trisaccharides **24** and **25** in a similar yield, 66% and 68%, respectively. When disaccharide acceptor **23** was coupled to donor **1**, trisaccharide **26** was produced in 80% yield. Coupling of **23** to donor **2** produced trisaccharide **27** in 96% yield. Benzylation of debenzoylated trisaccharides **28**, **29**, and **30**, which were synthesized as described in Chapter 2 gave protected trisaccharides **31**, **32** and **33** in 64%, 95% and 58% yield, respectively. The results of the synthesis of *M. leprae* of Chapter 2 and this Chapter are summarized in Table 1.



Scheme 2. Multiple synthetic routes towards protected *M. leprae* trisaccharides. Reagents and conditions: (a) Donor **3**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 66%, (b) Donor **4**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 47%, (c) Na, MeOH/THF, 97%, (d) NaH, BnBr, DMF, 0 °C → RT, 100% (**19**), 64% (**31**), 95% (**32**), 58% (**33**), (e) HCl/HFIP, HFIP/DCM, 90% (**20**), 98% (**22**), (f) Donor **1**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 66% (**24**), 68% (**25**), 80% (**26**), (g) Donor **2**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, 96%.

In the route of PGL-I the glycosylation with donor **1** (Entry 2) gave a lower yield when compared to the benzoyl donor (Entry 1), but circumventing the subsequent debenzoylation and benzylation steps not only saved time but increased the overall yield from 36% over seven steps to 46% over five steps.

Table 1. Summarized yield comparisons of Bz and Cbz donors and acceptors for the assembly of *M. leprae* trisaccharides (* = result from Chapter 2).



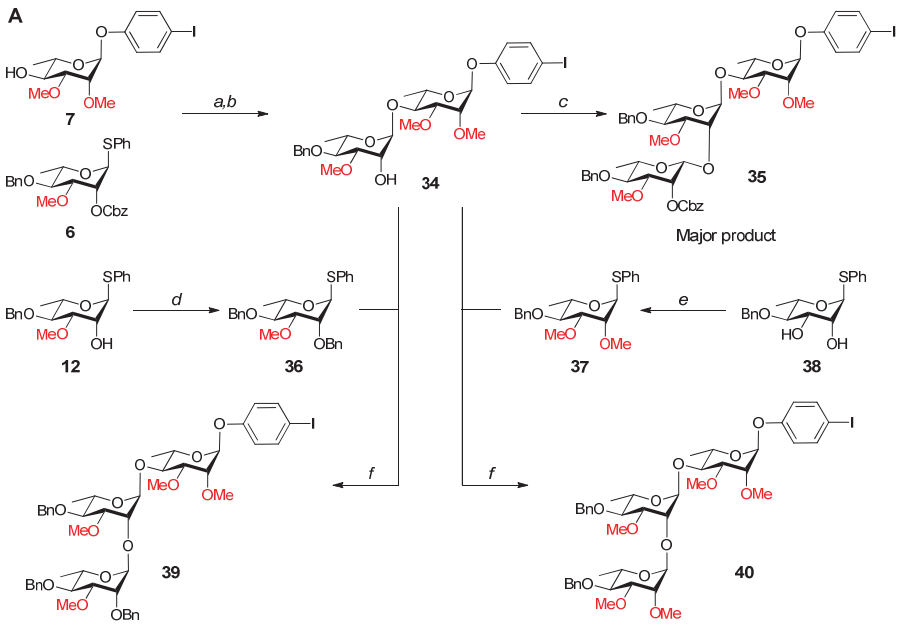
Reagents and conditions: (a) Ph_2SO, Tf_2O, TTBP, DCM -60 °C, (b) Na, MeOH/THF, (c) NaH, BnBr, DMF, 0 °C → RT.

Entry	Acceptor (Yield, steps)	R	R'	R''	PGL	a	b	c	Product	Yield (steps)
1	**23** (57%, 4)*	Me	Bz/ Bn	Me	**I**	100%*	99%*	64%	**31**	36% (7)
2	**23** (57%, 4)*	Me	Cbz	Me	**I**	80%	n.a.	n.a.	**26**	46% (5)
3	**34** (66%, 2)*	Me	Bz/ Bn	Bz/ Bn	**II**	88%*	84%*	95%	**32**	46% (5)
4	**20** (58%, 4)	Me	Cbz	Bz/ Bn	**II**	66%	n.a.	n.a.	**24**	38% (5)
5	**22** (46%, 2)	Me	Cbz	Cbz	**II**	68%	n.a.	n.a.	**25**	31% (3)
6	**23** (57%, 4)*	Bn	Bz/ Bn	Me	**III**	93%*	97%*	58%	**33**	30% (7)
7	**23** (57%, 4)*	Bn	Cbz	Me	**III**	96%	n.a.	n.a.	**27**	55% (5)

In a similar fashion the yield of the PGL-III trisaccharide was improved by Cbz glucose donor **2** from 30% over seven steps (Entry 6) to 55% over five steps (Entry 7). In the case of PGL-II, debenzoylation and subsequent benzylation in the trisaccharide stadium (Entry 3) gave protected trisaccharide **32** in 46% over a total of five steps. Entry 4 shows a slightly lower yield (38%) over the same number of steps and Entry 5 presents the PGL-II trisaccharide in 31% yield over three steps. Reducing the number of steps from five to three is an improvement in terms of time but leads to the lowest overall yield of all.

This was mostly due to the coupling of the Cbz bearing rhamnose donor **4** to acceptor **5**. Perhaps the intrinsically low reactivity of axial acceptor **5** could explain the difference in outcome between the Cbz glucose and rhamnose donors. This hypothesis can be tested during the assembly of *M. haemophilum* trisaccharides which is described below.

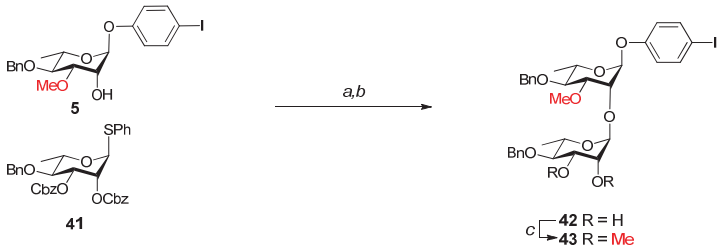
The synthesis of *M. haemophilum* trisaccharides started with the coupling of acceptor **7** to donor **6** (Scheme 3), which selectively produced the α-linked disaccharide. To aid in the purification the yield was determined after methanolysis of the C-2' Cbz under mild basic conditions, which gave disaccharide acceptor **34** in 65% yield over 2



Scheme 3. Synthesis of *M. haemophilum* trisaccharides **39** and **40** (**A**) *Reagents and conditions:* (a) Ph_2SO, Tf_2O, TTBP, DCM -60 °C, (b) K_2CO_3, MeOH, 65% over 2 steps (**34**), (c) Donor **6**, Ph_2SO, Tf_2O, TTBP, DCM -60 °C, (d) NaH, BnBr, DMF, 0 °C → RT, 86%, (e) NaH, MeI, DMF, 0 °C → RT, 92%, (f) IDCP, Et_2O/DCE (4:1), 0 °C → 4 °C, 95% (6:1) (**39**), 84% (4:1) (**40**).

steps. Encouraged by these results, disaccharide acceptor **34** was then coupled to donor **6**. However, this produced a 1:3 α/β mixture in moderate yield. This result is in line with the results that were obtained during the synthesis of *M. leprae* trisaccharides, whereby the Cbz protecting group is able to selectively and efficiently form 1,2-*trans* linkages when coupled to the reactive equatorial C-4 alcohol of rhamnose but to a much lesser extent

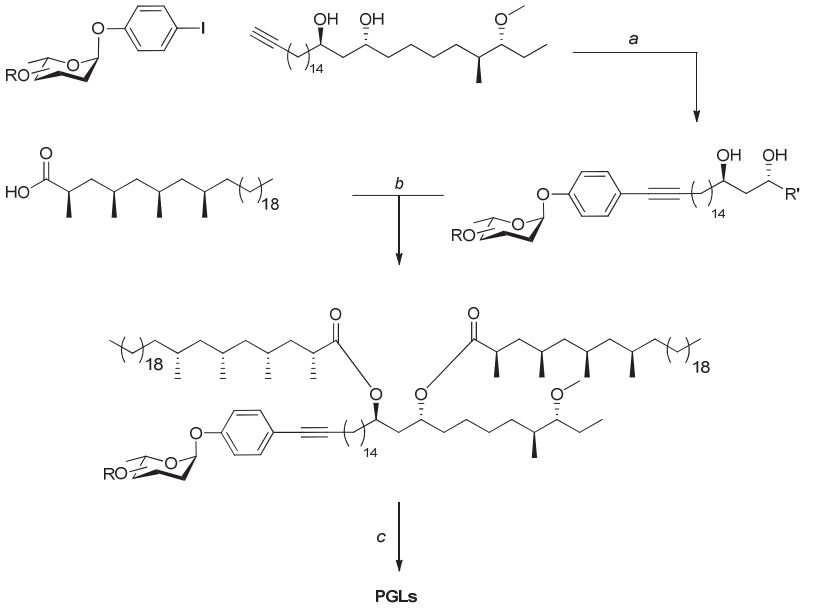
when coupled to the more unreactive axial C-2 alcohol. While these are interesting results that warrant further investigations, a new approach had to be taken to effectively synthesize the *M. haemophilum* trisaccharides. Therefore, as an alternative to rhamnose donor **6**, disaccharide acceptor **34** was coupled to peralkylated donors **36** and **37**, which were derived from **12** and **38**, respectively. These donors were chosen because of their high reactivity and these would limit the number of reactions required in the trisaccharide stadium. IDCP was used as a mild coupling reagent and trisaccharides **39** and **40** were obtained in 95% (α/β 6:1) and 84% (α/β 4:1) yield, respectively. The anomers could be separated by careful column chromatography. This leaves the *M. leprae* disaccharide as the final glycan to be synthesized (Scheme 4).



Scheme 4. Synthesis of *M. leprae* disaccharide **43**. *Reagents and conditions:* (a) Ph_2SO, Tf_2O, TTBP, DCM -60 °C, (b) K_2CO_3, MeOH, 69% over 2 steps, (c) NaH, MeI, DMF, 0 °C → RT, 77%.

Initially disaccharide **43** was to be synthesized from donor **6** like the *M. haemophilum* disaccharide acceptor. However, the results obtained during the glycosylation of donor **6** with hindered acceptor **34** were discouraging. Alternatively, disaccharide **43** could have been synthesized from 2,3-di-*O*-methyl rhamnose donor **37** but the stereoselectivity of this donor was relatively poor when it was coupled to **34**. Moreover, the resulting α/β mixture was particularly difficult to separate. It was therefore chosen to synthesize the disaccharide with 2,3-di-*O*-Cbz donor **41** which was used in Chapter 4 for the synthesis of the *M. bovis* disaccharide. Interestingly the combination of this donor with acceptor **5**, featuring an axial C-2 alcohol, selectively produced the α-product in good yield and after methanolysis and subsequent methylation the target disaccharide **43** was produced in 53% yield over 3 steps. With the final iodoaryl bearing glycan now prepared, the final steps of the PGL assembly could be undertaken, the yields of which are depicted in Table 2.

Table 2. Yields of the final stages of PGL assembly



Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, 40 °C, (b) DIC, DMAP, DCM, 0 °C → RT → 40 °C, (c) Pd/C, H_2, THF/EtOH.

Starting material	Sonogashira	Esterification	Hydrogenation	Overall yield
26	83%	79%	79%	52%
25	93%	80%	76%	57%
27	83%	76%	40%	25%
43	86%	81%	86%	60%
39	94%	79%	81%	60%
40	100%	80%	73%	58%

The glycans were attached to the phthiocerol alkyne derivative through a Sonogashira cross-coupling in excellent yields. The resulting diols were then esterified with two equivalents of mycocerosic acid under Steglich conditions in good yields. The hydrogenation that served as global deprotection proceeded smoothly in most cases. However, in the case of PGL-III only a moderate yield (40%) was obtained, even though

TLC analysis showed the formation of a single product. Perhaps part of the material was lost because of interactions with the catalyst or the Celite used during work-up.[21]

Conclusion

This Chapter describes the synthesis of all known phenolic glycolipids from *Mycobacterium leprae* and *M. haemophilum*. The carboxybenzyl (Cbz) protecting group, which was probed in Chapter 4, was applied in the synthesis of these complex glycolipids. For the *M. leprae* PGLs, glucose Cbz donors **1** and **2** were synthesized and these were successfully used in the assembly of the desired trisaccharides **25**, **26** and **27**. Although the yields for the glycosylation reactions were in most cases lower when compared to the corresponding benzoyl donors, the overall yield turned out higher as the debenzoylation and benzylation steps could be omitted. When rhamnose Cbz donor **4** was coupled to hindered acceptor **5** the yield was lower when compared to the benzoyl donor, and this low yield could not be compensated by circumventing the debenzoylation and benzylation steps. It seems that a relatively reactive acceptor is required in glycosylation reactions that use a donor with a C-2 Cbz group to outcompete the reactions featuring a donor with a C-2 benzoyl ester. This trend also holds true for the synthesis of *M. haemophilum* trisaccharides, where rhamnose donor **6** gave was coupled in good yield and selectivity to reactive acceptor **7**, but when the same donor was used for hindered disaccharide acceptor **34** the β product was isolated as the major product. The final rhamnosylations were therefore achieved with peralkylated donors **36** and **37** using IDCP as a mild activating agent. Finally, the *M. leprae* disaccharide **43** was synthesized using donor **41**, carrying a Cbz-group at both the C-2 and C-3 positions and which was used for the synthesis of the *M. bovis* disaccharide (Chapter 4). The iodoaryl-bearing glycans were then coupled to the phthiocerol alkyne derivative using a Sonogashra coupling, which was followed by a Steglich esterification of the resulting diol with mycocerosic acid. Finally, global deprotection with H_2 and Pd/C resulted in the complete assembly of all the phenolic glycolipids originating from *Mycobacterium leprae* and *haemophilum* and these are at present being investigated for their immunomodulatory capabilities.

EXPERIMENTAL:

General procedures

All reactions were carried out in oven-dried glassware (80 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under N_2 atmosphere (balloon). Commercially available reagents and solvents (Aldrich Chemistry, Honeywell, Merck, Fischer Scientific, Biosolve, Fluka, VWR Chemicals, Acros Organics, Fluorochem, Brunschwig, Carbosynth) were used as received unless stated otherwise.

Solvents for reactions were reagent grade and dried by storage over flame dried 4 Å molecular sieves when needed. Tf_2O used in glycosylations was dried by distillation over P_2O_5 and stored under N_2 atmosphere in a Schlenk flask at -20 °C. Et_2O used for column chromatography was distilled before use and stored over iron filings. EtOAc used for column chromatography was distilled before use. NEt_3 used for Sonogashira couplings was distilled from KOH, degassed with N_2, and stored over KOH for a maximum of 24 hours. DMAP used for Steglich esterifications was recrystallized from toluene before use.

Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, F254); visualization was carried out by irradiation with UV light (254 nm), and spraying with 20% H_2SO_4 in EtOH (w/v) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% H_2SO_4 or $KMnO_4$ (7.5 g/L) and K_2CO_3 (50 g/L) in H_2O, followed by charring. Additional analysis with TLC-MS was used when needed.

Column chromatography was carried out using silica gel (Fluka, 40-63 μm mesh). The column was prepared using the apolar component mentioned in the corresponding experimental. If the apolar component was pentane the product was brought up in toluene. If the apolar component was DCM the product was brought up in DCM, possibly with a few drops of methanol if needed. Colum chromatography was performed using a gradient ranging from 0% polar component up to the ratio mentioned in the corresponding experimental in 2 to 5 steps depending on the ease of separation.

NMR spectra were recorded at ambient temperature on a Bruker AV-400LIQ or AV-850 spectrometer. Samples were prepared in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) in $CDCl_3$ are reported in ppm relative to Me_4Si (δ: 0.00 ppm) for ^{1}H-NMR and $CDCl_3$ (δ: 77.16 ppm) for ^{13}C-NMR. Chemical shifts in CD_3OD are reported in ppm relative to H_2O (δ: 4.87 ppm) for ^{1}H-NMR and CD_3OD (δ: 49.00 ppm) for ^{13}C-NMR. ^{13}C-APT spectra are ^{1}H decoupled and structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants (J) are given in Hz. Coupling constants of anomeric carbon atoms ($J_{H1,C1}$) were determined using HMBC-GATED experiments. Optical rotations were measured on an Anton Paar Modular Circular Polarimeter MCP 100/150. High resolution mass spectra were recorded on a Synapt G2-Si or a Q Exactive HF Orbitrap equipped with an electron spray ion source positive mode. Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR.

General procedure A: Pre-activation glycosylation

Donor (1.5 eq), Ph_2SO (2.0 eq) and TTBP (3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -60 °C after which Tf_2O (2.0 eq) was added to the solution. After stirring for 30 minutes, acceptor (1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (1-4 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography.

General procedure B: IDCP mediated glycosylation

Starting material (1.0 eq) and donor (1.5 eq) were coevaporated together with toluene and subsequently dissolved in Et_2O/DCE (0.05 M, 4:1). Flame-dried 3Å molecular sieves were added and the resulting solution was stirred for 15 minutes while it was cooled to 0 °C, after which IDCP (3.0 eq) was added. The reaction was allowed to stir while warming to rT. When TLC indicated complete consumption of the starting material the reaction mixture was filtered over celite, diluted with Et_2O and transferred to a separation funnel. The organic layer was then washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, sat. aq. $CuSO_4$ and brine, after which it was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography.

General procedure C: Sonogashira cross coupling

Iodoaryl glycoside (1.0 eq) was dissolved in freshly distilled NEt_3 (0.05 M) together with phthiocerol (1.2 eq). A mixture of $Pd(PPh_3)_2Cl_2$, PPh_3 and CuI (ratio 1:1:2) was dissolved in freshly distilled NEt_3 and was stirred for 15 minutes at 40 °C. Of this cocktail, enough was added to the sugar/alkyne mixture to amount to 0.05 eq $Pd(PPh_3)_2Cl_2$, 0.05 eq PPh_3 and 0.1 eq CuI. The reaction was allowed to stir at 40 °C until the complete consumption of the starting material as indicated by TLC (2-16 h). The solvent was then removed under a stream of N_2. The crude was then transferred to a silica column in toluene and the column was flushed with toluene. Thereafter the product was purified by means of column chromatography.

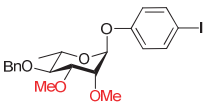
General procedure D: Esterification with mycocerosic acid

Starting material (1.0 eq) was dissolved in dry DCM (0.05 M) together with mycocerosic acid (3.0 eq) and DMAP (9 eq). The resulting mixture was cooled to 0 °C after which DIC (6 eq) was added. The reaction was allowed to stir for 16 hours while warming to rT, after which it was warmed to 40 °C and stirred for a further 5 hours. The reaction mixture was then diluted with Et_2O and the organic layer was washed 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography. Note: In order to detect the most prevalent byproducts on TLC, staining with $KMnO_4$ is required.

General procedure E: Hydrogenation

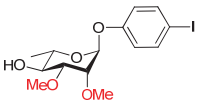
Starting material (1.0 eq) was dissolved in a mixture of THF and EtOH (1:1, 0.007 M) and the solution was purged with N_2. Pd/C (10%, 1.0 eq) was then added to the solution and the resulting mixture was purged with H_2. The reaction was left to stir under H_2 atmosphere until TLC complete conversion of the starting material and reaction intermediates to a single low running spot (DCM-MeOH 19:1). The reaction mixture was then purged with N_2 and filtered over celite and the celite was rinsed with acetone. Purification by means of column chromatography.

4-iodophenyl 2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (9)



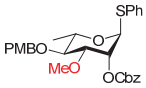
Compound **8** (2.74 g, 6.0 mmol, 1.0 eq) was dissolved in dry DMF (50 mL, 0.12 M) and MeI (1.12 mL, 18 mmol, 3.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.72 g, 18 mmol, 3.0 eq) was added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (2.81 g, 5.80 mmol, 97%) as a clear oil. $[\alpha]_D^{25}$ = -96.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.36-7.26 (m, 5H, C*H*$_{arom}$); 6.85-6.82 (m, 2H, C*H*$_{arom}$); 5.52 (s, 1H, H-1); 4.77 (dd, 2H, *J* = 10.8, 120.4 Hz, PhC*H*$_2$); 3.79-3.75 (m, 2H, H-2, H-3); 3.72-3.66 (m, 1H, H-5); 3.59 (s, 3H, OC*H*$_3$); 3.58 (s, 3H, OC*H*$_3$); 3.49 (t, 1H, *J* = 9.0 Hz, H-4); 1.25 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2, 138.6 (C$_{q,arom}$); 138.5, 128.5, 128.1, 127.8, 118.7 (*C*H$_{arom}$); 95.3 (C-1); 84.9 (*C*I$_{arom}$); 81.3 (C-3); 80.3 (C-4); 77.3 (C-2); 68.8 (C-5); 59.5, 58.1 (O*C*H$_3$); 18.1 (C-6). IR (thin film, cm^{-1}): 1046, 1093, 1119, 1138, 1178, 1232, 1275, 1454, 1484. HRMS calculated for $C_{21}H_{25}IO_5Na$ 507.06389 $[M+Na]^+$; found 507.06400.

4-iodophenyl 2,3-di-*O*-methyl-α-L-rhamnopyranoside (7)



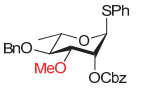
Compound **9** (0.58 g, 1.19 mmol, 1.0 eq) was dissolved in DCM/H_2O (20:1, 12 mL, 0.1 M) and the solution was cooled to 0 °C. After stirring for a few minutes DDQ (0.54 g, 2.38 mmol, 2.0 eq) was added to the solution. The reaction was stirred vigorously overnight after which it was quenched by addition of sat. aq. $NaHCO_3$. The organic layer was then washed sat. aq. $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 3:7) gave the title compound (455 mg, 1.15 mmol, 97%) as a pale oil. $[\alpha]_D^{25}$ = -66.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.60-7.57 (m, 2H, C*H*$_{arom}$); 6.88-6.84 (m, 2H, C*H*$_{arom}$); 5.54 (d, 1H, *J* = 2.0 Hz, H-1); 3.81 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2); 3.70-3.58 (m, 3H, H-3, H-4, H-5); 3.55 (s, 3H, OC*H*$_3$); 3.54 (s, 3H, OC*H*$_3$); 2.60 (bs, 1H, 4-O*H*); 1.27 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 138.5, 118.7 (*C*H$_{arom}$); 95.6 (C-1); 85.0 (*C*I$_{arom}$); 80.9 (C-3); 75.8 (C-2); 71.5 (C-4); 69.2 (C-5); 59.4, 57.3 (O*C*H$_3$); 17.8 (C-6). IR (thin film, cm^{-1}): 1046, 1086, 1120, 1135, 1201, 1232, 1484, 3470. HRMS calculated for $C_{14}H_{20}IO_5$ 395.03499 $[M+H]^+$; found 395.03463.

Phenyl 2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-(4-methoxybenzyl)-1-thio-α-L-rhamnopyranoside (4)



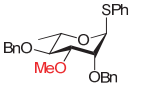
Compound **11** (14 mg, 0.37 mmol, 1.0 eq) was dissolved in DCM (2 mL, 0.2 M) and DMAP (124 mg, 0.94 mmol, 2.5 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (0.11 mL, 0.75 mmol, 2.0 eq) was slowly added. The reaction was allowed to stir for 4 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (184 mg, 0.35 mmol, 94%) as a clear oil. $[\alpha]_D^{25}$ = -105 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47-7.43 (m, 2H, C*H*$_{arom}$); 7.42-7.23 (m, 12H, C*H*$_{arom}$); 6.90-6.86 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.38 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2); 5.18 (dd, 2H, *J* = 12.4, 18.0 Hz, PhC*H*$_2$); 4.68 (dd, 2H, *J* = 10.4, 28.4 Hz, PhC*H*$_2$); 4.19-4.15 (m, 1H, H-5); 3.79 (s, 3H, C*H*$_{3,PMB}$); 3.62 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.49-3.43 (m, 4H, H-4, OC*H*$_3$); 1.31 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.4 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 135.0, 134.0 (C$_{q,arom}$); 131.8 (*C*H$_{arom}$); 130.7 (C$_{q,arom}$); 129.8, 129.2, 128.7, 128.7, 128.6, 127.8, 113.9 (*C*H$_{arom}$); 85.9 (C-1); 80.6 (C-3); 79.8 (C-4); 75.3 (Ph*C*H$_2$); 74.4 (C-2); 70.1 (Ph*C*H$_2$); 69.2 (C-5); 58.0 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 17.8 (C-6). IR (thin film, cm^{-1}): 1027, 1086, 1172, 1248, 1302, 1382, 1457, 1514, 1747. HRMS calculated for $C_{29}H_{36}NO_7S$ 542.2212 $[M+NH_4]^+$; found 542.2208.

Phenyl 2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-benzyl)-1-thio-α-L-rhamnopyranoside (6)



Compound **12**[20] (3.30 g, 9.16 mmol, 1.0 eq) was dissolved in DCM (92 mL, 0.1 M) and DMAP (2.24 g, 18.3 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (2.58 mL, 18.3 mmol, 2.0 eq) was slowly added. The reaction was allowed to stir for 3 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (3.07 g, 6.2 mmol, 68%) as a clear oil. $[\alpha]_D^{25}$ = -116.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.46-7.43 (m, 2H, C*H*$_{arom}$); 7.41-7.24 (m, 13H, C*H*$_{arom}$); 5.52 (d, 1H, *J* = 1.6 Hz, H-1); 5.39 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 5.18 (dd, 2H, *J* = 12.0, 18.0 Hz, PhC*H*$_2$); 4.76 (dd, 2H, *J* = 11.0, 113.0 Hz, PhC*H*$_2$); 4.22-4.18 (m, 1H, H-5); 3.63 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.50-3.45 (m, 4H, H-4, OC*H*$_3$); 1.32 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 154.8 (*C*O$_{Cbz}$); 138.6, 135.0, 133.9 (C$_{q,arom}$); 131.9, 129.2, 128.7, 128.7, 128.6, 128.5, 128.1, 127.9, 127.8 (*C*H$_{arom}$); 85.9 (C-1); 80.6 (C-3); 80.2 (C-4); 75.6 (Ph*C*H$_2$); 74.4 (C-2); 70.2 (Ph*C*H$_2$); 69.2 (C-5); 58.0 (O*C*H$_3$); 17.8 (C-6). IR (thin film, cm^{-1}): 1027, 1086, 1100, 1262, 1382, 1454, 1482, 1747. HRMS calculated for $C_{28}H_{30}O_6SNa$ 517.16653 $[M+Na]^+$; found 517.16525.

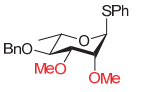
Phenyl 2,4-di-*O*-benzyl-3-*O*-methyl-1-thio-α-L-rhamnopyranoside (36)



Compound **12**[20] (1.26 g, 3.40 mmol, 1.0 eq) was dissolved in dry DMF (34 mL, 0.1 M) and BnBr (0.49 mL, 4.09 mmol, 1.2 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.20 g, 5.11 mmol, 1.5 eq) was added. The reaction mixture was warmed to rt while stirring for 6 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in*

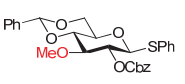
vacuo. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (1.33 g, 2.94 mmol, 86%) as a clear oil. $[\alpha]_D^{25}$ = -21.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.22 (m, 15H, C*H*$_{arom}$); 5.52 (s, 1H, H-1); 4.94 (dd, 1H, *J* = 11.2 Hz, PhC*H*H); 4.76-4.62 (m, 3H, PhC*H*H, PhCH_2); 4.14 (dq, 1H, *J* = 2.0, 6.4 Hz, H-5); 4.05 (dd, 1H, *J* = 1.6, 2.0 Hz, H-2); 3.62-3.54 (m, 2H, H-3, H-4); 3.41 (s, 3H, OCH_3); 1.35 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 138.8, 138.0, 134.9 ($C_{q,arom}$); 131.4, 129.1, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.4 (*C*H$_{arom}$); 85.8 (C-1); 82.2 (C-3); 80.6 (C-4); 75.9 (C-2); 75.5, 72.2 (Ph*C*H$_2$); 69.2 (C-5); 57.7 (O*C*H$_3$); 18.0 (C-6). IR (thin film, cm^{-1}): 1046, 1202, 1232, 1275, 1452, 1484, 1584, 3486. HRMS calculated for $C_{27}H_{30}O_4SNa$ 473.17570 [M+Na]$^+$; found 473.17562.

Phenyl 2,3-di-*O*-methyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (37)



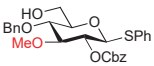
Compound **38** (2.39 g, 6.90 mmol, 1.0 eq) was dissolved in dry DMF (50 mL, 0.12 M) and MeI (1.3 mL, 20.7 mmol, 3.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.83 g, 15.7 mmol, 3.0 eq) was added. The reaction mixture was warmed to rt while stirring for 2 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (2.37 g, 6.33 mmol, 92%) as a clear oil. $[\alpha]_D^{25}$ = -108.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.48-7.45 (m, 2H, C*H*$_{arom}$); 7.39-7.23 (m, 8H, C*H*$_{arom}$); 5.60 (d, 1H, *J* = 1.6 Hz, H-1); 4.76 (dd, 2H, *J* = 10.8, 120.4 Hz, PhCH_2); 4.18-4.14 (m, H-5); 3.88 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2); 3.58-3.47 (m, 8H, H-3, H-4, OCH_3); 1.33 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 138.7, 134.9 ($C_{q,arom}$); 131.1, 129.1, 128.5, 128.1, 127.8, 127.4 (*C*H$_{arom}$); 84.7 (C-1); 81.9 (C-3); 80.6 (C-4); 79.1 (C-2); 75.5 (Ph*C*H$_2$); 69.0 (C-5); 58.3, 57.9 (O*C*H$_3$); 17.9 (C-6). IR (thin film, cm^{-1}): 1027, 1086, 1116, 1454, 1482. HRMS calculated for $C_{21}H_{26}O_4SNa$ 397.14440 [M+Na]$^+$; found 397.14431.

Phenyl 2-*O*-benzyloxycarbonyl-3-*O*-methyl-4,6-*O*-benzylidene-1-thio-ß-D-glucopyranoside (15)



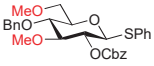
Compound **13** (0.57 g, 1.41 mmol, 1.0 eq) was dissolved in DCM (14 mL, 0.1 M) and DMAP (0.38 g, 3.10 mmol, 2.2 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (0.4 mL, 2.82 mmol, 2.0 eq) was slowly added. The reaction was allowed to stir for 6 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (0.637 g, 1.25 mmol, 89%) as a white solid. $[\alpha]_D^{25}$ = 2.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.52-7.18 (m, 15H, C*H*$_{arom}$); 5.49 (s, 1H, PhC*H*); 5.23 (dd, 2H, *J* = 12.0, 22.8 Hz, PhC$H_{2,Cbz}$); 4.78-4.69 (m, 2H, H-1, H-2); 4.32 (dd, 1H, *J* = 5.0, 10.6 Hz, H-6); 3.74-3.68 (m, 1H, H-6); 3.62-3.49 (m, 5H, H-3, H-4, OCH_3); 3.46-3.39 (m, 1H, H-5). ^{13}C-APT NMR (101 MHz) δ: 154.3 (CO_{Cbz}); 137.0, 135.1 ($C_{q,arom}$); 132.9 (*C*H$_{arom}$); 132.0 ($C_{q,arom}$); 129.0, 128.9, 128.6, 128.5, 128.2, 128.0, 126.0 (*C*H$_{arom}$); 101.1 (Ph*C*H); 86.6 (C-1); 81.8 (C-4); 80.8 (C-3); 75.7 (C-2); 70.3 (C-5); 70.0 (Ph*C*H$_{2,Cbz}$); 68.4 (C-6); 60.7 (O*C*H$_3$). IR (thin film, cm^{-1}): 1026, 1070, 1093, 1248, 1382, 1457, 1753. HRMS calculated for $C_{28}H_{28}O_7SNa$ 531.1453 [M+Na]$^+$; found 531.1444.

Phenyl 2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-benzyl-1-thio-ß-D-glucopyranoside (44)



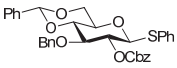
Compound **15** (0.63 g, 1.24 mmol, 1.0 eq.) was co-evaporated with toluene (3x) under N_2 atmosphere before it was dissolved in dry DCM (12.4 mL, 0.1 M). BH_3·THF (1 M in THF, 6.2 mL, 6.2 mmol, 5.0 eq.) was added dropwise to the solution after which TMSOTf (22 µL, 0.12 mmol, 0.1 eq.) was added to the mixture. The reaction mixture was stirred for 5 h and slowly quenched with NEt_3 (1.2 mL) followed by MeOH, which was added until the formation of H_2 ceased. The mixture was concentrated and co-evaporated with MeOH (2x). Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (0.628 g, 1.23 mmol, 99%) as a white solid. $[\alpha]_D^{25}$ = 16.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.25 (m, 15H, C*H*$_{arom}$); 5.27 (s, 2H, PhC*H*$_2$); 4.82 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.72-4.61 (m, 3H, H-1, H-2, PhCH*H*); 3.86 (dd, 1H, *J* = 2.4, 12.0 Hz, H-6); 3.67 (dd, 1H, *J* = 4.6, 12.0 Hz, H-6); 3.52-3.50 (m, 4H, H-3, OC*H*$_3$); 3.47-3.42 (m, 1H, H-4); 3.39-3.35 (m, 1H, H-5); 1.87 (bs, 1H, 6-O*H*). ^{13}C-APT NMR (101 MHz) δ: 154.4 (*C*O$_{Cbz}$); 137.8, 135.3 (C$_{q,arom}$); 132.7 (*C*H$_{arom}$); 132.5 (C$_{q,arom}$); 129.2, 129.1, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1 (*C*H$_{arom}$); 86.2 (C-1); 86.0 (C-4); 79.5 (C-5); 77.0 (C-3); 76.4 (C-2); 75.2, 70.3 (Ph*C*H$_2$); 32.0 (C-6); 61.1 (O*C*H$_3$). IR (thin film, cm^{-1}): 1029, 1040, 1055, 1078, 1089, 1119, 1142, 1259, 1757, 2930. HRMS calculated for $C_{35}H_{36}O_7SNa$ 533.1610 [M+Na]$^+$; found 533.1605.

Phenyl 2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-1-thio-ß-D-glucopyranoside (1)



Compound **44** (179 mg, 0.35 mmol, 1.0 eq.) and TTBP (362 mg, 1.46 mmol, 4.0 eq) were co-evaporated with toluene (3x) under N_2 atmosphere and dissolved in dry DCM (7.2 mL, 0.05 M) and flame-dried rod shaped 3Å molecular sieves were added. Trimethyloxonium tetrafluoroborate (160 mg, 1.08 mmol, 3.0 eq) was then added to the mixture and the reaction was left to stir for 1.5 hours. The reaction was quenched with NEt_3 (0.5 mL), filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (143 mg, 0.27 mmol, 78%) as a white solid. $[\alpha]_D^{25}$ = 13.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.43-7.22 (m, 15H, C*H*$_{arom}$); 5.27 (s, 2H, PhC*H*$_{2,Cbz}$); 4.81 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.73 (t, 1H, *J* = 9.4 Hz, H-2); 4.62-4.59 (m, 2H, H-1, PhCH*H*); 3.66-3.55 (m, 3H, H-3, H-6); 3.49 (s, 3H, OC*H*$_3$); 3.48-3.39 (m, 2H, H-4, H-5); 3.36 (s, 3H, OC*H*$_3$). 13C-APT NMR (101 MHz) δ: 154.4 (*C*O$_{Cbz}$); 138.1, 135.3, 133.1 (C$_{q,arom}$); 128.9, 128.7, 128.6, 128.6, 128.4, 128.2, 128.2, 128.1, 128.0 (*C*H$_{arom}$); 86.4 (C-1); 86.3 (C-4); 79.2 (C-5); 77.0 (C-3); 76.7 (C-2); 75.1 (Ph*C*H$_2$); 71.1 (C-6); 70.1 (Ph*C*H$_{2,Cbz}$); 60.9, 59.5 (O*C*H$_3$). IR (thin film, cm^{-1}): 1002, 1026, 1076, 1088, 1143, 1148, 1251, 1381, 1455, 1756, 2929. HRMS calculated for $C_{29}H_{32}O_7SNa$ 547.1766 [M+Na]$^+$; found 547.1761.

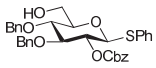
Phenyl 2-*O*-benzyloxycarbonyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-ß-D-glucopyranoside (16)



Compound **14** (2.03 g, 4.51 mmol, 1.0 eq) was dissolved in DCM (173 mL, 0.03 M) and DMAP (1.65 g, 13.5 mmol, 3.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (1.9 mL, 13.5 mmol, 3.0 eq) was slowly added. The reaction was allowed to stir for 5 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (2.14 g, 3.66 mmol, 81%) as a white solid. $[\alpha]_D^{25}$ = 7.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.46-7.22 (m, 20H, C*H*$_{arom}$); 5.56

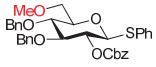
(s, 1H, PhC*H*); 5.23 (s, 2H, PhC$H_{2,Cbz}$); 4.85-4.82 (m, 2H, H-2, PhC*H*H); 4.73-4.64 (m, 2H, H-1, PhCH*H*); 4.37 (dd, 1H, *J* = 4.8, 10.4 Hz, H-6); 3.82-3.70 (m, 3H, H-3, H-4, H-6); 3.51-3.45 (m, 1H, H-5). ^{13}C-APT NMR (101 MHz) δ: 154.3 (CO_{Cbz}); 138.0, 137.1, 135.2 ($C_{q,arom}$); 133.2 (CH_{arom}); 131.9 ($C_{q,arom}$); 129.2, 129.1, 128.7, 128.5, 128.4, 127.9, 127.8, 126.1 (CH_{arom}); 101.3 (Ph*C*H); 86.7 (C-1); 81.2 (C-4); 79.9 (C-3); 75.8 (C-2); 74.7 (Ph*C*H$_2$); 70.6 (C-5); 70.2 (Ph*C*H$_{2,Cbz}$); 68.6 (C-6). IR (thin film, cm^{-1}): 1027, 1069, 1096, 1249, 1312, 1382, 1441, 1455, 1754. HRMS calculated for $C_{34}H_{32}O_7SNa$ 607.1766 [M+Na]$^+$; found 607.1761.

Phenyl 2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-1-thio-ß-D-glucopyranoside (45)



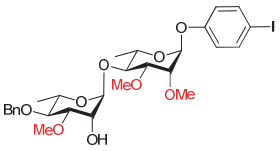
Compound **16** (257 mg, 0.44 mmol, 1.0 eq.) was co-evaporated with toluene (3x) under N_2 atmosphere before it was dissolved in dry DCM (4.4 mL, 0.1 M). A 1M solution of BH_3·THF (4.4 mL, 4.4 mmol, 10.0 eq) in THF was added dropwise to the solution after which TMSOTf (0.08 mL, 0.44 mmol, 1.0 eq) was added to the mixture. The reaction mixture was stirred for 4 h and slowly quenched with NEt_3 (1 mL) followed by MeOH, which was added until the formation of H_2 ceased. The mixture was concentrated and co-evaporated with MeOH (2x). Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (0.234 g, 0.40 mmol, 91%) as a white solid. $[\alpha]_D^{25}$ = 21.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.41 (m, 2H, CH_{arom}); 7.37-7.17 (m, 18H, CH_{arom}); 5.18 (dd, 2H, *J* = 12.2, 16.6 Hz, PhC$H_{2,Cbz}$); 4.83-4.74 (m, 3H, H-2, PhC*H*H, PhC*H*H); 4.68-4.60 (m, 3H, H-1, PhCH*H*, PhCH*H*); 3.86 (dd, 1H, *J* = 2.4, 12.0 Hz, H-6); 3.74-3.57 (m, 2H, H-4, H-6); 3.40 (t, 1H, *J* = 2.4 Hz, H-3); 3.39-3.36 (m, 1H, H-5); 2.11 (bs, 1H, 6-O*H*). ^{13}C-APT NMR (101 MHz) δ: 154.3 (CO_{Cbz}); 137.8, 137.7, 135.1 ($C_{q,arom}$); 129.1, 129.0, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.8, 127.8 (CH_{arom}); 85.9 (C-1); 84.0 (C-4); 79.5 (C-5); 77.1 (C-3); 76.3 (C-2); 75.5, 75.1 (Ph*C*H$_2$); 70.1 (Ph*C*H$_{2,Cbz}$); 61.8 (C-6). IR (thin film, cm^{-1}): 1002, 1012, 1027, 1039, 1072, 1090, 1146, 1252, 1454, 1731, 1756, 2928. HRMS calculated for $C_{34}H_{34}O_7SNa$ 609.1923 [M+Na]$^+$; found 609.1918.

Phenyl 2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-1-thio-ß-D-glucopyranoside (2)



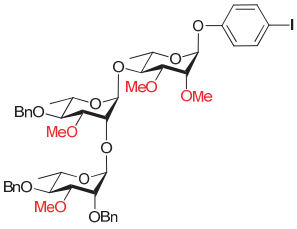
Compound **45** (135 mg, 0.23 mmol, 1.0 eq.) and TTBP (229 mg, 0.92 mmol, 4.0 eq) were co-evaporated with toluene (3x) under N_2 atmosphere and dissolved in dry DCM (4.6 mL, 0.05 M) and flame-dried rod shaped 3Å molecular sieves were added. Trimethyloxonium tetrafluoroborate (102 mg, 0.69 mmol, 3.0 eq) was then added to the mixture and the reaction was left to stir for 2 hours. The reaction was quenched with NEt_3 (0.5 mL), filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (99 mg, 0.165 mmol, 72%) as a white solid. $[\alpha]_D^{25}$ = 26.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.48-7.44 (m, 2H, CH_{arom}); 7.39-7.18 (m, 18H, CH_{arom}); 5.19 (dd, 2H, *J* = 12.2, 19.4 Hz, PhC$H_{2,Cbz}$); 4.85-4.74 (m, 3H, H-2, PhC*H*H, PhC*H*H); 4.68-4.60 (m, 3H, H-1, PhCH*H*, PhCH*H*); 3.73-3.59 (m, 4H, H-3, H-4, H-6); 3.47-3.43 (m, 1H, H-5); 3.37 (OCH_3). ^{13}C-APT NMR (101 MHz) δ: 154.3 (CO_{Cbz}); 138.0, 138.0, 135.2, 133.1 ($C_{q,arom}$); 132.6, 129.0, 128.7, 128.7, 128.6, 128.5, 128.1, 128.1, 128.0, 127.9, 127.8 (CH_{arom}); 86.5 (C-1); 84.4 (C-4); 79.3 (C-5); 77.5 (C-3); 76.4 (C-2); 75.6, 75.3 (Ph*C*H$_2$); 71.2 (C-6); 70.2 (Ph*C*H$_{2,Cbz}$); 59.6 (O*C*H$_3$). IR (thin film, cm^{-1}): 1000, 1026, 1076, 1142, 1246, 1362, 1381, 1440, 1454, 1753. HRMS calculated for $C_{35}H_{36}O_7SNa$ 623.2079 [M+Na]$^+$; found 623.2074.

4-iodophenyl 2,3-di-*O*-methyl-4-*O*-(3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (34)



Donor **6** (0.554 g, 1.12 mmol, 1.5 eq), Ph_2SO (0.295 g, 1.46 mmol, 2.0 eq) and TTBP (0.696 g, 2.80 mmol, 3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (20 mL, 0.08 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -65 °C after which Tf_2O (0.244 mL, 1.46 mmol, 2.0 eq) was added to the solution. After stirring for 30 minutes, acceptor **7** (0.294 g, 0.747 mmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (1.9 mL, 0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (4 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 3:1) and all fractions containing product were concentrated *in vacuo*. The resulting residue (0.424 g, 0.55 mmol, 73% crude yield) was then dissolved in MeOH (11 mL, 0.05 M) and a catalytic amount of K_2CO_3 was added. The reaction was allowed to stir for 16 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (0.314 g, 0.49 mmol, 65% over 2 steps) as a pale oil. $[\alpha]_D^{25}$ = -109.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.60-7.56 (m, 2H, C*H*$_{arom}$); 7.36-7.26 (m, 5H, C*H*$_{arom}$); 6.87-6.83 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.21 (d, 1H, *J* = 2.0 Hz, H-1'); 4.70 (dd, 2H, *J* = 11.0 87.6 Hz, PhC*H*$_2$); 4.09 (dd, 1H, *J* = 2.0, 4.8 Hz, H-2'); 3.78-3.73 (m, 2H, H-2, H-5'); 3.69-3.62 (m, 3H, H-3, H-4, H-5); 3.55 (s, 3H, OC*H*$_3$); 3.51-3.48 (m, 7H, H-3', OC*H*$_3$); 3.38 (t, 1H, *J* = 9.2 Hz, H-4'); 2.40 (d, 1H, *J* = 2.0 Hz, 2'-O*H*); 1.35-1.25 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 156.3, 138.5 (C$_{q,arom}$); 138.5, 128.5, 128.1, 127.9, 118.7 (*C*H$_{arom}$); 101.1 (C-1'); 95.7 (C-1); 85.0 (*C*I$_{arom}$); 81.7 (C-3'); 81.5 (C-3); 79.9 (C-4'); 78.5 (C-4); 76.3 (C-2); 75.3 (Ph*C*H$_2$); 68.4 (C-2'); 68.3 (C-5); 68.1 (C-5'); 59.5, 57.5, 57.3 (O*C*H$_3$); 18.3 (C-6); 17.8 (C-6'). IR (thin film, cm^{-1}): 1089, 1116, 1203, 1232, 1452, 1484, 2931, 3476. HRMS calculated for $C_{28}H_{37}IO_9Na$ 667.13745 [M+Na]$^+$; found 667.13729.

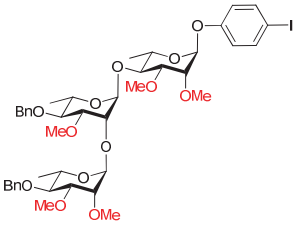
4-iodophenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,4-di-*O*-benzyl-3-*O*-methyl-α-L-rhamnopyranoside)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (39)



Prepared according to general procedure B using donor **36** (71 mg, 0.158 mmol, 1.5 eq), acceptor **34** (68 mg, 0.106 mmol, 1.0 eq) and IDCP (149 mg, 0.149 mmol, 3.0 eq) the title compound was obtained after column chromatography (DCM-EtOAc 9:1) as a slightly orange oil (99 mg, 0.100 mmol, 95%, α/ß 6:1). $[\alpha]_D^{25}$ = -71.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.47-7.43 (m, 2H, C*H*$_{arom}$); 7.40-7.26 (m, 13H, C*H*$_{arom}$); 6.99-6.95 (m, 2H, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 2.0 Hz, H-1); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 5.13 (d, 1H, *J* = 1.6 Hz, H-1''); 4.93 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.80-4.78 (m, 3H, PhC*H*H, PhC*H*$_2$); 4.63 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.55 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.04 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2'); 3.88 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2''); 3.80-3.75 (m, 2H, H-2, H-

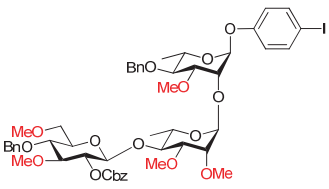
5''); 3.71-3.55 (m, 5H, H-3, H-3', H-4, H-5, H-5'); 3.53-3.42 (m, 11H, H-3'', H-4'', OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.28 (t, 1H, *J* = 9.4 Hz, H-4'); 1.33 (d, 3H, *J* = 6.0 Hz, H-6''); 1.22-1.19 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 156.3, 139.1, 138.6, 138.5 (C$_{q,arom}$); 138.5, 128.8, 128.5, 128.4,, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6, 118.7 (*C*H$_{arom}$); 100.7 (C-1'); 99.2 (C-1''); 96.0 (C-1); 85.0 (*C*I$_{arom}$); 82.2 (C-3'); 81.9 (C-3); 81.5 (C-3''); 80.8 (C-4''); 80.0 (C-4'); 77.8 (C-4); 76.2 (C-2); 75.2 (Ph*C*H$_2$); 74.0 (C-2''); 73.4 (C-2'); 72.6 (Ph*C*H$_2$); 68.6 (C-5''); 68.4 (C-5'); 68.3 (C-5''); 59.7, 57.9, 57.8, 57.4 (O*C*H$_3$); 18.4 (C-6''); 18.3 (C-6'); 17.9 (C-6). IR (thin film, cm^{-1}): 1055, 1092, 1118, 1203, 1232, 1454, 1484. HRMS calculated for $C_{49}H_{61}IO_{13}Na$ 1007.30491 [M+Na]$^+$; found 1007.30508.

4-iodophenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (40)



Prepared according to general procedure B using donor **37** (67 mg, 0.179 mmol, 1.5 eq), acceptor **34** (77 mg, 0.120 mmol, 1.0 eq) and IDCP (168 mg, 0.359 mmol, 3.0 eq) the title compound was obtained after column chromatography (DCM-EtOAc 9:1) as a slightly orange oil (91 mg, 0.100 mmol, 84%, α/ß 4:1). $[\alpha]_D^{25}$ = -102.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.56 (m, 2H, C*H*$_{arom}$); 7.37-7.26 (m, 10H, C*H*$_{arom}$); 6.86-6.83 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.17 (d, 1H, *J* = 1.6 Hz, H-1'); 5.15 (d, 1H, *J* = 1.6 Hz, H-1''); 4.92 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.84 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.64-4.59 (m, 2H, PhCH*H*, PhCH*H*); 4.08 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2'); 3.79-3.60 (m, 8H, H-2, H-2'', H-3, H-3'', H-4, H-5, H-5', H-5''); 3.54-3.48 (m, 13H, H-3', OC*H*$_3$); 3.45-3.32 (m, 5H, H-4', H-4'', OC*H*$_3$); 1.31 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25-1.22 (m, 6H, H-6, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.3, 139.0, 138.7 (C$_{q,arom}$); 138.5, 128.5, 128.4, 128.2, 127.9, 127.8, 127.6 (*C*H$_{arom}$); 118.7 (*C*H$_{arom}$); 100.7 (C-1'); 98.5 (C-1''); 96.0 (C-1); 85.0 (*C*I$_{arom}$); 82.1 (C-3'); 81.9 (C-3); 81.2 (C-3''); 80.7 (C-4''); 80.1 (C-4'); 77.9 (C-4); 77.8 (C-2''); 76.2 (C-2); 75.3, 75.1 (Ph*C*H$_2$); 73.7 (C-2'); 68.7 (C-5'); 68.4 (C-5''); 68.3 (C-5); 59.7, 59.2, 58.1, 58.0, 57.3 (O*C*H$_3$); 18.4 (C-6'); 18.1, 18.0 (C-6, and C-6''). IR (thin film, cm^{-1}): 1029, 1075, 1093, 1119, 1176, 1232, 1484. HRMS calculated for $C_{43}H_{57}IO_{13}Na$ 931.27361 [M+Na]$^+$; found 931.27320.

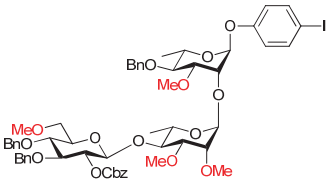
4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (26)



Prepared according to general procedure A using donor **1** (2.57 g, 4.9 mmol, 1.4 eq) and acceptor **23** (2.23 g, 3.47 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et$_2$O 2:3) as a pale oil (2.93 g, 2.77 mmol, 80%). $[\alpha]_D^{25}$ = -63.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.40-7.26 (m, 15H, C*H*$_{arom}$); 6.82 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 1.6 Hz, H-1); 5.29-5.22 (m, 2H, PhC*H*$_2$); 5.18 (d, 1H, *J* = 1.2 Hz, H-1'); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.79 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (t, 1H, *J* = 2.4 Hz, H-2); 3.78 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.75-3.33

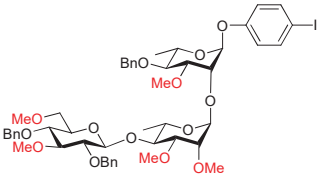
(m, 27H, H-2', H-3, H-3', H-3'', H-4, H-4', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 1.29-1.26 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 155.9 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.4, 138.2, 135.6 (C$_{q,arom}$); 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 118.6 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 97.0 (C-1); 84.9 (*C*I$_{arom}$); 84.9 (C-3''); 80.8 (C-4'); 80.0 (C-4); 78.1 (C-3); 77.6 (C-4''); 77.6 (C-5''); 76.9 (C-2); 75.2, 75.0 (Ph*C*H$_2$); 74.8 (C-3'); 72.9 (C-2); 71.0 (Ph*C*H$_2$); 69.8 (C-6''); 68.8, 67.9 (C-5 and C-5'); 61.0, 59.8, 59.1, 58.3, 57.6 (O*C*H$_3$); 18.2, 18.0 (C-6 and C-6'). IR (thin film, cm^{-1}): 1029, 1055, 1072, 1092, 1120, 1139, 1235, 1259, 1454, 1484, 1757, 2932. HRMS calculated for $C_{51}H_{63}IO_{16}Na$ 1081.3058 [M+Na]$^+$; found 1081.3053.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (27)



Prepared according to general procedure A using donor **2** (105 mg, 0.17 mmol, 1.5 eq) and acceptor **23** (91 mg, 0.12 mmol) the title compound was obtained after column chromatography (*n*-pentane-Et$_2$O 1:4) as a slightly yellow oil (127 mg, 0.11 mmol, 96%). [α]$_D^{25}$ = -66.3 ° (c = 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz) δ: 7.58 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.36-7.21 (m, 20H, C*H*$_{arom}$); 6.83 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.24-5.15 (m, 3H, H-1', PhC*H*$_2$); 4.89 (d, 1H, *J* = 7.2 Hz, PhC*H*H); 4.80-4.76 (m, 4H, H-1'', H-2'', PhC*H*H, PhC*H*H); 4.70-4.62 (m, 3H, PhCH*H*, PhCH*H*, PhCH*H*); 4.24 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.80-3.63 (m, 9H, H-2', H-3, H-3'', H-4'', H-5, H-5', H-5'', H-6''); 3.56-3.42 (m, 10H, H-4, H-4', H-6'', OC*H*$_3$, OC*H*$_3$); 3.37-3.27 (m, 7H, H-3'', OC*H*$_3$); 1.30-1.26 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 155.9 (C$_{q,arom}$); 154.7, (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.4, 138.3, 138.2, 135.5 (C$_{q,arom}$); 128.7, 128.6, 128.5, 128.5, 128.4, 128.1, 128.1, 127.9, 127.9, 127.7, 127.7, 118.6 (*C*H$_{arom}$); 101.0 (C-1''); 98.5 (C-1'); 97.0 (C-1); 84.9 (*C*I$_{arom}$); 83.3 (C-4''); 81.9 (C-3); 80.8, 80.0 (C-4 and C-4'); 78.2 (C-2''); 77.8, 77.7, 76.9 (C-2', C-3'', and C-5''); 75.4, 75.2, 75.1 (Ph*C*H$_2$); 74.9 (C-3'); 72.9 (C-2); 71.1 (C-6''); 69.8 (Ph*C*H$_2$); 68.8, 67.9 (C-5 and C-5'); 59.8, 59.1, 58.3, 57.6 (O*C*H$_3$); 18.2, 18.0 (C-6 and C-6'). IR (thin film, cm^{-1}): 1005, 1016, 1030, 1053, 1072, 1093, 1120, 1140, 1236, 1259, 1484, 1757. HRMS calculated for $C_{57}H_{67}IO_{16}Na$ 1157.3371 [M+Na]$^+$; found 1157.3366.

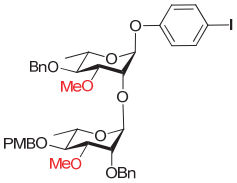
4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2,4-di-*O*-benzyl-3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (31)



Trisaccharide **28**[22] (20 mg, 22 µmol, 1.0 eq) was dissolved in DMF (1 mL, 0.02 M) and BnBr (13 µL, 011 mmol, 5.0 eq) was added to the solution. The solution was cooled to 0 °C and it was stirred for 5 minutes before NaH (4 mg, 0.11 mmol, 5.0 eq) was added. The reaction mixture was stirred for 4 hours while slowly warming to rT. The reaction was quenched by addition of H$_2$O, and extracted with Et$_2$O (3x). The organic layers were combined, washed with brine, dried with MgSO$_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et$_2$O, 1:4) gave the title compound (14 mg, 14 µmol, 64%) as a pale oil. [α]$_D^{25}$ = -77.0 ° (c = 1.0, CHCl$_3$). ^{1}H NMR (400 MHz) δ 7.60-7.53 (m, 2H, C*H*$_{arom}$); 7.44-7.34 (m, 2H, C*H*$_{arom}$); 7.39-7.28 (m, 9H, C*H*$_{arom}$); 7.32-7.24 (m, 4H, C*H*$_{arom}$); 6.85-6.78 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.16

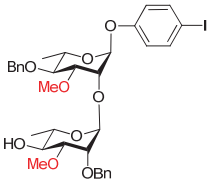
(d, 1H, *J* = 2.0 Hz, H-1'); 4.94-4.88 (m, 2H, PhC*H*H, PhC*H*H); 4.82 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.78-4.70 (m, 2H, H-1'', PhC*H*H); 4.66-4.61 (m, 2H, PhCH*H*, PhCH*H*); 4.22 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.82-3.61 (m, 5H, H-2', H-3, H-4'', H-5, H-5'); 3.67-3.62 (m, 4H, H-6'', OCH_3); 3.59-3.42 (m, 10H, H-3', H-4, H-4', H-6'', OCH_3); 3.36-3.29 (m, 8H, H-3'', H-5'', OCH_3); 3.25 (dd, 1H, *J* = 7.6, 9.2 Hz, H-2''); 1.30 (d, 3H, *J* = 6.0 Hz, H-6'); 1.26 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 139.3, 138.6 ($C_{q,arom}$); 138.6, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5, 118.7 (*C*H$_{arom}$); 103.1 (C-1''); 98.9 (C-1'); 97.2 (C-1); 86.8 (C-3''); 84.9 (*C*I$_{arom}$); 82.8 (C-2''); 81.6 (C-3); 81.1 (C-3'); 80.1 (C-4''); 80.0 (C-4); 77.9 (C-4'); 75.3, 75.0, 74.6 (Ph*C*H$_2$); 74.5 (C-5''); 73.7 (C-2); 71.3 (C-6''); 68.8 (C-5); 68.1 (C-5'); 61.4, 59.8, 59.1, 58.3, 57.4 (O*C*H$_3$); 18.2 (C-6 and C-6'). IR (thin film, cm^{-1}): 1005, 1030, 1053, 1073, 1089, 1122, 1140, 1232, 1454, 1484, 2932. HRMS calculated for $C_{50}H_{63}IO_{14}Na$ 1037.3160 [M+Na]$^+$; found 1037.3155.

4-iodophenyl 2-*O*-(2-*O*-benzyl-3-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (19)



Compound **18**[22] (125 mg, 0.17 mmol, 1.0 eq) was dissolved in dry DMF (1.7 mL, 0.1 M) and BnBr (0.04 mL, 0.33 mmol, 1.5 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 10 mg, 0.25 mmol, 1.2 eq) and TBAI (3 mg, 8 µmol, 0.05 eq) were added. The reaction mixture was warmed to rT while stirring for 2 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (146 mg, 0.17 mmol, 100%) as a clear oil. $[\alpha]_D^{25}$ = -79 ° (c =0.7, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.56-7.52 (m, 2H, C*H*$_{arom}$); 7.46-7.44 (m, 2H, C*H*$_{arom}$); 7.38-7.26 (m, 10H, C*H*$_{arom}$); 6.90-6.87 (m, 2H, C*H*$_{arom}$); 6.78-6.74 (m, 2H, C*H*$_{arom}$); 5.37 (d, 1H, *J* = 2.0 Hz, H-1); 5.09 (d, 1H, *J* = 1.6 Hz, H-1'); 4.86-4.70 (m, 4H, PhC*H*H, PhC*H*H, PhC*H*$_2$); 4.59-4.54 (m, 2H, PhCH*H*, PhCH*H*); 4.13-4.12 (m, 1H, H-2); 3.92-3.91 (m, 1H, H-2'); 3.80 (s, 3H, C*H*$_{3,PMB}$); 3.74-3.69 (m, 2H, H-3, H-5'); 3.64-3.58 (m, 2H, H-3', H-5); 3.52 (t, 1H, *J* = 9.2 Hz, H-4'); 3.48 (s, 3H, OCH_3); 3.45 (s, 3H, OCH_3); 3.32 (t, 1H, *J* = 9.6 Hz, H-4); 1.29 (d, 3H, *J* = 6.0 Hz, H-6'); 1.18 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.4, 156.1 ($C_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.5, 138.4, 130.9 ($C_{q,arom}$); 129.9, 128.5, 128.5, 128.2, 128.2, 127.9, 127.9, 118.6, 114.0 (*C*H$_{arom}$); 99.8 (C-1'); 97.0 (C-1); 84.7 (*C*I$_{arom}$); 81.6 (C-3); 81.5 (C-3'); 80.3 (C-4'); 79.9 (C-4); 75.3, 75.1 (Ph*C*H$_2$); 74.1 (C-2'); 73.3 (C-2); 72.8 (Ph*C*H$_2$); 68.7 (C-5); 68.6 (C-5'); 58.0, 58.0 (O*C*H$_3$); 55.5 (*C*H$_{3,PMB}$); 18.2 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1035, 1070, 1090, 1120, 1175, 1233, 1248, 1454, 1484, 1514. HRMS calculated for $C_{42}H_{49}IO_{10}Na$ 863.2268 [M+Na]$^+$; found 863.2263.

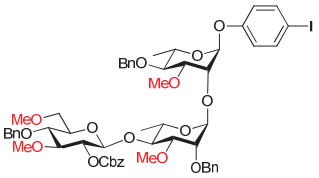
4-iodophenyl 2-*O*-(2-*O*-benzyl-3-*O*-methyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (20)



Compound **19** (139 mg, 0.17 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 1.7 mL, 0.1 M) after which a solution of HCl in HFIP (0.09 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with

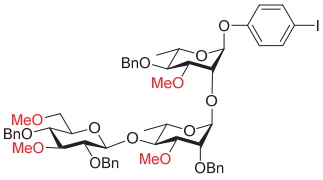
$MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (107 mg, 0.15 mmol, 90%) as a pale oil. $[\alpha]_D^{25}$ = -65.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.54 (m, 2H, C*H*$_{arom}$); 7.44-7.42 (m, 2H, C*H*$_{arom}$); 7.33-7.25 (m, 8H, C*H*$_{arom}$); 6.81-6.78 (m, 2H, C*H*$_{arom}$); 5.42 (d, 1H, *J* = 2.0 Hz, H-1); 5.18 (d, 1H, *J* = 1.6 Hz, H-1'); 4.86 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.72 (dd, 2H, *J* = 12.6, 21.8 Hz, PhCH_2); 4.61 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.18 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.93 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 3.79-3.65 (m, 4H, H-3, H-4', H-5, H-5'); 3.50 (s, 3H, OCH_3); 3.43 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3'); 3.38-3.34 (m, 4H, H-4, OCH_3); 1.32 (d, 3H, *J* = 6.0 Hz, H-6); 1.21 (d, 3H, *J* = 6.4 Hz, H-6'). ^{13}C-APT NMR (101 MHz) δ: 156.0 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.4, 138.1 (C$_{q,arom}$); 128.5, 128.3, 128.1, 128.0, 127.9, 118.6 (*C*H$_{arom}$); 99.6 (C-1'); 97.0 (C-1); 84.8 (*C*I$_{arom}$); 81.7 (C-3); 80.9 (C-3'); 79.9 (C-4); 75.2 (Ph*C*H$_2$); 73.4 (C-2); 72.5 (Ph*C*H$_2$); 72.4 (C-2'); 71.7 (C-4'); 69.0 (C-5'); 68.7 (C-5); 58.1, 57.0 (O*C*H$_3$); 18.1 (C-6'); 18.0 (C-6). IR (thin film, cm^{-1}): 1031, 1049, 1072, 1120, 1137, 1233, 1455, 1484, 2931, 3470. HRMS calculated for $C_{34}H_{41}IO_9Na$ 743.1693 [M+Na]$^+$; found 743.1708.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2,4-di-*O*-benzyl-3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (24)



Prepared according to general procedure A using donor **1** (73 mg, 0.14 mmol, 1.5 eq) and acceptor **20** (67 mg, 0.09 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 7:3) as a pale oil (70 mg, 0.06 mmol, 66%). $[\alpha]_D^{25}$ = -46.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.44-7.26 (m, 20H, C*H*$_{arom}$); 6.83-6.79 (m, 2H, C*H*$_{arom}$); 5.40 (d, 1H, *J* = 2.0Hz, H-1); 5.24 (s, 2H, Ph*C*H$_2$); 5.16 (d, 1H, *J* = 1.6 Hz, H-1'); 4.85-4.73 (m, 5H, H-1'', Ph*C*H$_2$, PhC*H*H); 4.67-4.57 (m, 3H, H-2'', PhCH*H*); 4.18 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.83 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2'); 3.74-3.64 (m, 5H, H-3, H-5, H-5', H-5'', H-6''); 3.61-3.54 (m, 2H, H-4', H-6''); 3.50 (s, 3H, OCH_3); 3.48 (s, 3H, OCH_3); 3.41-3.32 (m, 7H, H-3', H-3'', H-4, H-4'', OCH_3); 3.21 (s, 3H, OCH_3); 1.30 (d, 3H, *J* = 5.6 Hz, H-6'); 1.21 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.0 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.5, 138.3, 138.2, 135.6 (C$_{q,arom}$); 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 118.7 (*C*H$_{arom}$); 101.1 (C-1''); 99.3 (C-1'); 97.0 (C-1); 85.0 (C-4''); 84.9 (*C*I$_{arom}$); 81.9 (C-3); 81.0 (C-3'); 79.9 (C-4); 78.1 (C-5''); 78.1 (C-2''); 77.7 (C-4'); 75.3, 75.0 (Ph*C*H$_2$); 74.8 (C-3''); 73.1 (C-2'); 72.7 (C-2); 72.6 (Ph*C*H$_2$); 71.1 (C-6''); 69.8 (Ph*C*H$_2$); 68.8, 68.0 (C-5 and C-5'); 61.0, 59.8, 58.2, 57.5 (O*C*H$_3$); 18.1 (C-6 and C-6'). IR (thin film, cm^{-1}): 1000, 1027, 1055, 1120, 1139, 1205, 1235, 1259, 1325, 1348, 1385, 1454, 1484, 1497, 1756, 2932, 2968. HRMS calculated for $C_{57}H_{67}IO_{16}Na$ 1157.33660 [M+Na]$^+$; found 1157.33649.

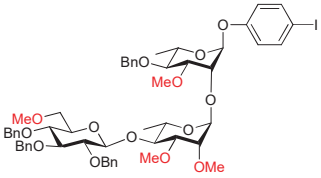
4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2,4-di-*O*-benzyl-3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (32)



Trisaccharide **29**[22] (14 mg, 15 µmol, 1.0 eq) was dissolved in DMF (1.5 mL, 0.01 M) and BnBr (9 µL, 77 µmol, 5.0 eq) was added to the solution. The solution was cooled to 0 °C and it was stirred for 5 minutes before NaH (3 mg, 77 µmol, 5.0 eq) was added. The reaction mixture was stirred for 16 hours while slowly warming

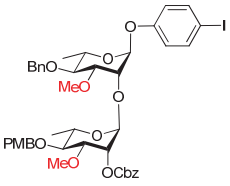
to rt. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 3:2) gave the title compound (16 mg, 15 µmol, 95%) as a pale oil. $[\alpha]_D^{25}$ = -47.7 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 7.56 (dd, 2H, *J*= 2.0, 7.0 Hz, C*H*$_{arom}$); 7.43-7.25 (m, 20H, C*H*$_{arom}$); 6.80 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 2.0 Hz, H-1); 5.12 (d, 1H, *J*= 1.6 Hz H-1'); 4.91 (d, 2H, *J* = 11.6 Hz PhC*H*$_2$); 4.84 (dd, 2H, *J* = 6.8, 10.0 Hz, PhC*H*$_2$); 4.74-4.71 (m, 4H, PhC*H*$_2$); 4.63 (d, 1H, *J* = 10.8 Hz, PhCH); 4.58 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.16 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.87 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.80-3.63 (m, 8H, H-3, H-4'', H-5, H-5', H-6'', OC*H*$_3$); 3.57 (dd, 1H, *J* = 1.6, 11.2 Hz, H-6''); 3.53-3.47 (m, 5H, H-3', H-4', OC*H*$_3$); 3.39-3.32 (m, 6H, H-3'', H-4, H-5'', OC*H*$_3$); 3.25 (dd, 1H, *J* = 7.8, 9.0 Hz, H-2''); 3.21 (s, 3H, OC*H*$_3$); 1.33 (d, 3H, *J*= 6.0 Hz, H-6'); 1.22 (d, 3H, *J*= 6.4 Hz, H-6). ^{13}C-APT NMR (100 MHz) δ: 156.1, 139.2, 138.6, 138.5 (C$_{q,arom}$); 138.4 (*C*H$_{arom}$); 138.2 (C$_{q,arom}$); 128.5, 128.5, 128.3, 128.3,128.2, 128.1, 127.9, 127.8, 127.5, 118.7 (*C*H$_{arom}$); 103.2 (C-1''); 99.7 (C-1'); 97.2 (C-1); 86.8 (C-3''); 84.9 (*C*I$_{arom}$); 82.7 (C-2''); 81.5 (C-3); 81.3 (C-3'); 80.0 (C-4); 77.9 (C-4'); 77.4 (C-4''); 75.3, 74.9, 74.6, (Ph*C*H$_2$); 74.5 (C-5''); 73.4 (C-2); 73.1 (C-2'); 72.6,(Ph*C*H$_2$); 71.3 (C-6''); 68.8 (C-5); 68.1 (C-5'); 61.4, 59.7, 58.0, 57.4 (O*C*H$_3$); 18.3 (C-6'), 18.2 (C-6). IR (thin film, cm^{-1}): 1000, 1029, 1073, 1120, 1140, 1205, 1232, 1279, 1454, 1484, 2929, 2972. HRMS calculated for $C_{56}H_{67}IO_{14}Na$ 1113.3473 $[M+Na]^+$; found 1113.3468.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (33)



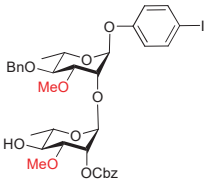
Trisaccharide **30**[22] (215 mg, 0.22 mmol, 1.0 eq) was dissolved in DMF (11 mL, 0.02 M) and cooled to 0 °C. To the solution were added BnBr (0.26 mL, 2.2 mmol, 10 eq) and TBAI (16 mg, 43 µmol, 0.2 eq) and it was stirred for 5 minutes before NaH (36 mg, 1.1 mmol, 5.0 eq) was added. The reaction mixture was stirred for 2 h while slowly warming to rT. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (135 mg, 0.12 mmol, 58%) as a pale oil. $[\alpha]_D^{25}$ = -21.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.54 (m, 2H, C*H*$_{arom}$); 7.38-7.12 (m, 20H, C*H*$_{arom}$); 6.82 (dd, 2H, *J*= 2.8, 11.6 Hz, C*H*$_{arom}$); 5.15 (s, 1H, H-1); 5.17 (s, 1H, H-1'); 4.98-4.74 (m, 8H, Ph*C*H$_2$); 4.66-4.63 (m, 2H, PhCH*H*, H-1''); 4.23 (d, 1H, *J* = 2.0 Hz, H-2); 3.81-3.50 (m, 18H, H-2', H-3, H-3', H-3'', H-4', H-4'', H-5, H-5', H-6''); 3.45 (t, 1H, *J* = 9.4 Hz, H-4); 3.40-3.35 (m, 8H, H-2'', H-5'', OC*H*$_3$); 1.29 (d, 3H, *J*= 7.2 Hz, H-6'); 1.26 (d, 3H, *J*= 6.4 Hz, H-6). ^{13}C-APT NMR (100 MHz) δ: 156.1, 139.0, 138.9 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.5, 138.4 (C$_{q,arom}$); 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.5, 127.5, 125.8, 118.6, 118.5 (*C*H$_{arom}$); 103.1 (C-1''); 98.8 (C-1'); 96.8 (C-1); 84.9 (*C*I$_{arom}$); 84.9 (C-4''); 82.9 (C-2''); 81.5 (C-3); 81.0 (C-4'); 80.0 (C-4); 77.9 (C-3''); 76.7 (C-2'); 76.7 (C-3''); 75.7, 75.2, 75.0 74.7; 74.6 (C-5''); 73.7 (C-2); 71.3 (C-6''); 68.8 (C-5), 68.1 (C-5'); 59.7, 59.1, 58.2, 57.3 (O*C*H$_3$); 18.2, 18.2 (HC6 and C-6'). IR (thin film, cm^{-1}): 1029, 1055, 1072, 1090, 1120, 1139, 1203, 1232, 1454, 1484. HRMS calculated for $C_{56}H_{67}IO_{14}Na$ 1113.3473 $[M+Na]^+$; found 1113.3468.

4-iodophenyl 2-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-(4-methoxybenzyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (21)



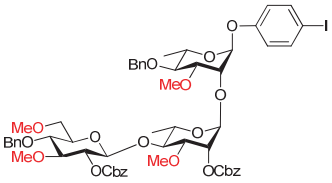
Prepared according to glycosylation procedure A using donor **4** (393 mg, 0.75 mmol, 1.5 eq) and acceptor **5** (235 mg, 0.5 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 4:1) as a slightly yellow oil (206 mg, 0.23 mmol, 47%). $[\alpha]_D^{25}$ = -69.5 ° (c =0.8, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.56-7.53 (m, 2H, C*H*$_{arom}$); 7.42-7.24 (m, 10H, C*H*$_{arom}$); 6.89-6.87 (m, 2H, C*H*$_{arom}$); 6.79-6.76 (m, 2H, C*H*$_{arom}$); 5.41 (s, 1H, H-1); 5.28-5.27 (m, 1H, H-2'); 5.27-5.18 (m, 2H, PhC*H*$_2$); 5.14 (s, 1H, H-1'); 4.90 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.81 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.63 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.53 (d, 1H, *J* = 10.4 Hz, PhCH*H*); 4.17 (t, 1H, *J* = 2.2 Hz, H-2); 3.79-3.65 (m, 7H, H-3, H-3', H-5, H-5', C*H*$_{3,PMB}$); 3.53 (s, 3H, OC*H*$_3$); 3.52 (s, 3H, OC*H*$_3$); 3.44-3.37 (m, 2H, H-4, H-4'); 1.28 (d, 3H, *J* = 6.0 Hz, H-6); 1.22 (d, 3H, *J* = 6.0 Hz, H-6'); ^{13}C-APT NMR (101 MHz) δ: 159.4, 156.0 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 135.2, 130.7 (C$_{q,arom}$); 128.7, 128.5, 128.5, 128.1, 127.8, 118.6, 114.0 (*C*H$_{arom}$); 99.0 (C-1'); 96.8 (C-1); 84.8 (*C*I$_{arom}$); 81.4 (C-3); 79.9 (C-3'); 79.9 (C-4); 79.6 (C-4'); 75.3, 75.3 (Ph*C*H$_2$); 73.5 (C-2); 72.6 (C-2'); 70.0 (Ph*C*H$_2$); 68.8 (C-5'); 68.5 (C-5); 58.1, 58.0 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 18.1 (C-6'); 18.0 (C-6). IR (thin film, cm^{-1}): 1036, 1072, 1093, 1120, 1173, 1233, 1264, 1387, 1457, 1484, 1513, 1750. HRMS calculated for $C_{43}H_{49}IO_{12}Na$ 907.2166 [M+Na]$^+$; found 907.2143.

4-iodophenyl 2-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-methyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (22)



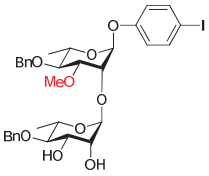
Compound **21** (192 mg, 0.22 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 2.2 mL, 0.1 M) after which a solution of HCl in HFIP (0.11 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material, indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (163 mg, 0.21 mmol, 98%) as a pale oil. $[\alpha]_D^{25}$ = -49.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 2H, C*H*$_{arom}$); 7.46-7.29 (m, 10H, C*H*$_{arom}$); 6.82-6.79 (m, 2H, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 2.0 Hz, H-1); 5.28 (dd, 1H, *J* = 1.8, 2.6 Hz, H-2'); 5.20-5.18 (m, 3H, H-1', PhC*H*$_2$); 4.91 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.65 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.21 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.81-3.68 (m, 3H, H-3, H-5, H-5'); 3.58-3.52 (m, 5H, H-3', H-4', OC*H*$_3$); 3.47-3.42 (m, 4H, H-4, OC*H*$_3$); 2.45 (d, 1H, *J* = 2.0 Hz, 4'-O*H*); 1.30 (d, 3H, *J* = 6.4 Hz, H-6); 1.25 (d, 3H, *J* = 6.4 Hz, H-6'); ^{13}C-APT NMR (101 MHz) δ: 156.0 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.5, 135.1 (C$_{q,arom}$); 128.7, 128.5, 128.5, 128.2, 127.9, 118.6 (*C*H$_{arom}$); 99.2 (C-1'); 96.9 (C-1); 84.9 (*C*I$_{arom}$); 81.4 (C-3); 79.9 (C-4); 79.4 (C-4'); 75.3 (Ph*C*H$_2$); 73.5 (C-2); 71.6 (C-3'); 71.3 (C-2'); 70.1 (Ph*C*H); 68.9 (C-5); 68.8 (C-5'); 58.2, 57.7 (O*C*H$_3$); 18.2 (C-6'); 17.8 (C-6). IR (thin film, cm^{-1}): 1033, 1049, 1073, 1092, 1138, 1232, 1264, 1385, 1445, 1454, 1484, 1747, 2932, 3450. HRMS calculated for $C_{35}H_{41}IO_{11}Na$ 787.1591 [M+Na]$^+$; found 787.1567.

4-iodophenyl 2-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (25)



Prepared according to glycosylation procedure A using donor **1** (67 mg, 0.12 mmol, 1.5 eq) and acceptor **22** (63 mg, 0.08 mmol, 1.0 eq). The title compound was obtained after column chromatography (*n*-pentane-Et_2O 3:2) as a slightly yellow oil (66 mg, 0.06 mmol, 68%). $[\alpha]_D^{25}$ = -54.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 7.2 Hz, C*H*$_{arom}$); 7.42-7.24 (m, 20H, C*H*$_{arom}$); 6.81 (d, 2H, *J* = 9.2 Hz, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.2 Hz, H-1); 5.25-5.14 (m, 6H, H-1', H-2', PhC*H*$_2$); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.80 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.69-4.62 (m, 4H, H-1'', H-2'', PhCH*H*, PhCH*H*); 4.22 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.78-3.45 (m, 15H, H-3, H-3', H-4, H-4', H-4'', H-5, H-5', H-6'', OC*H*$_3$); 3.40-3.34 (m, 5H, H-3'', H-5'', OC*H*$_3$); 3.26 (s, 3H, OC*H*$_3$); 1.30-1.25 (m, 6H, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 155.9 (C$_{q,arom}$); 154.8, 154.8 (*C*O$_{Cbz}$); 138.5 (*C*H$_{arom}$); 138.5, 138.3, 135.5, 135.1 (C$_{q,arom}$); 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 118.7 (*C*H$_{arom}$); 101.2 (C-1''); 98.7 (C-1'); 96.9 (C-1); 84.9 (*C*I$_{arom}$); 84.9 (C-3''); 81.6 (C-3); 79.9 (C-3'); 79.3 (C-4); 78.0 (C-2''); 77.9 (C-4''); 77.5 (C-4'); 75.3, 75.0 (PhC*H*$_2$); 74.8 (C-5''); 72.8 (C-2); 72.1 (C-2'); 71.0 (C-6''); 70.1, 69.9 (PhC*H*$_2$); 68.8, 67.9 (C-5 and C-5'); 60.9, 59.8, 58.2, 57.8 (OC*H*$_3$); 18.1, 17.9 (C-6 and C-6'). IR (thin film, cm^{-1}): 1003, 1035, 1057, 1073, 1140, 1262, 1385, 1455, 1484, 1751. HRMS calculated for $C_{58}H_{67}IO_{18}Na$ 1201.3270 $[M+Na]^+$; found 1201.3257.

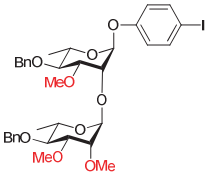
4-iodophenyl 2-*O*-(4-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (42)



Donor **41** (74 mg, 0.12 mmol, 1.0 eq), Ph_2SO (32 mg, 0.16 mmol, 1.3 eq) and TTBP (75 mg, 0.30 mmol, 2.5 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (2.5 mL, 0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -65 °C after which Tf_2O (26 µL, 0.16 mmol, 1.3 eq) was added to the solution. After stirring for 30 minutes, acceptor **5** (113 mg, 0.24 mmol, 2.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.6 mL, 0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (4 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 3:1) and all fractions containing product were concentrated *in vacuo*. The resulting residue (90 mg, 0.092 mmol, 77% crude yield) was then dissolved in MeOH (3 mL, 0.03 M) and a catalytic amount of K_2CO_3 was added. The reaction was allowed to stir for 16 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-acetone 7:3) gave the title compound (59 mg, 0.084 mmol, 69% over 2 steps) as a pale oil. $[\alpha]_D^{25}$ = -82.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.54 (m, 2H, C*H*$_{arom}$); 7.40-7.25 (m, 10H, C*H*$_{arom}$); 6.81-6.78 (m, 2H, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.08 (d, 1H, *J* = 1.6 Hz, H-1'); 4.86 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.75 (s, 2H, PhC*H*$_2$); 4.59 (d, 1H,

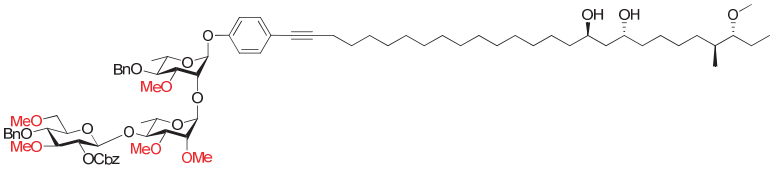
J = 10.8 Hz, PhCH*H*); 4.19 (dd, 1H, *J* = 2.4, 4.8 Hz, H-2); 4.12 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2'); 4.00 (dd, 1H, *J* = 3.4, 9.0 Hz, H-3'); 3.84 (dq, 1H, *J* = 3.2, 6.0 Hz, H-5'); 3.75 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.68 (dq, 1H, *J* = 3.6, 6.4 Hz, H-5); 3.52 (s, 3H, OC*H*$_3$); 3.43-3.37 (m, 2H, H-4, H-4'); 1.34 (d, 3H, *J* = 6.0 Hz, H-6'); 1.22 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.1 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.2 (C$_{q,arom}$); 128.8, 128.5, 128.3, 128.2, 128.1, 127.9, 118.6 (*C*H$_{arom}$); 101.1 (C-1'); 96.9 (C-1); 84.8 (*C*I$_{arom}$); 81.6 (C-4'); 81.5 (C-3); 80.2 (C-4); 75.5, 75.3 (Ph*C*H$_2$); 73.7 (C-2); 71.3 (C-3'); 71.2 (C-2'); 68.8 (C-5); 68.2 (C-5'); 58.2 (O*C*H$_3$); 18.2 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1029, 1049, 1073, 1099, 1105, 1139, 1178, 1232, 1278, 1454, 1484, 3431. HRMS calculated for $C_{33}H_{39}IO_9Na$ 729.15310 [M+Na]$^+$; found 729.15255.

4-iodophenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (43)



Compound **42** (44 mg, 62 µmol, 1.0 eq) was dissolved in dry DMF (0.6 mL, 0.1 M) and MeI (16 µL, 0.249 mmol, 4.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 8 mg, 0.19 mmol, 3.0 eq) was added. The reaction mixture was warmed to rt while stirring for 2 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (33 mg, 45 µmol, 72%) as a clear oil. $[\alpha]_D^{25}$ = -87.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55 (dd, 2H, *J* = 3.2, 12.0 Hz, C*H*$_{arom}$); 7.37-7.25 (m, 10H, C*H*$_{arom}$); 6.79 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.41 (s, 1H, H-1); 5.15 (s, 1H, H-1'); 4.93-4.87 (m, 2H, PhC*H*H, PhC*H*H); 4.66-4.59 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (s, 1H, H-2); 3.77-3.62 (m, 5H, H-2', H-3, H-3', H-5, H-5'); 3.57 (s, 3H, OC*H*$_3$); 3.56 (s, 3H, OC*H*$_3$); 3.55 (s, 3H, OC*H*$_3$); 3.48-3.39 (m, 2H, H-4, H-4'); 1.29 (d, 3H, *J* = 6.4 Hz, H-6'); 1.23 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.1, 138.6 (C$_{q,arom}$); 138.5, 128.6, 128.5, 128.2, 128.1, 127.9, 127.9, 118.6 (*C*H$_{arom}$); 98.9 (C-1'); 97.0 (C-1); 84.8 (*C*I$_{arom}$); 81.7 (C-3'); 81.2 (C-3); 80.5 (C-4); 80.0 (C-4'); 77.6 (C-2'); 75.6, 75.3 (Ph*C*H$_2$); 73.5 (C-2); 68.8 (C-5); 68.5 (C-5'); 59.2, 58.2, 58.1 (O*C*H$_3$); 18.1 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1029, 1052, 1072, 1096, 1120, 1232, 1484. HRMS calculated for $C_{35}H_{43}IO_9Na$ 757.18440 [M+Na]$^+$; found 757.18410.

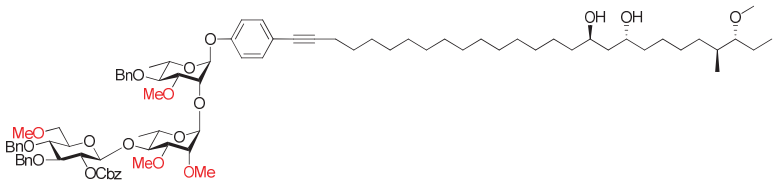
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (44)



The title compound was synthesized according to general procedure C using **26** (23 mg, 22 µmol, 1.0 eq) and phthiocerol (12 mg, 26 µmol, 1.2 eq). Column chromatography (DCM-acetone 4:1) yielded the product (25 mg, 18 µmol, 83%) as a yellow oil. $[\alpha]_D^{25}$ = -50.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.26 (m, 17, C*H*$_{arom}$); 6.96-6.94 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.39-5.32 (m, 2H, PhC*H*$_2$); 5.18 (d, 1H, *J* =

1.2 Hz, H-1'); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.79 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (s, 1H, H-2); 3.96-3.90 (m, 2H, C*H*$_{Phth}$); 3.67-3.33 (m, 30H, H-2', H-3, H-3', H-3'', H-4, H-4', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 2.05 (bs, 2H, O*H*$_{Phth}$); 1.72-1.64 (m, 1H, C*H*$_{Phth}$); 1.62-1.05 (m, 60H, C*H*$_{2,Phth}$, H-6, H-6'); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.3 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5, 138.3, 135.6 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 85.0 (C-3''); 82.0 (C-3); 80.8 (C-4'); 80.1 (C-4); 80.1 (C$_{q,alkyne}$); 78.1 (C-2''); 77.7, 77.6 (C-4'' and C-5''); 77.0 (C-2'); 75.3, 75.0 (Ph*C*H$_2$); 74.8 (C-3'); 73.0 (C-2); 71.1 (C-6''); 69.9 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.2, 18.0 (C-6 and C-6'); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1000, 1030, 1055, 1075, 1093, 1122, 1139, 1175, 1205, 1235, 1259, 1383, 1455, 1507, 1749, 2854, 2928, 3470. HRMS calculated for $C_{80}H_{118}O_{19}Na$ 1405.8165 [M+Na]$^+$; found 1405.8160.

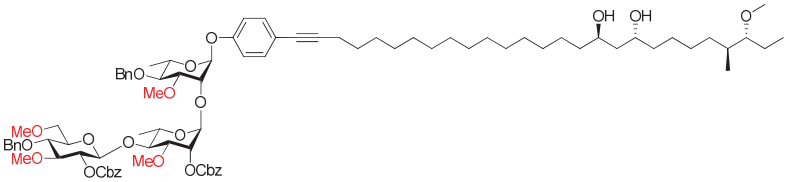
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (45)



The title compound was synthesized according to general procedure C using **27** (62 mg, 55 µmol, 1.0 eq) and phthiocerol (30 mg, 66 µmol, 1.2 eq). Column chromatography (DCM-EtOAc 1:1) yielded the product (66 mg, 45 µmol, 83%) as a yellow oil. [α]$_D^{25}$ = -51.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.36-7.21 (m, 22H, C*H*$_{arom}$); 6.96-6.94 (m, 2H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.24-5.15 (m, 3H, H-1', PhC*H*$_2$); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.80-4.76 (m, 4H, H-1'', H-2'', PhC*H*H, PhC*H*H); 4.69-4.62 (m, 3H, PhCH*H*, PhCH*H*, PhCH*H*); 4.24 (d, 1H, *J* = 2.0 Hz, H-2); 3.98-3.89 (m, 2H, C*H*$_{Phth}$); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.76-3.61 (m, 7H, H-2', H-3'', H-4'', H-5, H-5', H-5'', H-6''); 3.58-3.42 (m, 7H, H-6'', OC*H*$_3$); 3.38-3.33 (m, 7H, H-3', OC*H*$_3$); 2.90-2.82 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 1H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.95 (bs, 2H, O*H*$_{Phth}$); 1.72-1.64 (m, 1H, C*H*$_{Phth}$); 1.62-1.25 (m, 47H, C*H*$_{2,Phth}$, H-6, H-6'); 1.15-1.05 (m, 1H, C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, $CH_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.3 (C$_{q,arom}$); 154.7 (*C*O$_{Cbz}$); 138.5, 138.4, 138.2, 135.5 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 101.1 (C-1''); 98.6 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 83.3 (C-4''); 82.0 (C-3); 80.8, 80.1 (C-4 and C-4'); 80.1 (C$_{q,alkyne}$); 78.2 (C-2''); 77.9, 77.8 77.0 (C-2', C-3'', C-5''); 75.4, 75.3, 75.2 (Ph*C*H$_2$); 75.0 (C-3') 73.0 (C-2); 71.1 (C-6''); 69.9 (Ph*C*H$_2$); 69.7, 69.6 (*C*H$_{Phth}$); 68.7 (C-5); 68.0 (C-5'); 59.9, 59.1, 58.3, 57.6, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.2, 18.1 (C-6 and C-6'); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1002, 1009,

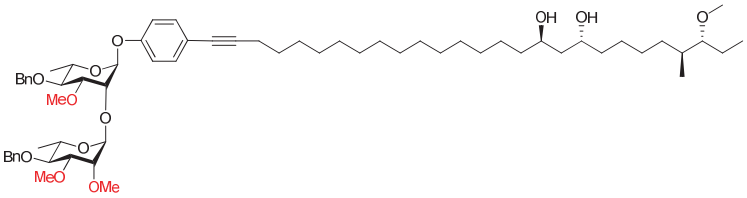
1020, 1027, 1053, 1073, 1093, 1110, 1120, 1136, 1143, 1236, 1263, 1457, 1507, 1734, 2855, 2869, 2927, 2965, 2969. HRMS calculated for $C_{86}H_{122}O_{19}Na$ 1481.8478 [M+Na]$^+$; found 1481.8473.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (46)



The title compound was synthesized according to general procedure C using **25** (59 mg, 50 µmol, 1.0 eq) and phthiocerol (27 mg, 60 µmol, 1.2 eq). Column chromatography (DCM-acetone 4:1) yielded the product (70 mg, 47 µmol, 93%) as a yellow oil. $[\alpha]_D^{25}$ = -174.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.41-7.26 (m, 22H, C*H*$_{arom}$); 6.94 (dd, 2H, *J* = 2.0, 8.8 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.25-5.17 (m, 6H, H-1', H-2', PhC*H*$_2$); 4.92 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.80 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.67-4.61 (m, 4H, H-1'', H-2'', PhCH*H*, PhCH*H*); 4.22 (s, 1H, H-2); 3.96-3.90 (m, 2H, C*H*$_{Phth}$); 3.64-3.47 (m, 15H, H-3, H-3', H-4, H-4', H-4'', H-5, H-5', H-6'', OC*H*$_3$); 3.37-3.33 (m, 8H, H-3'', H-5'', OC*H*$_3$); 3.26 (s, 3H, OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 2.05 (bs, 2H, O*H*$_{Phth}$); 1.62-1.05 (m, 60H, H-6, H-6', C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.3 (C$_{q,arom}$); 154.8, 154.8 (*C*O$_{Cbz}$); 138.5, 138.3, 135.5, 135.1 (C$_{q,arom}$); 133.0, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.2, 128.2, 128.0, 127.8 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 101.3 (C-1''); 98.8 (C-1'); 96.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.9 (C-3''); 81.7 (C-3); 80.1 (C$_{q,alkyne}$); 80.0 (C-3'); 79.3 (C-4); 78.0 (C-4''); 77.9 (C-2''); 77.6 (C-4'); 75.3, 75.0 (Ph*C*H$_2$); 74.8 (C-5''); 72.9 (C-2); 72.1 (C-2'); 71.1 (C-6''); 70.1, 69.9 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 68.8 (C-5'); 67.9 (C-5); 61.0, 59.8, 58.2, 57.8, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.1, 17.9 (C-6 and C-6'); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1029, 1037, 1057, 1073, 1093, 1125, 1142, 1262, 1507, 1753, 2855, 2926. HRMS calculated for $C_{87}H_{122}O_{21}Na$ 1525.8376[M+Na]$^+$; found 1525.8374.

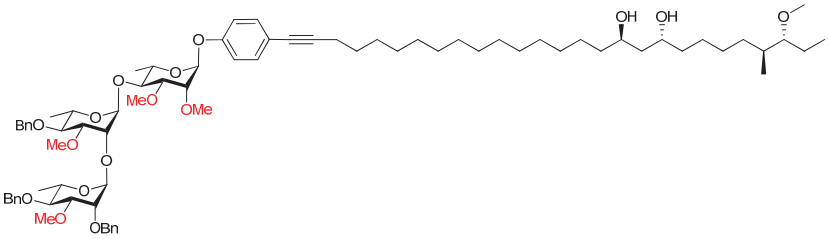
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (47)



The title compound was synthesized according to general procedure C using **43** (29 mg, 39 µmol, 1.0 eq) and phthiocerol (21 mg, 47 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:9) yielded the

product (36 mg, 34 µmol, 86%) as a yellow oil. $[\alpha]_D^{25}$ = -80.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.38-7.26 (m, 12H, C*H*$_{arom}$); 6.93-6.90 (m, 2H, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 2.0 Hz, H-1); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 4.93-4.87 (m, 2H, PhC*H*H, PhC*H*H); 4.66-4.59 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.98-3.89 (m, 2H, C*H*$_{Phth}$); 3.79-3.68 (m, 4H, H-2', H-3, H-5. H-5'); 3.64 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3'); 3.57 (s, 3H, OC*H*$_3$); 3.56 (s, 3H, OC*H*$_3$); 3.55 (s, 3H, OC*H*$_3$); 3.47-3.41 (m, 2H, H-4, H-4'); 3.34 (s, 3H, OC*H*$_3$); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{Phth}$); 1.70-1.22 (m, 49H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 1.15-1.05 (m, 2H, C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 7.2 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.5, 138.7, 138.5 ($C_{q,arom}$); 133.0, 128.5, 128.5, 128.2, 128.1, 127.9, 127.8 (*C*H$_{arom}$); 117.9 ($C_{q,arom}$); 116.1 (*C*H$_{arom}$); 98.9 (C-1'); 96.9 (C-1); 89.5 ($C_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 81.8 (C-3); 81.2 (C-3'); 80.6 (C-4'); 80.1 ($C_{q,alkyne}$); 80.1 (C-4); 77.6 (C-2'); 75.5, 75.3 (Ph*C*H$_2$); 73.6 (C-2); 69.6, 69.6 (*C*H$_{Phth}$); 68.7 (C-5); 68.5 (C-5'); 59.2, 58.2, 58.1, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.1 (C-6); 18.1 (C-6'); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1032, 1036, 1055, 1073, 1095, 1123, 1233, 1454, 1507, 2853, 2927, 3451. HRMS calculated for $C_{64}H_{99}O_{12}$ 1059.71310 $[M+H]^+$; found 1059.71213.

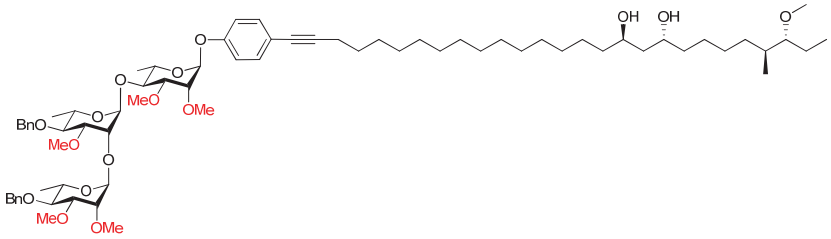
4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,4-di-*O*-benzyl-3-*O*-methyl-α-L-rhamnopyranoside)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (48)



The title compound was synthesized according to general procedure C using **39** (32 mg, 33 µmol, 1.0 eq) and phthiocerol (18 mg, 39 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the product (40 mg, 31 µmol, 94%) as a yellow oil. $[\alpha]_D^{25}$ = -63.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47-7.44 (m, 2H, C*H*$_{arom}$); 7.38-7.26 (m, 15H, C*H*$_{arom}$); 6.99-6.95 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 2.0 Hz, H-1); 5.15 (d, 1H, *J* = 2.0 Hz, H-1'); 5.14 (d, 1H, *J* = 2.0 Hz, H-1''); 4.93 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.80-4.78 (m, 3H, PhC*H*H, Ph*CH*$_2$); 4.63 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.55 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.05 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2'); 3.97-3.89 (m, 2H, C*H*$_{Phth}$); 3.88 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2''); 3.80-3.76 (m, 2H, H-2, H-5''); 3.70-3.58 (m, 5H, H-3, H-3', H-4, H-5, H-5'); 3.53-3.42 (m, 14H, H-3'', H-4'', OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.28 (t, 1H, *J* = 9.4 Hz, H-4'); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.73-1.63 (m, 2H, C*H*$_{2,Phth}$); 1.63-1.02 (m, 56H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 0.91 (t, 1H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.8, 139.1, 138.7, 138.5 ($C_{q,arom}$); 133.0, 128.5, 128.4,, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6 (*C*H$_{arom}$); 118.1 ($C_{q,arom}$); 116.3 (*C*H$_{arom}$); 100.7 (C-1'); 99.2 (C-1''); 95.8 (C-1); 89.6 ($C_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.2 (C-3'); 81.9 (C-3); 81.5 (C-3''); 80.8 (C-4''); 80.1 ($C_{q,alkyne}$); 79.9 (C-4'); 77.8 (C-4); 76.2 (C-2); 75.2 (Ph*C*H$_2$); 74.0 (C-2''); 73.4 (C-2'); 72.6 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 68.6 (C-5''); 68.3 (C-

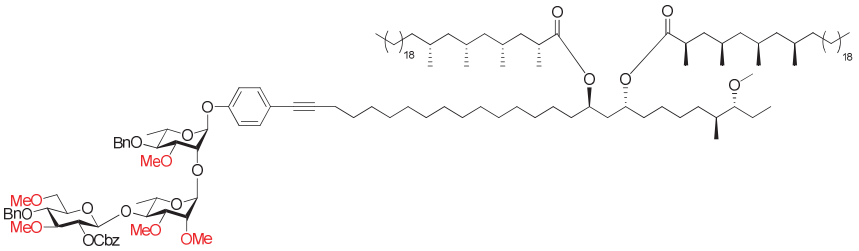
5 and C-5''); 59.7, 57.9, 57.8, 57.5, 57.3 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.4, 18.3, 17.9 (C-6, C-6' and C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1000, 1020, 1029, 1056, 1073, 1093, 1119, 1136, 1233, 1457, 1484, 1507, 2855, 2868, 2926, 2966, 3451. HRMS calculated for $C_{78}H_{120}O_{16}N$ 1326.86016 $[M+NH_4]^+$; found 1326.85909.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (49)



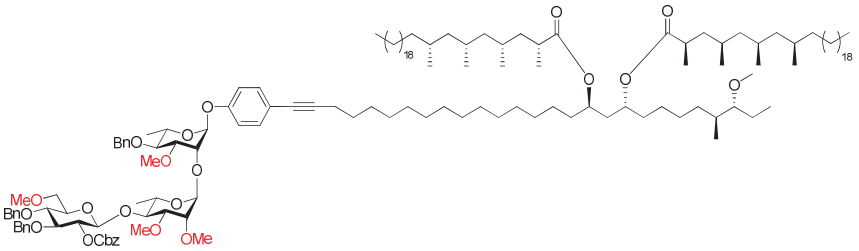
The title compound was synthesized according to general procedure C using **40** (30 mg, 33 µmol, 1.0 eq) and phthiocerol (18 mg, 39 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et$_2$O 1:9) yielded the product (40 mg, 33 µmol, 100%) as a yellow oil. $[\alpha]_D^{25}$ = -72.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.26 (m, 12H, C*H*$_{arom}$); 6.99-6.96 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 2.0 Hz, H-1); 5.17 (d, 1H, *J* = 1.6 Hz, H-1'); 5.15 (d, 1H, *J* = 1.6 Hz, H-1''); 4.92 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.84 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.64-4.60 (m, 2H, PhCH*H*, PhCH*H*); 4.09 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2'); 3.98-3.90 (m, 2H, C*H*$_{Phth}$); 3.79-3.61 (m, 8H, H-2, H-2'', H-3, H-3'', H-4, H-5, H-5', H-5''); 3.54-3.49 (m, 16H, H-3', O*CH*$_3$); 3.45-3.32 (m, 5H, H-4', H-4'', O*CH*$_3$); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.73-1.00 (m, 65H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.2 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.8, 139.0, 138.7 (C$_{q,arom}$); 133.0, 128.5, 128.4, 128.2, 127.9, 127.8, 127.6 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.3 (*C*H$_{arom}$); 100.7 (C-1'); 98.4 (C-1''); 95.9 (C-1); 89.6 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.2 (C-3'); 82.0 (C-3); 81.2 (C-3''); 80.7 (C-4''); 80.1 (C$_{q,alkyne}$); 80.0 (C-4'); 77.9 (C-4); 77.8 (C-2''); 76.2 (C-2); 75.3, 75.1 (Ph*C*H$_2$); 73.7 (C-2'); 69.6, 69.6 (*C*H$_{Phth}$); 68.6 (C-5'); 68.3 (C-5 and C-5''); 59.7, 59.2, 58.1, 58.0, 57.5, 57.3 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.4, 18.1, 18.0 (C-6, C-6' and C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1002, 1029, 1055, 1073, 1093, 1120, 1233, 1454, 1507, 2853, 2928, 3454. HRMS calculated for $C_{72}H_{113}O_{16}$ 1234.80572 $[M+H]^+$; found 1234.80391.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (50)



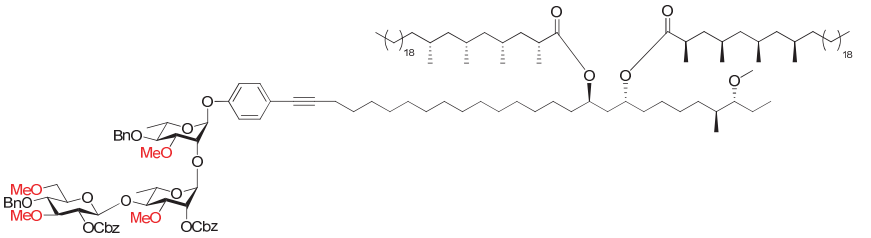
The title compound was synthesized according to general procedure D using **44** (34 mg, 25 µmol, 1.0 eq), mycocerosic acid (35 mg, 74 µmol, 3.0 eq), DIC (23 µL, 147 µmol, 6.0 eq) and DMAP (27 mg, 221 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (45 mg, 19 µmol, 79%) as a waxy solid. $[\alpha]_D^{25}$ = -36.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.26 (m, 17H, C*H*$_{arom}$); 6.96-6.93 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.26 (dd, 2H, *J* = 3.6, 12.2 Hz, PhC*H*$_2$); 5.19 (d, 1H, *J* = 1.2 Hz, H-1'); 4.91-4.78 (m, 4H, PhC*H*H, PhC*H*H, C*H*$_{Phth}$); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, PhCH*H*, PhCH*H*, H-2''); 4.24 (dd, 1H, *J* = 2.2, 2.6 Hz, H-2); 3.79 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.76-3.49 (m, 17H, H-2, H-4', H-4'', H-5, H-5', H-6'', OC*H*$_3$); 3.47-3.39 (m, 2H, H-3', H-4); 3.37-3.31 (m, 11H, H-3'', H-5'', OC*H*$_3$); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 204H, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 155.3 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5, 138.3, 133.0 (C$_{q,arom}$); 128.8, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 85.0 (C-3''); 82.0 (C-3); 80.8 (C-3'); 80.1 (C$_{q,alkyne}$); 80.1 (C-4); 78.1 (C-2''); 77.7 (C-4'); 77.6 (C-4''); 77.0 (C-2'); 75.3, 75.1 (Ph*C*H$_2$); 74.8 (C-5''); 73.0 (C-2); 71.1 (C-6''); 70.4 (*C*H$_{Phth}$); 69.9 (Ph*C*H$_2$); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.1 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6); 18.0 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1093, 1173, 1259, 1378, 1457, 1464, 1507, 1734, 1760, 2853, 2923. HRMS calculated for $C_{144}H_{243}O_{21}$ 2309.79755 $[M+H]^+$; found 2309.80566.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (51)



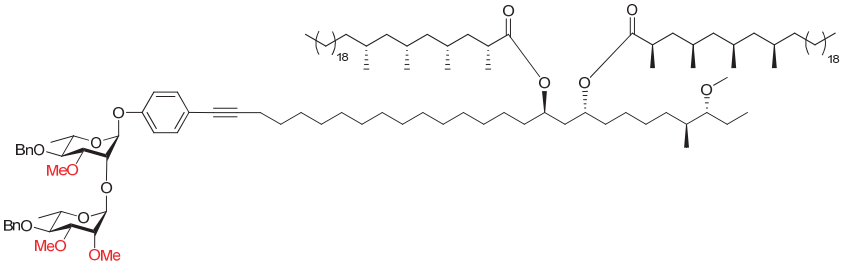
The title compound was synthesized according to general procedure D using **45** (26 mg, 18 µmol, 1.0 eq), mycocerosic acid (25 mg, 53 µmol, 3.0 eq), DIC (16 µL, 105 µmol, 6.0 eq) and DMAP (19 mg, 158 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (32 mg, 13.4 µmol, 76%) as a waxy solid. $[\alpha]_D^{25}$ = -32.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.21 (m, 22H, C*H*$_{arom}$); 6.97-6.93 (m, 2H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.24-5.15 (m, 3H, H-1', PhC*H*$_2$,); 4.91-4.73 (m, 7H, H-1", H-2", C*H*$_{Phth}$, PhC*H*H, PhC*H*H, PhC*H*H); 4.70-4.62 (m, 3H, PhCH*H*, PhCH*H*, PhCH*H*); 4.25 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.76-3.60 (m, 7H, H-2', H-3'', H-4', H-4'', H-5, H-5', H-6''); 3.59-3.51 (m, 7H, H-6", OC*H*$_3$); 3.48-3.41 (m, 2H, H-3', H-4); 3.38-3.31 (m, 10H, H-5", OC*H*$_3$); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 1.77-0.81 (m, 181H, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$, H-6, H-6'). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.3 (C$_{q,arom}$); 154.7 (*C*O$_{Cbz}$); 138.5, 138.4, 138.2, 135.5 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 101.1 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 83.3 (C-3"); 82.0 (C-3); 80.8 (C-3'); 80.1 (C$_{q,alkyne}$); 80.1 (C-4); 78.2 (C-2"); 77.9 (C-4'); 77.7 (C-4''); 77.0 (C-2'); 75.4, 75.3, 75.2 (Ph*C*H$_2$); 75.0 (C-5''); 73.0 (C-2); 71.1 (C-6''); 70.4 (*C*H$_{Phth}$); 69.9 (Ph*C*H$_2$); 68.7 (C-5); 68.0 (C-5'); 59.9, 59.1, 58.3, 57.6, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.1 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6); 18.0 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1073, 1095, 1140, 1259, 1379, 1457, 1464, 1507, 1734, 1756, 1763, 2853, 2923. HRMS calculated for $C_{150}H_{247}O_{21}$ 2385.82885 [M+H]$^+$; found 2385.83921.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (52)



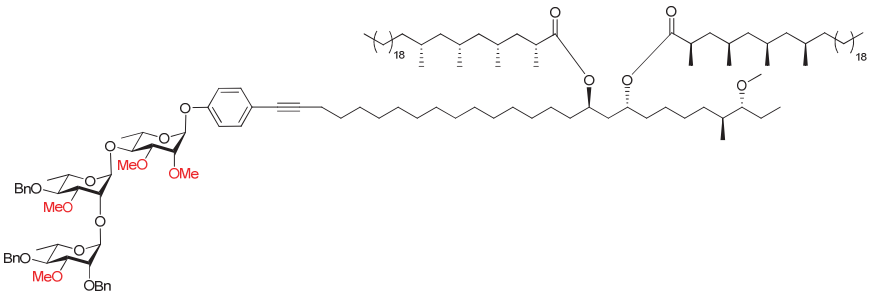
The title compound was synthesized according to general procedure D using **46** (37 mg, 25 µmol, 1.0 eq), mycocerosic acid (35 mg, 74 µmol, 3.0 eq), DIC (23 µL, 148 µmol, 6.0 eq) and DMAP (27 mg, 221 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 4:1) yielded the product (48 mg, 20 µmol, 80%) as a waxy solid. $[\alpha]_D^{25}$ = -35.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.42-7.26 (m, 22H, C*H*$_{arom}$); 6.95-6.92 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.28-5.14 (m, 6H, H-1', H-2', PhC*H*$_2$, PhC*H*$_2$); 4.93-4.78 (m, 4H, PhC*H*H, PhC*H*H, C*H*$_{Phth}$); 4.69-4.61 (m, 4H, H-1", H-2", PhCH*H*, PhCH*H*); 4.22 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.78 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.75-3.61 (m, 3H, H-5, H-5', H-6"); 3.59-3.45 (m, 11H, H-3', H-4, H-4', H-4'', H-6", OC*H*$_3$); 3.39-3.33 (m, 8H, H-3", H-5", OC*H*$_3$); 3.26 (s, 3H, OC*H*$_3$); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 205H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 155.3 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.6, 138.3, 135.5, 135.1 (C$_{q,arom}$); 133.0, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.2, 128.2, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 101.3 (C-1"); 98.8 (C-1'); 96.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.9 (C-3"); 81.7 (C-3); 80.1 (C$_{q,alkyne}$); 80.0 (C-4); 79.3 (C-3'); 78.0 (C-4'); 78.0 (C-4"); 77.6 (C-2"); 75.4, 75.0 (Ph*C*H$_2$); 74.8 (C-5"); 72.9 (C-2); 72.1 (C-2'); 71.1 (C-6"); 70.4 (*C*H$_{Phth}$); 70.1, 69.9 (Ph*C*H$_2$); 68.8 (C-5); 67.9 (C-5'); 61.0, 59.8, 58.2, 57.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.5, 29.4, 29.2, 29.1 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.1 (C-6); 17.9 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1095, 1176, 1259, 1379, 1457, 1507, 1736, 1756, 2853, 2923. HRMS calculated for $C_{151}H_{247}O_{23}$ 2429.81868 [M+H]$^+$; found 2429.82801.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (53)



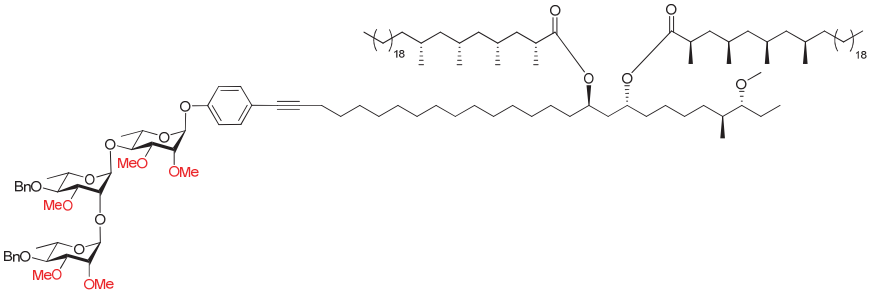
The title compound was synthesized according to general procedure D using **47** (29 mg, 27 µmol, 1.0 eq), mycocerosic acid (39 mg, 82 µmol, 3.0 eq), DIC (25 µL, 164 µmol, 6.0 eq) and DMAP (32 mg, 264 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 3:2) yielded the product (44 mg, 22 µmol, 81%) as a waxy solid. $[\alpha]_D^{25}$ = -53.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.38-7.26 (m, 12H, C*H*$_{arom}$); 6.91 (d, 2H, *J* = 8.8 Hz, CH$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 4.93-4.83 (m, 4H, PhC*H*H, PhC*H*H, C*H*$_{Phth}$); 4.66-4.59 (m, 2H, PhCH*H*, PhCH*H*); 4.20 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 3.79-3.68 (m, 4H, H-2', H-3, H-5. H-5'); 3.64 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3'); 3.57 (s, 3H, OC*H*$_3$); 3.56 (s, 3H, OC*H*$_3$); 3.55 (s, 3H, OC*H*$_3$); 3.47-3.39 (m, 2H, H-4, H-4'); 3.33 (s, 3H, OC*H*$_3$); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.77-0.81 (m, 229H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.5, 138.7, 138.6 (C$_{q,arom}$); 133.0, 128.5, 128.5, 128.2, 128.1, 127.9, 127.8 (*C*H$_{arom}$); 117.9 (C$_{q,arom}$); 116.1 (*C*H$_{arom}$); 98.9 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 81.8 (C-3); 81.2 (C-3'); 80.6 (C-4'); 80.1 (C$_{q,alkyne}$); 80.1 (C-4); 77.6 (C-2'); 75.5, 75.3 (Ph*C*H$_2$); 73.6 (C-2); 70.4 (*C*H$_{Phth}$); 68.7 (C-5); 68.5 (C-5'); 59.2, 58.2, 58.1, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5 (*C*H$_{3,Myc}$); 19.5 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.1 (C-6); 18.1 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1053, 1096, 1123, 1132, 1176, 1233, 1379, 1457, 1465, 1507, 1734, 2853, 2923. HRMS calculated for $C_{128}H_{223}O_{14}$ 1985.68006 $[M+H]^+$; found 1985.68007.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,4-di-*O*-benzyl-3-*O*-methyl-α-L-rhamnopyranoside)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (54)



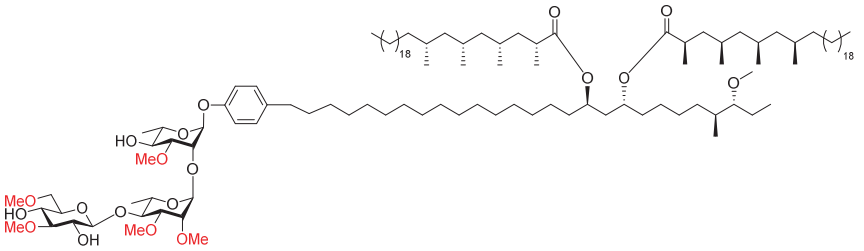
The title compound was synthesized according to general procedure D using **48** (32 mg, 24 µmol, 1.0 eq), mycocerosic acid (35 mg, 73 µmol, 3.0 eq), DIC (23 µL, 147 µmol, 6.0 eq) and DMAP (27 mg, 220 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 7:3) yielded the product (43 mg, 19 µmol, 79%) as a waxy solid. $[\alpha]_D^{25}$ = -37.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47-7.44 (m, 2H, C*H*$_{arom}$); 7.37-7.26 (m, 15H, C*H*$_{arom}$); 6.99-6.95 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.15 (d, 1H, *J* = 2.0 Hz, H-1'); 5.14 (d, 1H, *J* = 1.6 Hz, H-1''); 4.93 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.88-4.78 (m, 5H, PhC*H*H, PhC*H*$_2$, C*H*$_{Phth}$); 4.63 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.55 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.05 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2'); 3.88 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2''); 3.81-3.73 (m, 2H, H-2, H-5''); 3.71-3.57 (m, 5H, H-3, H-3', H-4, H-5, H-5'); 3.53-3.42 (m, 14H, H-3'', H-4'', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.28 (t, 1H, *J* = 9.4 Hz, H-4'); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.57-2.48 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.77-0.93 (m, 180H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$); 0.91-0.81 (m, 41H, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 171.1, 171.1 (*C*O$_{Myc}$); 155.8, 139.1, 138.7, 138.5 (C$_{q,arom}$); 133.0, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.3 (*C*H$_{arom}$); 100.7 (C-1'); 99.2 (C-1''); 95.9 (C-1); 89.6 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.2 (C-3'); 82.0 (C-3); 81.5 (C-3''); 80.8 (C-4''); 80.1 (C$_{q,alkyne}$); 80.0 (C-4'); 77.8 (C-4); 76.3 (C-2); 75.1 (Ph*C*H$_2$); 74.0 (C-2''); 73.4 (C-2'); 72.6 (Ph*C*H$_2$); 70.4 (*C*H$_{Phth}$); 68.6 (C-5''); 68.3 (C-5 and C-5''); 59.7, 57.9, 57.8, 57.5, 57.3 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.4, 18.3, 17.9 (C-6, C-6', and C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1055, 1069, 1095, 1120, 1139, 1176, 1259, 1378, 1457, 1464, 1507, 1734, 2853, 2951. HRMS calculated for $C_{142}H_{241}O_{18}$ 2234.79375 $[M+H]^+$; found 2234.79804.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,3-di-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (55)



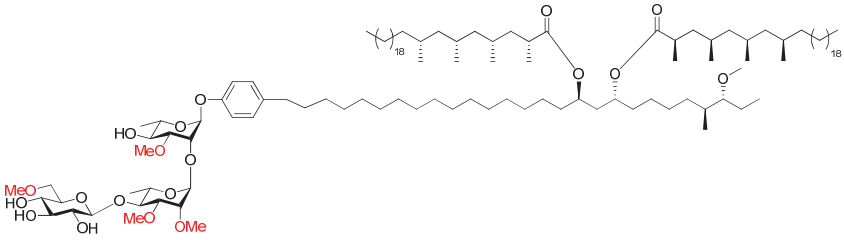
The title compound was synthesized according to general procedure D using **49** (27 mg, 22 µmol, 1.0 eq), mycocerosic acid (32 mg, 66 µmol, 3.0 eq), DIC (20 µL, 131 µmol, 6.0 eq) and DMAP (24 mg, 197 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (38 mg, 18 µmol, 80%) as a waxy solid. $[\alpha]_D^{25}$ = -45.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.25 (m, 12H, C*H*$_{arom}$); 6.99-6.96 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 2.0 Hz, H-1); 5.18 (d, 1H, *J* = 1.6 Hz, H-1'); 5.15 (d, 1H, *J* = 1.6 Hz, H-1''); 4.92 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.88-4.81 (m, 3H, PhC*H*H, C*H*$_{Phth}$); 4.64-4.60 (m, 2H, PhCH*H*, PhCH*H*); 4.09 (dd, 1H, *J* = 2.0 2.4 Hz, H-2'); 3.79-3.60 (m, 8H, H-2, H-2", H-3, H-3", H-4, H-5, H-5', H-5"); 3.54-3.49 (m, 16H, H-3', O*CH*$_3$); 3.45-3.33 (m, 5H, H-4', H-4", O*CH*$_3$); 2.88-2.85 (m, 1H, C*H*$_{Phth}$); 2.57-2.48 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.77-0.93 (m, 184H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$); 0.91-0.81 (m, 43H, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.8, 139.0, 138.7 (C$_{q,arom}$); 133.0, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.3 (*C*H$_{arom}$); 100.7 (C-1'); 98.5 (C-1"); 95.9 (C-1); 89.6 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.2 (C-3'); 82.0 (C-3); 81.2 (C-3"); 80.7 (C-4"); 80.1 (C$_{q,alkyne}$); 80.0 (C-4'); 77.9 (C-4); 77.8 (C-2"); 76.2 (C-2); 75.3, 75.1 (Ph*C*H$_2$); 73.8 (C-2'); 70.4 (*C*H$_{Phth}$); 68.7 (C-5"); 68.3 (C-5 and C-5"); 59.7, 59.2, 58.1, 58.0, 57.5, 57.3 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.4, 18.1, 18.0 (C-6, C-6', and C-6"); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1006, 1030, 1056, 1096, 1120, 1175, 1235, 1258, 1378, 1457, 1462, 1507, 1734, 2853, 2923. HRMS calculated for $C_{136}H_{237}O_{18}$ 2159.76586 $[M+H]^+$; found 2159.76870.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (56)



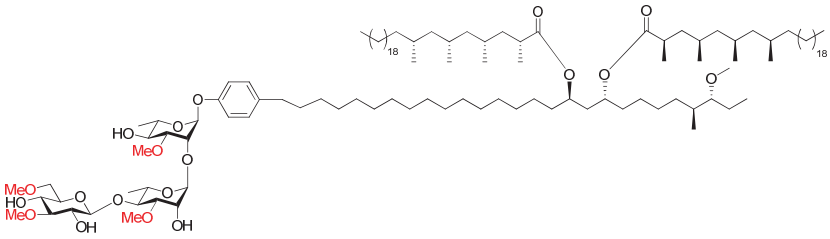
The title compound was synthesized according to general procedure E using **50** (32 mg, 14 µmol, 1.0 eq) and Pd/C (10%, 15 mg, 14 µmol, 1.0 eq). Column chromatography (DCM-acetone 3:2) yielded the product (22 mg, 11 µmol, 79%) as a waxy solid. $[\alpha]_D^{25}$ = -25.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (850 MHz) δ: 7.10 (d, 2H, *J* = 9.4 hz, C*H*$_{arom}$); 6.94 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 1.7 Hz, H-1); 5.10 (d, 1H, *J* = 1.7 Hz, H-1'); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.41 (d, 1H, *J* = 7.7 Hz, H-1"); 4.22 (dd, 1H, *J* = 1.7, 3.4 Hz, H-2); 3.89 (s, 1H, 2"-O*H*); 3.77-3.74 (m, 3H, H-2', H-5, H-5'); 3.69-3.66 (m, 4H, H-3', OC*H*$_3$); 3.65-3.61 (m, 4H, H-3, H-4', H-6"); 3.58 (dt, 1H, *J* = 1.7, 9.4 Hz, H-4); 3.55-3.52 (m, 4H, H-4", OC*H*$_3$); 3.50 (s, 3H, OC*H*$_3$); 3.48 (s, 3H, OC*H*$_3$); 3.17 (t, 1H, *J* = 9.4 Hz, H-3");); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.80 (bs, 1H, 4"-O*H*); 2.56-2.51(m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.30 (bs, 1H, 4-O*H*); 1.77-0.81 (m, 190H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (214 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.6 (C-1"); 98.5 (C-1'); 97.4 (C-1); 86.8 (*C*H$_{Phth}$); 85.6 (C-3"); 81.8 (C-4'); 81.5 (C-3); 80.3 (C-3'); 75.6 (C-2'); 75.1 (C-2"); 74.1 (C-5"); 73.0 (C-6"); 72.2 (C-2); 71.9 (C-4); 71.4 (C-4"); 70.4, 70.4 (*C*H$_{Phth}$); 69.1 (C-5); 68.4 (C-5'); 60.7, 59.7, 59.2, 57.8, 57.5, 56.7 (O*C*H$_3$); 45.6, 45.6, 45.4 45.4 (*C*H$_{2,Myc}$); 41.1, 41.1, 38.5 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.7, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.0 (*C*H$_{Myc}$); 29.9, 29.9, 29.9, 29.9, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5 (*C*H$_2$); 28.1 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.4 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5, 18.6, 18.6 (*C*H$_{3,Myc}$); 17.9 (C-6); 17.7 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1010, 1070, 1123, 1175, 1229, 1261, 1378, 1457, 1464, 1511, 1734, 2853, 2922, 3434. HRMS calculated for $C_{122}H_{229}O_{19}$ 1998.69476 $[M+H]^+$; found 1998.69683.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (57)



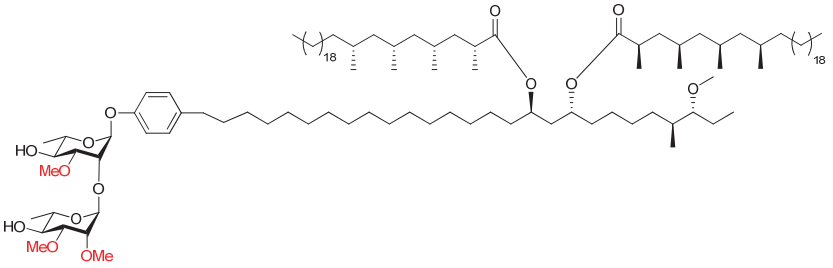
The title compound was synthesized according to general procedure E using **51** (24 mg, 10 µmol, 1.0 eq) and Pd/C (10%, 11 mg, 10 µmol, 1.0 eq). Column chromatography (DCM-MeOH 19:1) yielded the product (8 mg, 4 µmol, 40%) as a waxy solid. $[\alpha]_D^{25}$ = -28 ° (c = 0.2, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.94 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 2.0 Hz, H-1); 5.11 (d, 1H, *J* = 1.6 Hz, H-1'); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.45 (d, 1H, *J* = 7.6 Hz, H-1"); 4.23 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2); 3.99 (bs, 1H, O*H*); 3.79-3.71 (m, 3H, H-2', H-5, H-5'); 3.69-3.60 (m, 5H, H-3, H-3', H-4', H-6"); 3.58-3.54 (m, 6H, H-3", H-4, H-5", OC*H*$_3$); 3.50 (s, 3H, OC*H*$_3$); 3.49 (s, 3H, OC*H*$_3$); 3.46-3.42 (m, 1H, H-4"); 3.39-3.36 (m, 4H, H-2", OC*H*$_3$); 3.35 (s, 3H, OC*H*$_3$); 2.98 (bs, 1H, O*H*); 2.88-2.79 (m, 2H, C*H*$_{Phth}$, O*H*); 2.57-2.50 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.32 (bs, 1H, O*H*); 1.77-0.81 (m, 207H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$,). ^{13}C-APT NMR (101 MHz) δ: 176.2 (*C*O$_{Myc}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.3 (C-1"); 98.5 (C-1'); 97.5 (C-1); 86.8 (*C*H$_{Phth}$); 81.5 (C-3); 81.5 (C-4'); 80.3 (C-3'); 76.7 (C-3"); 75.9 (C-2'); 74.8 (C-2"); 74.0 (C-4"); 73.1 (C-6"); 72.3 (C-2); 72.0 (C-4); 71.9 (C-5"); 70.4 (*C*H$_{Phth}$); 69.1 (C-5); 68.3 (C-5'); 59.8, 59.1, 57.8, 57.5, 56.7 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.6, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6 18.6, 18.5 (*C*H$_{3,Myc}$); 17.9 (C-6); 17.7 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1016, 1069, 1123, 1229, 1261, 1378, 1457, 1511, 1736, 2853, 2923, 3436. HRMS calculated for $C_{121}H_{227}O_{19}$ 1985.68253 $[M+H]^+$; found 1985.68265.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(3-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (58)



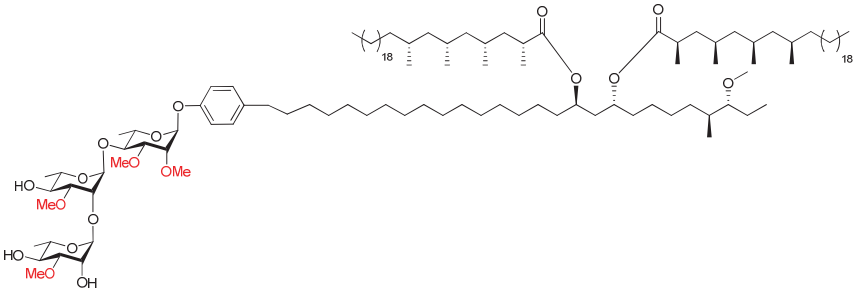
The title compound was synthesized according to general procedure E using **52** (37 mg, 15 µmol, 1.0 eq) and Pd/C (10%, 16 mg, 15 µmol, 1.0 eq). Column chromatography (DCM-MeOH 11:1) yielded the product (23 mg, 12 µmol, 76%) as a waxy solid. $[\alpha]_D^{25}$ = -24.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (850 MHz) δ: 7.10 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 6.95-6.94 (m, 2H, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.7 Hz, H-1); 5.08 (d, 1H, *J* = 1.7 Hz, H-1'); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.39 (d, 1H, *J* = 7.7 Hz, H-1"); 4.22 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 4.20 (s, 1H, H-2'); 3.82 (dq, 1H, *J* = 3.4, 6.0 Hz, H-5'); 3.76 (dq, 1H, *J* = 3.4, 6.0 Hz, H-5); 3.71 (s, 1H, 2"-O*H*); 3.69 (s, 3H, OC*H*$_3$); 3.66-3.63 (m, 4H, H-3, H-3', H-6"); 3.61-3.57 (m, 2H, H-4, H-4'); 3.55 (dt, 1H, *J* = 2.0, 8.9 Hz, H-4"); 3.51 (s, 3H, OC*H*$_3$); 3.51 (s, 3H, OC*H*$_3$); 3.45-3.39 (m, 2H, H-2", H-5"); 3.18 (t, 1H, *J* = 8.9 Hz, H-3"); 2.87-2.85 (m, 2H, C*H*$_{Phth}$, 4"-O*H*); 2.55-2.53 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.34 (bs, 2H, 4-O*H*, 2'-O*H*); 1.77-0.81 (m, 189H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (214 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.7 (C-1"); 100.6 (C-1'); 97.4 (C-1); 86.8 (*C*H$_{Phth}$); 85.4 (C-3"); 81.2 (C-3); 81.1 (C-4'); 80.6 (C-3'); 75.2 (C-2"); 74.3 (C-5"); 73.0 (C-6"); 72.5 (C-2); 71.8 (C-4); 71.4 (C-4"); 70.4, 70.4 (*C*H$_{Phth}$); 69.0 (C-5); 67.9 (C-5'); 66.9 (C-2'); 60.8, 59.8, 57.7, 57.5, 56.9 (O*C*H$_3$); 45.6, 45.6, 45.4 45.4 (*C*H$_{2,Myc}$); 41.1, 41.1, 38.5 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.7, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.0 (*C*H$_{Myc}$); 29.9, 29.9, 29.9, 29.9, 29.9, 29.9, 29.8, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5 (*C*H$_2$); 28.1 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.4 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5, 18.6 (*C*H$_{3,Myc}$); 17.9 (C-6); 17.6 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1016, 1066, 1132, 1232, 1261, 1378, 1457, 1511, 1736, 2853, 2923, 3451. HRMS calculated for $C_{121}H_{227}O_{19}$ 1985.68253 $[M+H]^+$; found 1985.68284.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (59)



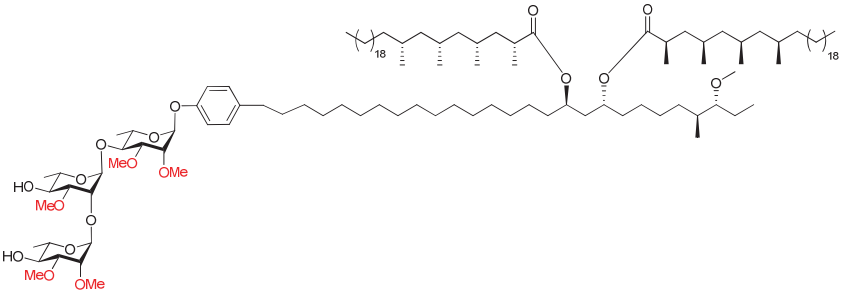
The title compound was synthesized according to general procedure E using **53** (28 mg, 14 µmol, 1.0 eq) and Pd/C (10%, 15 mg, 14 µmol, 1.0 eq). Column chromatography (DCM-MeOH 19:1) yielded the product (22 mg, 12 µmol, 86%) as a waxy solid. $[\alpha]_D^{25}$ = -21.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.96 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.26 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2); 3.78-3.71 (m, 3H, H-2', H-5, H-5'); 3.67-3.54 (m, 6H, H-3, H-4, H-4', OC*H*$_3$); 3.51 (s, 3H, OC*H*$_3$); 3.49 (s, 3H, OC*H*$_3$); 3.46 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3'); 3.33 (s, 3H, OC*H*$_3$); 2.87-2.85 (m, 1H, C*H*$_{Phth}$); 2.57-2.52 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.37 (d, 1H, *J* = 1.2 Hz, 4-O*H*); 2.32 (s, 1H, 4'-O*H*); 1.77-0.81 (m, 191H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.2 (*C*H$_{arom}$); 98.8 (C-1'); 97.6 (C-1); 86.8 (*C*H$_{Phth}$); 81.6 (C-3); 80.8 (C-3'); 76.0 (C-2'); 72.0 (C-2); 71.9 (C-4'); 71.7 (C-4); 70.4 (*C*H$_{Phth}$); 69.1 (C-5); 69.0 (C-5'); 59.1, 57.7, 57.5, 57.2 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.5 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 17.9 (C-6); 17.9 (C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1069, 1129, 1175, 1232, 1378, 1464, 1511, 1734, 2853, 2923, 3434. HRMS calculated for $C_{114}H_{215}O_{14}$ 1809.61405 $[M+H]^+$; found 1809.61455.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(3-*O*-methyl-α-L-rhamnopyranoside)-3-*O*-methyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (60)



The title compound was synthesized according to general procedure E using **54** (28 mg, 13 µmol, 1.0 eq) and Pd/C (10%, 13 mg, 13 µmol, 1.0 eq). Column chromatography (DCM-MeOH 19:1) yielded the product (20 mg, 10 µmol, 81%) as a waxy solid. $[\alpha]_D^{25}$ = -29.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.96 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 2.0 Hz, H-1); 5.28 (d, 1H, *J* = 1.6 Hz, H-1'); 5.12 (d, 1H, *J* = 1.2 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.15-4.13 (m, 2H, H-2', H-2''); 3.79-3.71 (m, 6H, H-2, H-3, H-4, H-5, H-5', H-5''); 3.55-3.52 (m, 8H, H-4', H-4'', OC*H*$_3$); 3.48 (s, 3H, OC*H*$_3$); 3.46 (s, 3H, OC*H*$_3$); 3.42 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3''); 3.36 (dd, 1H, *J* = 2.8, 9.6 Hz, H-3'); 3.33 (s, 3H, OC*H*$_3$); 2.87-2.85 (m, 1H, C*H*$_{Phth}$); 2.57-2.52 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.32 (bs, 1H, 4'-O*H*); 2.30 (bs, 1H, 4''-O*H*); 2.18 (bs, 1H, 2''-O*H*); 1.77-0.81 (m, 211H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (100 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 100.9 (C-1'); 100.5 (C-1''); 96.1 (C-1); 86.8 (*C*H$_{Phth}$); 82.0 (C-3); 81.7 (C-3'); 81.0 (C-3''); 78.0 (C-4); 76.3 (C-2); 71.8 (C-2'); 71.6 (C-4'and C-4''); 70.4 (*C*H$_{Phth}$); 69.2 (C-5'); 68.2 (C-5''); 67.0 (C-5); 59.6, 57.5, 57.4, 57.2, 57.2 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 18.6 (*C*H$_{3,Myc}$); 18.5 (C-6''); 17.9 (C-6 and C-6'); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1016, 1093, 1175, 1229, 1261, 1378, 1457, 1511, 1736, 2853, 2822, 3466. HRMS calculated for $C_{121}H_{227}O_{18}$ 1968.68420 $[M+H]^+$; found 1968.68577.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,3-di-*O*-methyl-4-*O*-(2-*O*-(2,3-di-*O*-methyl-α-L-rhamnopyranoside)-3-*O*-methyl-α-L-rhamnopyranoside)-α-L-rhamnopyranoside (61)



The title compound was synthesized according to general procedure E using **55** (24 mg, 11 µmol, 1.0 eq) and Pd/C (10%, 12 mg, 11 µmol, 1.0 eq). Column chromatography (DCM-MeOH 24:1) yielded the product (16 mg, 8 µmol, 73%) as a waxy solid. $[\alpha]_D^{25}$ = -36.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.96 (dd, 2H, *J* = 2.0, 6.4 Hz, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.26 (d, 1H, *J* = 1.6 Hz, H-1'); 5.15 (d, 1H, *J* = 1.6 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.16 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2'); 3.79-3.70 (m, 6H, H-2, H-3, H-4, H-5, H-5', H-5''); 3.68 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2''); 3.58-3.41 (m, 18H, H-3'', H-4', H-4'', OC*H*$_3$); 3.37 (dd, 1H, *J* = 2.6, 9.4 Hz, H-3'); 3.33 (s, 3H, OC*H*$_3$); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.57-2.52 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.29 (bs, 2H, 4'-O*H*, 4''-OH); 1.77-0.81 (m, 218H, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$, H-6, H-6', H-6''). ^{13}C-APT NMR (100 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 101.0 (C-1'); 98.3 (C-1''); 96.1 (C-1); 86.8 (*C*H$_{Phth}$); 82.1 (C-3 and C-3'); 80.8 (C-3''); 77.9 (C-4); 76.3 (C-2); 76.1 (C-2''); 71.8, 71.7 (C-4'and C-4''); 71.2 (C-2') 70.4 (*C*H$_{Phth}$); 69.2 (C-5'); 68.8 (C-5''); 68.0 (C-5); 59.6, 59.2, 57.5, 57.5, 57.1, 57.1 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.5 (C-6'); 17.9, 17.7 (C-6 and C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1009, 1075, 1082, 1093, 1106, 1122, 1262, 1378, 1457, 1464, 1510, 1736, 2853, 2923, 3430. HRMS calculated for $C_{122}H_{229}O_{18}$ 1983.70326 $[M+H]^+$; found 1983.70441.

References

1. Scollard, D. M. *et al.* The continuing challenges of leprosy. *Clin. Microbiol. Rev.* **19**, 338–381 (2006).
2. Oldenburg, R. *et al.* Mycobacterial phenolic glycolipids selectively disable TRIF-dependent TLR4 signaling in macrophages. *Front. Immunol.* **9**, 1–12 (2018).
3. Doz-Deblauwe, É. *et al.* CR3 Engaged by PGL-I Triggers Syk-Calcineurin-NFATc to Rewire the Innate Immune Response in Leprosy. *Front. Immunol.* **10**, 1–15 (2019).
4. Madigan, C. A. *et al.* A Macrophage Response to Mycobacterium leprae Phenolic Glycolipid Initiates Nerve Damage in Leprosy. *Cell* **170**, 973-985.e10 (2017).
5. Spencer, J. S. & Brennan, P. J. The role of Mycobacterium leprae phenolic glycolipid I (PGL-I) in serodiagnosis and in the pathogenesis of leprosy. *Lepr. Rev.* **82**, 344–357 (2011).
6. Arbues, A., Lugo-Villarino, G., Neyrolles, O., Guilhot, C. & Astarie-Dequeker, C. Playing hide-and-seek with host macrophages through the use of mycobacterial cell envelope phthiocerol dimycocerosates and phenolic glycolipids. *Front. Cell. Infect. Microbiol.* **4**, 1–7 (2014).
7. Fäldt, J. *et al.* Activation of human neutrophils by mycobacterial phenolic glycolipids. *Clin. Exp. Immunol.* **118**, 253–260 (1999).
8. Hunter, S. W. & Brennan, P. J. Further specific extracellular phenolic glycolipid antigens and a related diacylphthiocerol from Mycobacterium leprae. *J. Biol. Chem.* **258**, 7556–7562 (1983).
9. Hunter, S. W. & Brennan, P. J. A novel phenolic glycolipid from Mycobacterium leprae possibly involved in immunogenicity and pathogenicity. *J. Bacteriol.* **147**, 728–735 (1981).
10. Hunter, S. W., Fujiwara, T. & Brennan, P. J. Structure and antigenicity of the major specific glycolipid antigen of Mycobacterium leprae. *J. Biol. Chem.* **257**, 15072–15078 (1982).
11. Mehra, V., Brennan, P. J., Rada, E., Convit, J. & Bloom, B. R. Lymphocyte suppression in leprosy induced by unique *M. leprae* glycolipid. *Nature* **308**, 194–196 (1984).
12. Daffé, M. & Lanéelle, M.-A. Diglycosyl phenol phthiocerol diester of Mycobacterium leprae. *Biochim. Biophys. Acta - Lipids Lipid Metab.* **1002**, 333–337 (1989).
13. Lindeboom, J. A., van Coppenraet, L. E. S. B., van Soolingen, D., Prins, J. M. & Kuijper, E. J. Clinical manifestations, diagnosis, and treatment of mycobacterium haemophilum infections. *Clin. Microbiol. Rev.* **24**, 701–717 (2011).
14. Besra, G. S. *et al.* Structural Elucidation and Antigenicity of a Novel Phenolic Glycolipid Antigen from Mycobacterium haemophilum. *Biochemistry* **30**, 7772–7777 (1991).
15. Unpublished results.
16. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie* **124**, 11944–11947 (2012).
17. Barroso, S., Geerdink, D., Ter Horst, B., Casas-Arce, E. & Minnaard, A. J. Total synthesis of the phenolic glycolipid mycoside B and the glycosylated p-hydroxybenzoic acid methyl ester HBAD-I, virulence markers of mycobacterium tuberculosis. *European J. Org. Chem.* 4642–4654 (2013) doi:10.1002/ejoc.201300437.
18. Weber, J. *et al.* 2- O -Benzyloxycarbonyl protected glycosyl donors: a revival of carbonate-mediated anchimeric assistance for diastereoselective glycosylation. *Chem. Commun.* **55**, 12543–12546 (2019).
19. Cavedon, C. *et al.* Visible-Light-Mediated Oxidative Debenzylation Enables the Use of Benzyl Ethers as Temporary Protecting Groups. *Org. Lett.* **23**, 514–518 (2021).
20. Jakas, A. *et al.* Synthesis of anthrose lipidic derivative as mimic of B. anthracis BclA glycoprotein for use in ELISA-like binding assays. *J. Carbohydr. Chem.* **35**, 69–85 (2016).

21. When the same product was formed on a separate occasion from a different starting material (33) and the reaction was filtered over silica instead of celite the yield was improved to 100%. This result is not conclusive however and requires further investigation.

22. van Dijk, J. H. M. *et al.* Synthetic Phenolic Glycolipids for Application in Diagnostic Tests for Leprosy. *ChemBioChem* **22**, 1487–1493 (2021).

Chapter 6

Synthesis of PGLs originating from *M. kansasii* and *M. gastri*

Koen Rijpkema, Rutger Groeneveld, Stavroula Karageorgi, Bas van den Berg and many LO1/LO3 students contributed to this chapter.

Introduction

Mycobacterium kansasii is a pathogenic nontuberculous mycobacterium that was first isolated in 1953.[1] *M. kansasii* is known to cause pulmonary disease resembling tuberculosis[2,3] and is often considered to be the most pathogenic nontuberculous mycobacterium.[4–7] Unlike other pathogenic mycobacteria, *M. kansasii* can be isolated from (tap) water and soil,[8–11] and human-to-human transmission is not thought to occur.[12] It has been postulated that this may be due to the relatively hydrophilic nature of its (glyco)lipids,[13] as it has been demonstrated that hydrophobicity increases aerosol transmission, which increases virulence and pathogenicity.[14] The first isolated phenolic glycolipid ever, discovered in 1957, originated from *M. kansasii* and it was called "Mycoside A".[15–20] It is also referred to as PGL-K7, and its structure was determined to be a triglycosyl phenolic glycolipid, carrying a 2-*O*-methyl-α-L-fucopyranosyl-(1→3)-2-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-methyl-α-L-rhamnopyranosyl glycan. Thereafter several more PGLs of *M. kansasii* have been discovered, isolated and almost all of their structures have been elucidated (Figure 1).[18–24] *M. gastri*, the "mycobacterium of the stomach", was found to produce the same PGLs as *M. kansasii*.[22,28,29]

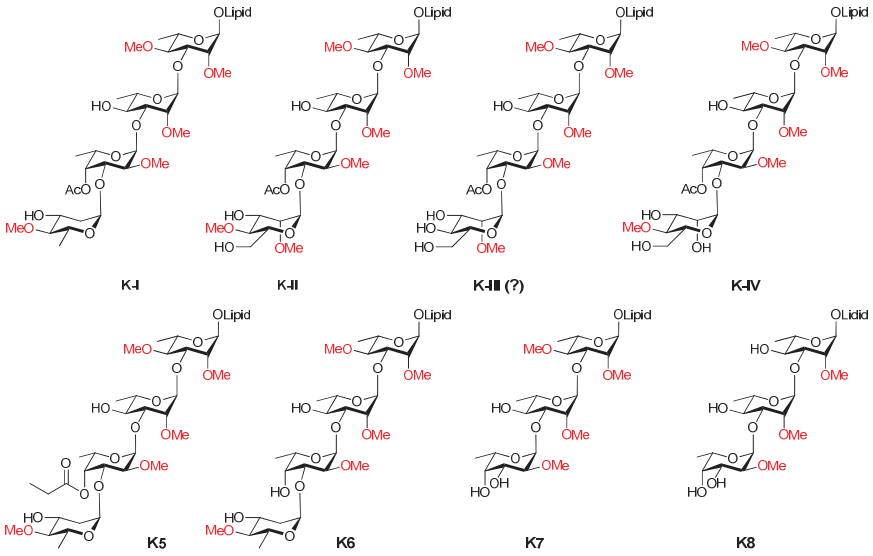


Figure 1. Glycoforms of *M. kansasii* and *M. gastri* PGLs, with the corresponding serovars below the structures.

Several syntheses of PGL glycans of *M. kansasii* have been published to date. Gurjar and Reddy were the first to synthesize a trisaccharide of *M. kansasii*.[30] Zegelaar-Jaarsveld *et al.* have reported the synthesis of three different tetrasaccharides (serovars I, II and IV), all bearing a tyramine moiety for conjugation purposes.[31–33] Lowary and coworkers have synthesized some of the natural glycans as well as many analogues of *M. kansasii* PGLs[34] and they have generated squaramide based glycoconjugates of these compounds as well.[35] However, in order to fully understand the interactions between PGLs and the host immune system, pure synthetic complete PGLs are required. Therefore, this chapter describes the synthesis of all known PGLs originating from *M. kansasii* and *M. gastri* as well as a hypothesized biosynthetic intermediate (K-III).[22,25]

The general strategy for the synthesis of these phenolic glycolipids follows the strategy described in Chapters 4 and 5 for the synthesis of complete PGLs (Figure 2).[36,37] Glycans bearing an iodophenol and protected with hydrogenation labile groups are to be synthesized from the 'reducing end', after which they can be attached to a phthiocerol

alkyne derivative using a Sonogashira cross coupling. The resulting diol can then be esterified with mycocerosic acids using Steglich conditions and a final hydrogenation will then lead to the global deprotection and concurrent reduction of the conjugated internal alkyne which is formed in the Sonogashira reaction.

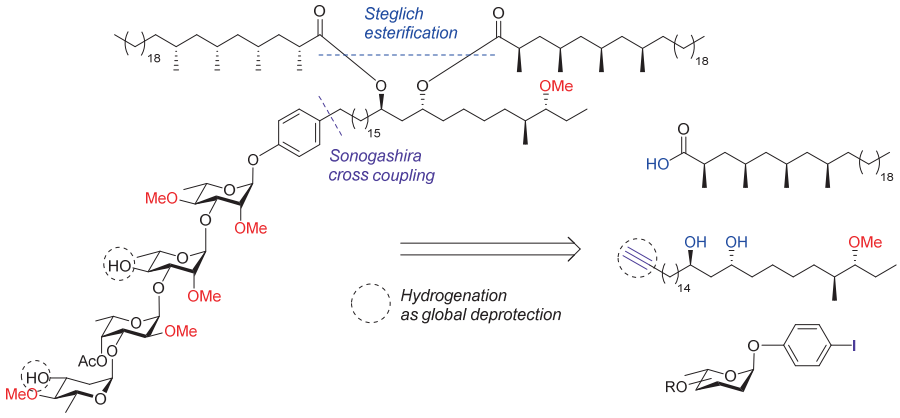


Figure 2. General synthetic strategy of *M. kansasii* PGLs with PGL K-I as an example.

This synthetic strategy requires the oligosaccharides to be protected with protecting groups that are susceptible to hydrogenation conditions. In Chapters 4 and 5 it was described that a carboxybenzyl (Cbz) protecting group can be used as a hydrogenation labile group which - in most cases - was capable of steering the stereoselective formation of 1,2-*trans* linkages by means of neighboring group participation. A common structural feature in the glycans of *M. kansasii* and *M. gastri* PGLs is the presence of a methyl ether on the C-2 position of the constituting monosaccharides, as well as the presence of a C-2 deoxy sugar. The C-2 methyl bearing rhamnosides are all 1,2-*trans* linked. It has previously been established that mannose configured donors acylated at the C-3 position are capable of selectively forming 1,2-*trans* linkages via remote participation.[38–40] It will therefore be investigated here, whether a C-3 Cbz moiety can provide a similar long range stereodirecting effect in the assembly of the PGLs outlined in this chapter as this could drastically improve the efficiency of the syntheses. The building blocks required for the synthesis of the various serotypes are depicted in Figure 3.

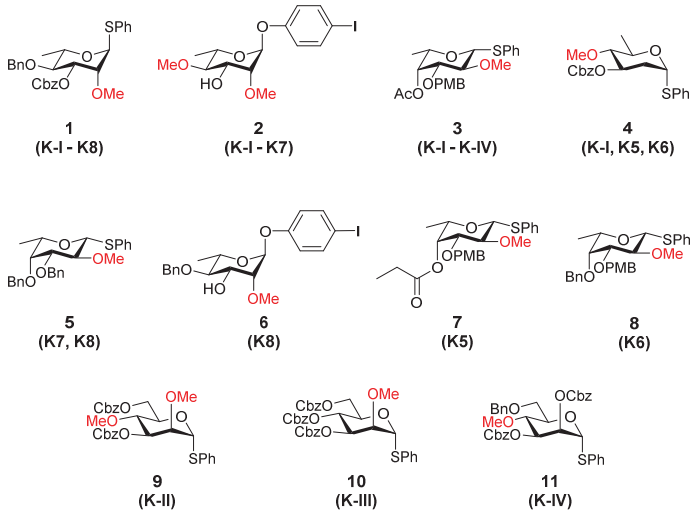
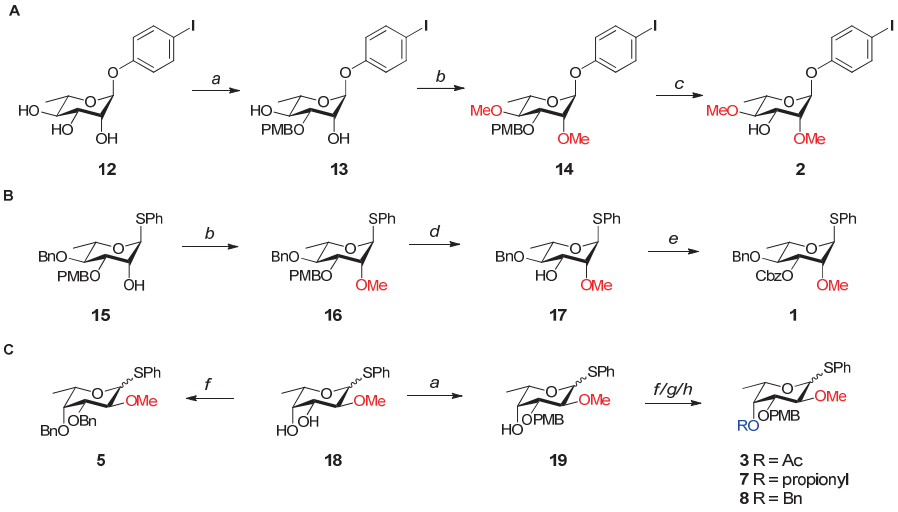


Figure 3. Required building blocks. Serovars which can be made with the corresponding building block are between brackets.

Four of the six tetrasaccharides outlined in Figure 1 (K-I – K-IV) contain the same trisaccharide core (phenyl (1→3)-2-*O*-methyl-4-*O*-acetyl-α-L-fucopyranosyl-(1→3)-2-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-methyl-α-L-rhamnopyranose) which can be synthesized with acceptor **2** and donors **1** and **3**. Donor **1** bears a C-3 Cbz moiety for remote participation, which can then be removed under mild basic conditions. Previously, Zegelaar-Jaarsveld *et al.* performed a fucosylation reaction in the assembly of *M. kansasii* PGL glycans, with a donor that is very similar to donor **3** using IDCP as a mild promotor.[31] Based on the high stereoselectivity reported by Zegelaar-Jaarsveld, donor **3** was selected for the assembly of the K-I - K-IV glycans. In line with this approach, fucose donors **7**, **8** and **5** will be probed for the assembly of the PGLs of serovars K5, K6 and K7/K8, respectively. Instead of a post-glycosylation deoxygenation approach, as described by Zegelaar-Jaarsveld,[33] 2,6-dideoxy donor **4** was designed to minimize the number of steps in the tetrasaccharide stadium for the synthesis of serovars K-I, K5 and K6. Acceptor **6** has been described in Chapter 4 and can be used for the assembly of the serovar K8 PGL. Finally, thiomannosides **9**, **10** and **11**, all bearing a Cbz moiety for (remote) participation were projected to be used as the terminal building blocks for the PGLs of serovars K-II, K-III, and K-IV, respectively.

Results and Discussion

The synthesis of the required rhamnose and fucose building blocks is depicted in Scheme 1. Rhamnose acceptor **2** was synthesized from triol **12** in 40% yield over 3 steps. First the C-3 position was selectively protected with a PMB ether, [41] after which the methyl ethers were introduced on the C-2 and C-4 positions and the PMB was removed with a catalytic amount of HCl in HFIP.[42]

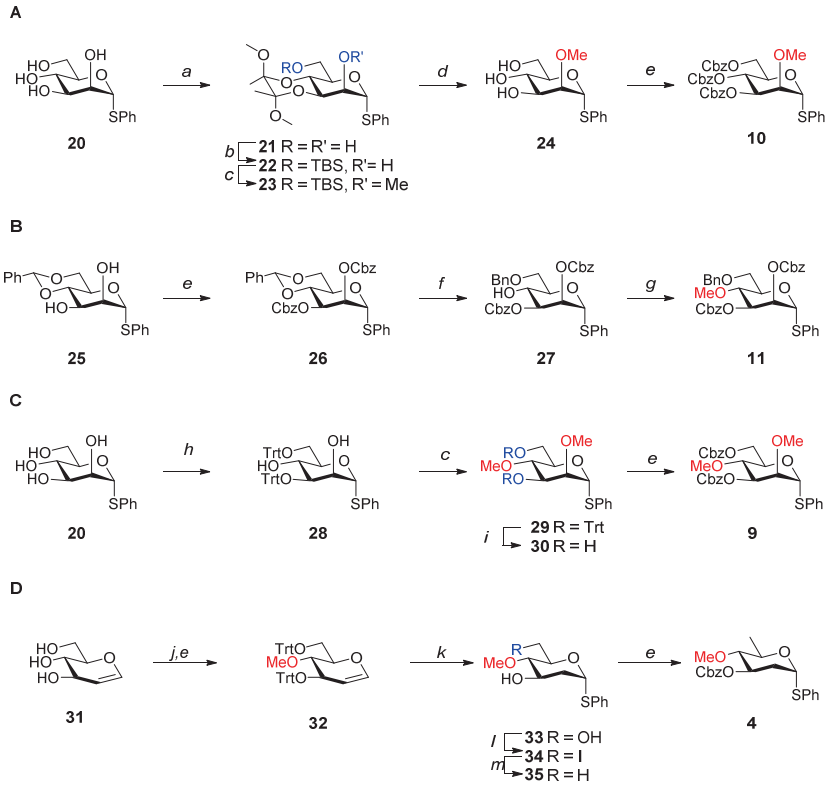


Scheme 1. Rhamnose and fucose building block synthesis. Reagents and conditions: (a) 1. Bu_2SnO, toluene reflux, 2. PMBCl, TBABr, toluene, reflux, 53% (**13**), 86% (**19**), (b) NaH, MeI, DMF, 0 °C → RT, 94%, (**14**), 97% (**16**), (c) HCl/HFIP, HFIP/DCM, 81%, (d) HCl/HFIP, TES, HFIP/DCM, 80%, (e) CbzCl, DMAP, DCM, 0 °C → RT, 100%. (f) NaH, BnBr, DMF, 0 °C → RT, 96%, (**5**), 96% (**8**), (g) Ac_2O, pyridine, DMAP, DCM 97%, (h) propionic anhydride, pyridine, DMAP, DCM 71%.

An alternative route towards this this acceptor from triol **12** involved the installation of an isopropylidene group on the 3,4-diol, methylation of the remaining alcohol, removal of the isopropylidene, regioselective installation of the PMB ether on the equatorial C-3 position, methylation of the C-4 alcohol and unmasking of the C-3 PMB ether. This latter route provided building block **2** in 66% yield over 6 steps. Rhamnose donor **1** was synthesized by methylating intermediate **15** (described in Chapter 4), removing the C-3 PMB ether and replacing it with a Cbz, giving **1** in 78% yield over 3 steps.

Fucose donor **5** was synthesized by benzylating diol **18** (described in Chapter 4), in 96% yield. Fucose donors **3, 7** and **8** could be formed from intermediate **19**, in turn regioselectively generated from **18**, in 97%, 71% and 96% yield, respectively.

The synthesis of the required terminal building blocks is depicted in Scheme 2. The installation of the C-2 methyl ether, present in thiomannoside **10** (Scheme **2A**) was accomplished by first protecting the 3,4-bis-equatorial diol of mannoside **20** with a butane 2,3-bisacetal (BDA),[43] after which the primary alcohol was silylated with TBSCl and imidazole in DMF. Subsequent methylation of the remaining C-2 alcohol and acidic hydrolysis of the BDA and silyl ether protecting groups was accomplished using 95% aqueous TFA, giving triol **24**, which was then reacted with CbzCl and DMAP in DCM[44] to provide donor **10** in 49% yield over 5 steps from **20**. Mannoside **11** was formed in three steps from benzylidene mannose **25** (Scheme **2B**). First the C-2 and C-3 positions were protected with a Cbz carbonate in 98% yield. Thereafter the benzylidene was reductively opened with TES and TFA to liberate the C-4 alcohol which was to be methylated. This turned out to be a challenging step as the adjacent Cbz groups can migrate or form a cyclic carbonate when conditions are used that are too basic or acidic. Initial conditions that were screened to accomplish this transformation included the use of MeI, Me_2S and Ag_2O in THF,[45] HBF_4 and $TMSCH_2N_2$ in DCM,[46] MeOTf and TTBP in DCM,[47] but all these conditions did not deliver a significant amount of the desired product, possibly due to the methylation of the anomeric thiophenol as a side reaction. Finally, it was found that the use of a large excess of trimethyloxonium tetrafluoroborate (BF_4OMe_3) and TTBP in DCM in combination with a short reaction time (<1 hour) delivered the desired product in 70% yield (63% over 3 steps from **25**). Using Proton Sponge® as an alternative sterically hindered base[48] also delivered the desired product but it proved to be much more difficult to remove traces of this compound, complicating product purification. For the 2,4-di-*O*-methyl mannosyl donor **9** (Scheme **2C**) a route was envisaged in which the C-3 and C-6 hydroxy groups are protected first, whereafter methylation can take place and removal of the temporary protecting groups then set the stage for introduction of a Cbz on the C-3 and C-6 positions.



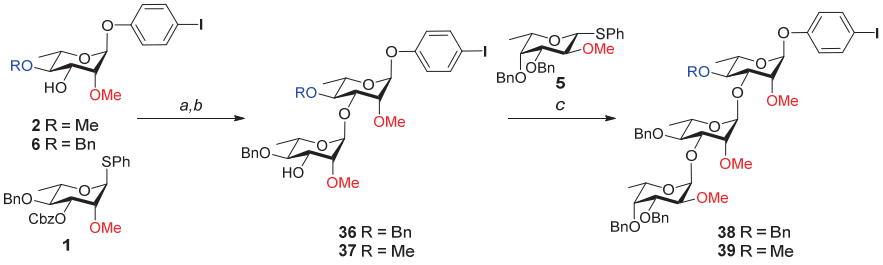
Scheme 2. Terminal sugar building block synthesis. Reagents and conditions: (a) 2,3-butadione, trimethyl orthoformate, CSA, MeOH reflux, 92%, (b) TBSCl, imidazole, DMF, 100%, (c) NaH, MeI, DMF, 0 °C → RT, 92%, (**23**), 90% (**29**), 62% (**32**), (d) 95% TFA, 74%, (e) CbzCl, DMAP, DCM, 0 °C → RT, 79% (**10**), 98% (**26**) 100% (**9**), 94% (**4**), (f) TES, TFA, DCM, 92%, (g) BF_4OMe_3, TTBP, DCM, 70%, (h) TrtCl, pyridine, 50 °C, 67%, (i) AcOH/H_2O, 4:1, 80 °C, 78%, (j) TrtCl, pyridine, 69 °C, 56%, (k) PhSH, [$Re^{V}OCl_3(Me_2S)(Ph_3PO)$], toluene, 75%, (l) I_2, PPh_3, imidazole, toluene, 69 °C, 61%, (m) Pd/C, H_2, $NaHCO_3$, DMF, 82%.

It has previously been reported that 3,6-di-*O* alkylated (Bn/PMB/All) mannosides can be prepared using tin ketal chemistry, but these results were difficult to reproduce.[32,49–51] It was also attempted to selectively protect the C-3 and C-6 positions using bulky pivaloyl esters,[52] which also have a low migratory aptitude under basic conditions.[53] Although the regioselective installation of the C-3- and C-6-pivaloyl esters proceeded smoothly, the subsequent methylation reaction using NaH and MeI produced an inseparable mixture of regioisomers. The methylation conditions used for the

transformation of **27** into **11** did not give any product, likely due to sterically encumbered environment of free alcohols and the relatively low reactivity of the axial C-2 hydroxyl of mannose. Finally, the trityl group was explored as a bulky, but base stable protecting group.[54] Although the yield for the installation of the trityl ethers at C-3 and C-6 positions was rather moderate (67%), the regioselectivity of the reaction was excellent and the product could be easily separated from its regioisomers. During the methylation that followed no migration occurred and the trityls could subsequently be easily removed using mild acidic conditions to replace them with a Cbz, giving donor **9** in 47% yield over 4 steps from **20**.

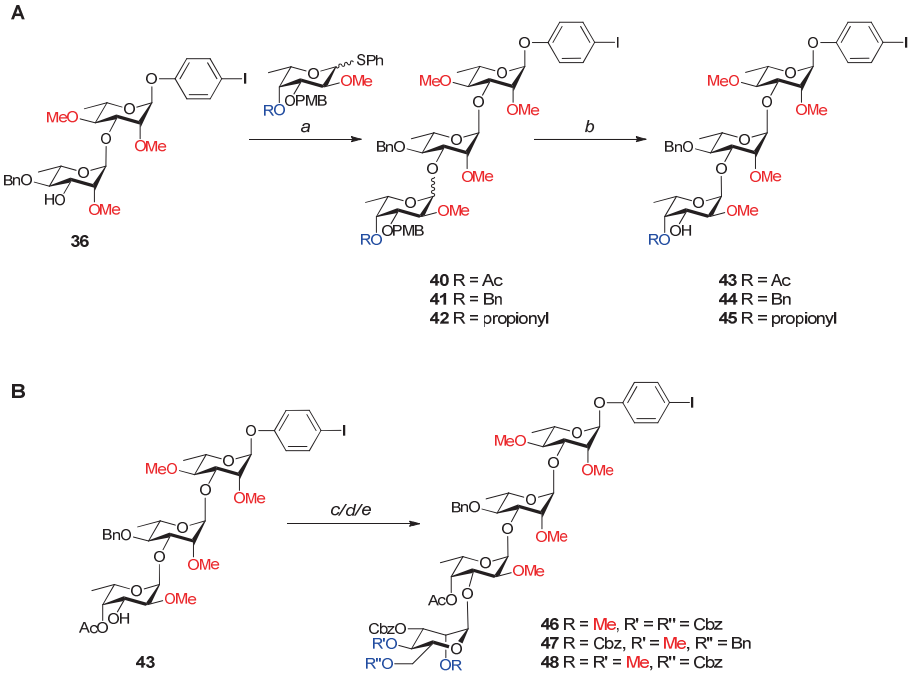
The synthesis of 2,6-dideoxydonor **4** started from D-glucal (Scheme **2D**). It was decided to methylate the C-4 position before deoxygenating the C-6 position as this would leave more options for regioselective manipulations. This way the same approach could be applied as in the assembly of mannose donor **9**. Thus, the C-3 and C-6 hydroxyls were selectively tritylated, after which the remaining free C-4 alcohol could be methylated under basic conditions to give peralkylated glucal **32** in 35% yield over 2 steps. From there on it was decided to first install the anomeric thiophenol before removing the trityls, as the presence of free alcohols during this reaction could possibly lead 1,6-anhydro sugars or polymerization products. In lieu of ordinary acidic conditions such as HCl in dioxane[55] or $PPh_3{\cdot}HBr$,[56] mild conditions using the rhenium complex ($[Re^{V}OCl_3(Me_2S)(Ph_3PO)]$) and PhSH were probed.[57] The first attempt with these conditions yielded a disheartening amount of product but close inspection of the reaction mixture revealed that mono and di-detritylated products were formed as major byproducts. This indicated that the rhenium complex could also cleave the trityl ethers, with PhSH possibly acting as a scavenger for the trityl cations. Therefore, the reaction was performed using a larger excess (4 equivalents) of PhSH and this delivered the desired thiophenol diol **33** in 75% yield. An Appel reaction with I_2, PPh_3 and imidazole next delivered the primary iodide **34** in 61% yield.[58] Reduction of the iodide with Bu_3SnH resulted in partial removal of the anomeric thiophenol, and therefore iodide **34** was hydrogenated with Pd/C and $NaHCO_3$ in DMF[59] to give **35** in 82% yield. Finally, the remaining free alcohol was protected with a Cbz carbonate to give 2,6-dideoxy donor **4** in 94% yield.

With all building blocks in hand, the synthesis of oligosaccharides could be undertaken, the start of which is depicted in Scheme 3. Rhamnose acceptors **2** and **6** were coupled to rhamnose donor **1** using the Ph_2SO/Tf_2O mediated pre-activation conditions to give the target disaccharides with excellent stereoselectivity. To aid in purification the C-3' Cbz was removed under mild basic conditions, to give disaccharide acceptors **36** and **37** in 83% and 85% yield over 2 steps, respectively. These could then be coupled to fucose donor **5** under the agency of IDCP to give the trisaccharides of the serovars K7 (**39**) and K8 (**38**) in good yields (99% and 74%, respectively) and selectivities (6:1).



Scheme 3. Synthesis of trisaccharides **38** and **39**. Reagents and conditions: (a) Ph_2SO, Tf_2O, TTBP, DCM -60 °C, (b) K_2CO_3, MeOH, 83% over 2 steps (**36**), 85% over 2 steps (**37**), (c) IDCP, Et_2O/DCE (4:1), 0 °C → 4 °C, 74% (6:1) (**38**), 99% (6:1) (**39**).

Alternatively, disaccharide acceptor **37** was coupled to fucose donors **3**, **7** and **8** (Scheme 4A). This produced trisaccharides **40, 41** and **42** in good yields and with good stereoselectivity. The resulting α/β-mixtures were difficult to separate. When the C-3'' PMB ether was removed this proved to be much easier and pure trisaccharide acceptors **43, 44** and **45** were synthesized in 53%, 65% and 67% yield over 2 steps, respectively.

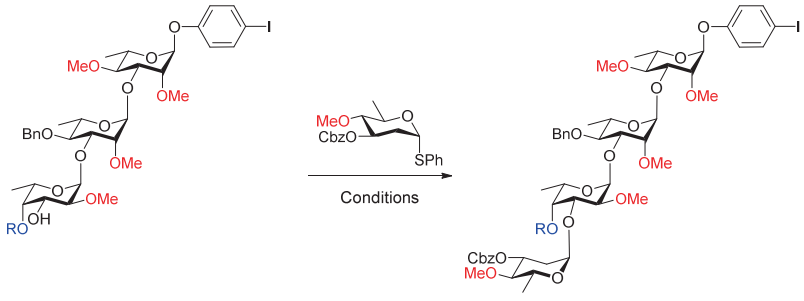


Scheme 4. A. Synthesis of trisaccharide acceptors **43**, **44** and **45**. Reagents and conditions: (a) IDCP, Et_2O/DCE (4:1), 0 °C → 4 °C, 67%, 6:1, (**40**), 84%, 6:1, (**42**), 96%, 6:1, (**41**), (b) DDQ, DCM/H_2O (19:1), 79% (**43**), 77% (**45**), 70% (**44**). **B**. Synthesis of tetrasaccharides **46**, **47** and **48**. Reagents and conditions: (c) Donor **10**, Ph_2SO, Tf_2O, TTBP, DCM -70 → 60 °C, 85% (**46**) (d) conditions c with donor **11**, 64% (**47**) (e) conditions c with donor **9,** 100% (**48**).

Trisaccharide acceptor **43** was then coupled to mannose donors **9, 10** and **11** under pre-activation conditions which stereoselectively delivered the α-linked tetrasaccharides **48**, **46** and **47** corresponding to the serovars K-II, K-III and K-IV, respectively, in good to excellent yields (Scheme 4B).

The coupling of dideoxydonor **4** to trisaccharide acceptors **43** and **44** was attempted with the same pre-activation conditions and this led to varying results which are described in Table 1. The glycosylation of acceptor **43**, carrying an acetyl on the C-4" position proceeded with a good yield (73%) but low selectivity (2:1). Coupling of **4** to benzylated acceptor **44** gave the tetrasaccharide in moderate yield (48%) but excellent stereoselectivity (1:0).

Table 1. Synthesis of tetrasaccharides **49**, **50** and **51**.



43 R = Ac
44 R = Bn
45 R = propionyl

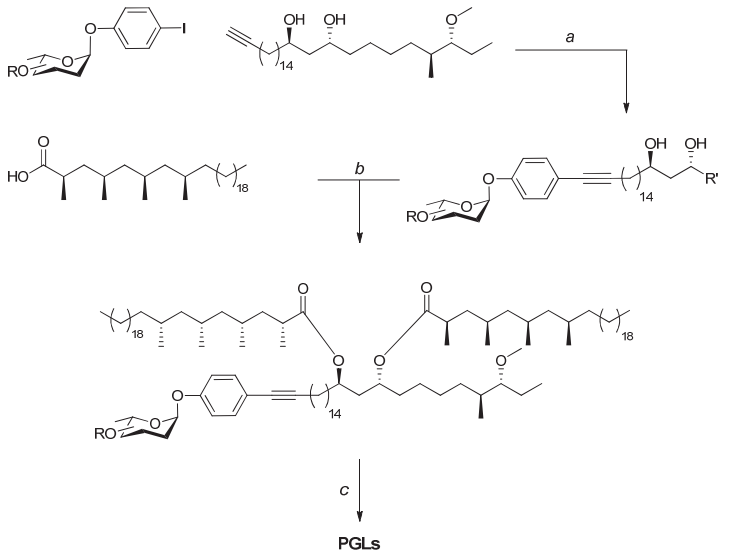
49 R = Ac
50 R = Bn
51 R = propionyl

Acceptor	Activator (eq)	Temperature	Solvent	Time	Yield	α/β
43	Ph_2SO (1.1) / Tf_2O (1.1)	-70 → -60 °C	DCM (0.05 M)	2 h	48%	1:0
42	Ph_2SO (1.1) / Tf_2O (1.1)	-70 → -60 °C	DCM (0.05 M)	2 h	73%	2:1
42	IDCP (1.5)	0 → 4 °C	DCM (0.05 M)	16 h	90%	4:1
44	IDCP (1.5)	0 → 4 °C	DCM (0.05 M)	16 h	89%	4:1
43	IDCP (1.5)	0 → 4 °C	DCM (0.05 M)	16 h	52%	1:0

This is in line with the results of the previous chapter, where it was found that a reactive acceptor was required in the glycosylations using the stereodirecting effect of the Cbz carbonate to give the α-product with good selectivity. While in Chapter 5 the reactivity of the acceptors originating from *M. leprae* and *M. haemophilum* were diminished because of steric factors, the relatively low reactivity of acceptor **43** is caused by the proximal electron-withdrawing substituent, which has been shown to strongly influence the nucleophilicity of the adjacent alcohol.[60] In an attempt to improve the results, the coupling of acetylated acceptor **43** was performed next using IDCP as activating agent. This produced the desired tetrasaccharide **49** in 90% yield with a 4:1 α/β ratio, a clear improvement over the pre-activation conditions. Encouraged by these results the propionyl bearing acceptor **45** was subjected to the same conditions and this provided tetrasaccharide **51** in 89% yield and with a 4:1 α/β-selectivity. When acceptor **44** was coupled to **4** using IDCP the yield only marginally improved in comparison to the reaction using pre-activation conditions. The excellent stereoselectivity was maintained

in this condensation. With all iodoaryl bearing glycans now prepared, the stage was set for the final steps of the PGL assembly, the yields of which are depicted in Table 2.

Table 2. Yields of final stages of PGL assembly.



Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, 40 °C, (b) DIC, DMAP, DCM, 0 °C → RT → 40 °C, (c) Pd/C, H_2, THF/EtOH.

Starting glycan	Sonogashira	Esterification	Hydrogenation	Overall yield
38	79%	66%	84%	44%
39	78%	68%	61%	32%
46	85%	54%	89%	41%
47	65%	65%	78%	33%
48	73%	52%	88%	33%
49	100%	63%	100%	63%
50	81%	52%	86%	36%
51	82%	60%	83%	41%

The glycans were attached to the phthiocerol alkyne derivative using a Sonogashira cross-coupling in good yields. The resulting diols were then esterified with two equivalents of mycocerosic acid under Steglich conditions. The hydrogenation that followed uneventfully produced all known PGL*s* originating from *M. kansasii* and *M. gastrii* in good yields.

Conclusion

This chapter has described the synthesis of all known phenolic glycolipids originating from *Mycobacterium kansasii* and *M. gastri*. A common structural feature in the glycans is the presence of a methyl ether on the C-2 position of 1,2-*trans* linked monosaccharides. It was therefore investigated whether a C-3 Cbz protecting group could be used to steer the stereoselectivity via remote participation. The C-3 Cbz indeed proved to be an adequate protecting group enabling the stereoselective formation of the target tetrasaccharides. The iodoaryl-bearing glycans were then coupled to the phthiocerol alkyne derivative using a Sonogashira coupling, which was followed by a Steglich esterification of the resulting diol with mycocerosic acid. Finally, global deprotection with H_2 and Pd/C resulted in the complete assembly of all the phenolic glycolipids originating from *Mycobacterium kansasii* and *Mycobacterium gastri* and these are at present being investigated for their immunomodulatory capabilities.

EXPERIMENTAL:

General procedures

All reactions were carried out in oven-dried glassware (80 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under N_2 atmosphere (balloon). Commercially available reagents and solvents (Aldrich Chemistry, Honeywell, Merck, Fischer Scientific, Biosolve, Fluka, VWR Chemicals, Acros Organics, Fluorochem, Brunschwig, Carbosynth) were used as received unless stated otherwise.

Solvents for reactions were reagent grade and dried by storage over flame dried 4 Å molecular sieves when needed. Tf_2O used in glycosylations was dried by distillation over P_2O_5 and stored under N_2 atmosphere in a Schlenk flask at -20 °C. Et_2O used for column chromatography was distilled before use and stored over iron filings. EtOAc used for column chromatography was distilled before use. NEt_3 used for Sonogashira couplings was distilled from KOH, degassed with N_2, and stored over KOH for a maximum of 24 hours. DMAP used for Steglich esterifications was recrystallized from toluene before use.

Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, F254); visualization was carried out by irradiation with UV light (254 nm), and spraying with 20% H_2SO_4 in EtOH (w/v) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% H_2SO_4, followed by charring. Additional analysis with TLC-MS was used when needed.

Column chromatography was carried out using silica gel (Fluka, 40-63 μm mesh). The column was prepared using the apolar component mentioned in the corresponding experimental. If the apolar component was pentane the product was brought up in toluene. If the apolar component was DCM the product was brought up in DCM, possibly with a few drops of methanol if needed. Colum chromatography was performed using a gradient ranging from 0% polar component up to the ratio mentioned in the corresponding experimental in 2 to 5 steps depending on the ease of separation.

NMR spectra were recorded at ambient temperature on a Bruker AV-400LIQ spectrometer. Samples were prepared in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) in $CDCl_3$ are reported in ppm relative to Me_4Si (δ: 0.00 ppm) for ^{1}H-NMR and $CDCl_3$ (δ: 77.16 ppm) for ^{13}C-NMR. Chemical shifts in CD_3OD are reported in ppm relative to H_2O (δ: 4.87 ppm) for ^{1}H-NMR and CD_3OD (δ: 49.00 ppm) for ^{13}C-NMR. ^{13}C-APT spectra are ^{1}H decoupled and structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants (J) are given in Hz. Coupling constants of anomeric carbon atoms ($J_{H1,C1}$) were determined using HMBC-GATED experiments**.** Optical rotations were measured on an Anton Paar Modular Circular Polarimeter MCP 100/150. High resolution mass spectra were recorded on a Synapt G2-Si or a Q Exactive HF Orbitrap equipped with an electron spray ion source positive mode. Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR.

General procedure A: Pre-activation glycosylation:

Donor (2 eq), Ph_2SO (2.2 eq) and TTBP (5 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -70 °C after which Tf_2O (2.2 eq) was added to the solution. After stirring for 30 minutes, acceptor (1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (0.2 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (1-4 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography.

General procedure B: IDCP mediated glycosylation:

Starting material (1.0 eq) and donor (2.0 eq) were co-evaporated together with toluene and subsequently dissolved in Et_2O/DCE (0.05 M, 4:1). Flame-dried 3Å molecular sieves were added and the resulting solution was stirred for 15 minutes while it was cooled to 0 °C, after which IDCP (3.0 eq) was added. The reaction was allowed to stir for 16 hours at 4 °C after which it was filtered over celite, diluted with Et_2O and transferred to a separation funnel. The organic layer was then washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, sat. aq. $CuSO_4$ and brine, after which it was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography.

General procedure C: Sonogashira cross coupling

Iodoaryl glycoside (1.0 eq) was dissolved in freshly distilled NEt_3 (0.05 M) together with phthiocerol (1.2 eq). A mixture of $Pd(PPh_3)_2Cl_2$, PPh_3 and CuI (ratio 1:1:2) was dissolved in freshly distilled NEt_3 and was stirred for 15 minutes at 40 °C. Of this cocktail, enough was added to the sugar/alkyne mixture to amount to 0.05 eq $Pd(PPh_3)_2Cl_2$, 0.05 eq PPh_3 and 0.1 eq CuI. The reaction was allowed to stir at 40 °C until the complete consumption of the starting material as indicated by TLC. The solvent was then removed under a stream of N_2. The crude was then transferred to a silica column in toluene and the column was flushed with toluene. Thereafter the product was purified by means of column chromatography.

General procedure D: Esterification with mycocerosic acid

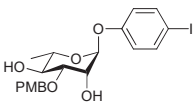
Starting material (1.0 eq) was dissolved in dry DCM (0.05 M) together with mycocerosic acid (3.0 eq) and DMAP (9 eq). The resulting mixture was cooled to 0 °C after which DIC (6 eq) was added. The reaction was allowed to stir for 16 hours while warming to rT, after which it was warmed to 40 °C and stirred for a further 5 hours. The reaction mixture was then diluted with Et_2O and the organic layers was washed 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography. Note: In order to detect the most prevalent byproducts, staining with $KMnO_4$ is required.

General procedure E: Hydrogenation

A 1:1 mixture of EtOH and THF was purged with N_2, Pd/C (10 wt%, undetermined amount) was added and the resulting solution was again purged with N_2. The flask containing starting material (1.0 eq) was flushed

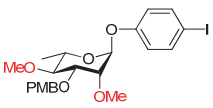
with N_2 and 5 mL of the Pd solution was added. The resulting mixture was again purged with N_2 and then with H_2 and allowed to stir under H_2 atmosphere (balloon) until TLC indicated complete conversion of the starting material and reaction intermediates to a single low running spot (DCM-MeOH 19:1). The reaction mixture was then purged with N_2 and filtered over a small amount of celite. Purification by means of column chromatography (DCM-MeOH 19:1).

4-iodophenyl 3-*O*-(4-methoxybenzyl)-α-L-rhamnopyranoside (13)



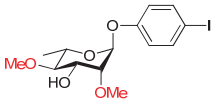
Compound **12** (11.0 g, 30 mmol, 1.0 eq) was dissolved in toluene (600 mL, 0.05 M) and Bu_2SnO (8.22 g, 33 mmol, 1.1 eq) was added to the solution. The mixture was refluxed for 1.5 hours and then cooled to 80 °C. PMBCl (5.3 mL, 39 mmol, 1.3 eq) and TBAB (11.6 g, 36 mmol, 1.2 eq) were added to the mixture and it was refluxed for 2 hours. The reaction mixture was then concentrated *in vacuo* and purified by means of column chromatography (*n*-pentane-Et_2O 1:1) to give the crude product (7.71 g, 15.9 mmol, 53%, mixture of regioisomers) as a slightly yellow oil. The product was used in the next step without further purification or analysis.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(4-methoxybenzyl)-α-L-rhamnopyranoside (14)



Compound **13** (7.71 g, 15.9 mmol, 1.0 eq) was dissolved in dry DMF (125 mL, 0.13 M) and MeI (4 mL, 63.4 mmol, 4.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 1.58 g, 39.6 mmol, 2.5 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (7.65 g, 14.9 mmol, 94%) as a pale oil. $[\alpha]_D^{25}$ = -89.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.55-7.53 (m, 2H, C*H*$_{arom}$); 7.35 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 6.91-6.88 (m, 2H, C*H*$_{arom}$); 6.81 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 2.0 Hz, H-1); 4.69 (dd, 2H, *J* = 11.4, 19.4 Hz, PhC*H*$_2$); 3.88 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 3.79 (s, 3H, C*H*$_{3,PMB}$); 3.62-3.57 (m, 5H, H-2, H-5, OC*H*$_3$); 3.52 (s, 3H, OC*H*$_3$); 3.25 (t, 1H, *J* = 9.4 Hz, H-4); 1.25 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.2, 156.1 (C$_{q,arom}$); 138.3 (*C*H$_{arom}$); 130.5 (C$_{q,arom}$); 129.4, 118.6, 13.8 (*C*H$_{arom}$); 95.5 (C-1); 84.7 (*C*I$_{arom}$); 81.9 (C-4); 78.9 (C-3); 77.9 (C-2); 72.2 (Ph*C*H$_2$); 68.9 (C-5); 61.1, 59.6 (O*C*H$_3$); 55.2 (*C*H$_{3,PMB}$); 17.9 (C-6). IR (thin film, cm^{-1}): 1102, 1139, 1251, 1484, 1514, 1613. HRMS calculated for $C_{22}H_{27}IO_6Na$ 537.07500 $[M+Na]^+$; found 537.07459.

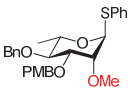
4-iodophenyl 2,4-di-*O*-methyl-α-L-rhamnopyranoside (2)



Compound **14** (7.65 g, 14.9 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 150 mL, 0.1 M) after which a solution of HCl in HFIP (7.5 mL, 0.2 M, 0.1 eq) was added. After complete conversion of the starting material (5 min), indicated by a dark purple colour, the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (4.74 g, 12.0 mmol, 81%) as a white amorphous solid. $[\alpha]_D^{25}$ = -77.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR

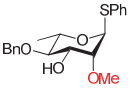
(400 MHz) δ: 7.59-7.56 (m, 2H, C*H*$_{arom}$); 6.86-6.83 (m, 2H, C*H*$_{arom}$); 5.50 (s, 1H, H-1); 4.01 (dd, 1H, *J* = 3.6, 9.2 Hz, H-3); 3.66-3.58 (m, 5H, H-2, H-5, OC*H*$_3$); 3.55 (s, 3H, OC*H*$_3$); 3.05 (t, 1H, *J* = 9.4 Hz, H-4; 1.26 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.3, (C$_{q,arom}$); 138.5, 118.7 (*C*H$_{arom}$); 94.6 (C-1); 84.9 (*C*I$_{arom}$); 83.6 (C-4); 80.4 (C-2); 71.2 (C-3); 68.3 (C-5); 61.1, 59.3 (O*C*H$_3$); 18.0 (C-6). IR (thin film, cm^{-1}): 1002, 1098, 1232, 1484, 3449. HRMS calculated for $C_{14}H_{19}IO_5Na$ 417.01749 [M+Na]$^+$; found 417.01694.

Phenyl 2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (16)



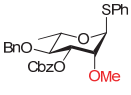
Compound **15** (30.2 g, 64.7 mmol, 1.0 eq) was dissolved in dry DMF (600 mL, 0.11 M) and MeI (8.0 mL, 129 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 3.9 g, 97 mmol, 1.5 eq) was then added. The reaction mixture was warmed to rt while stirring for 1.5 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (26.7 g, 55.5 mmol, 96%) as a clear oil. $[\alpha]_D^{25}$ = -152.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.43 (m, 2H, C*H*$_{arom}$); 7.35-7.24 (m, 10H, C*H*$_{arom}$); 6.88 (dd, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.53 (d, 1H, *J* = 1.2 Hz, H-1); 4.95 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.67-4.61 (m, 3H, PhCH*H*, PhC*H*$_2$); 4.18-4.10 (m, 1H, H-5); 3.82-3.79 (m, 4H, H-3, C*H*$_{3,PMB}$); 3.68 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.56 (t, 1H, *J* = 9.4 Hz, H-4); 3.45 (s, 3H, OC*H*$_3$); 1.32 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.5, 138.7, 134.9 (C$_{q,arom}$); 131.1, 130.3, 129.8, 129.1, 128.5, 128.1, 127.8, 127.3, 114.0 (*C*H$_{arom}$); 85.0 (C-1); 80.5 (C-4); 79.9 (C-2); 79.6 (C-3); 75.7, 72.2 (Ph*C*H$_2$); 69.3 (C-5); 58.6 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 18.0 (C-6). IR (thin film, cm^{-1}): 1033, 1084, 1097, 1173, 1249, 1453, 1513, 1612. HRMS calculated for $C_{28}H_{32}O_5SNa$ 503.18681 [M+Na]$^+$; found 503.18596.

Phenyl 2-*O*-methyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (17)



Compound **16** (711 mg, 1.50 mmol, 1.0 eq) was dissolved in a mixture of DCM and HFIP (1:1, 1 mL, 0.1 M) and TES (0.7 mL, 4.6 mmol, 3.0 eq) was added to the solution. The resulting mixture was cooled to 0 °C and a solution of HCl in HFIP (3.8 mL, 0.2 M, 0.5 eq) was added. After stirring for 30 minutes the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted with DCM, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (425 mg, 1.2 mmol, 80%) as a pale oil. Spectroscopic data were in accordance with those previously reported in the literature.[31]

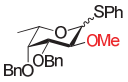
Phenyl 2-*O*-methyl-3-*O*-benzyloxycarbonyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (1)



Compound **17** (355 mg, 0.93 mmol, 1.0 eq) was dissolved in DCM (7.5 mL, 0.14 M) and DMAP (0.23 g, 1.9 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (0.3 mL, 1.9 mmol, 2.0 eq) was slowly added. The reaction was allowed to stir for 3 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 4:1) gave the title compound (462 mg, 0.93 mmol, 100%) as a clear oil. $[\alpha]_D^{25}$ = -196.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.48-7.45 (m, 2H,

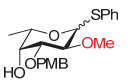
C*H*$_{arom}$); 7.40-7.23 (m, 13H, C*H*$_{arom}$); 5.53 (d, 1H, *J* = 1.2 Hz, H-1); 5.23-5.16 (m, 2H, PhC*H*$_2$); 5.06 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.67 (dd, 2H, *J* = 10.8, 58.4 Hz, PhC*H*$_2$); 4.23 (dq, 1H, *J* = 3.2, 6.0 Hz, H-5); 3.96 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.65 (t, 1H, *J* = 9.4 Hz, H-4); 3.42 (s, 3H, OC*H*$_3$); 1.33 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 154.7, 138.1, 135.3, 134.6 (C$_{q,arom}$); 131.4, 129.2, 128.7, 128.7, 128.5, 128.5, 128.1, 127.9, 127.5 (*C*H$_{arom}$); 84.8 (C-1); 80.1 (C-2); 79.1 (C-4); 78.1 (C-3); 75.5, 70.0 (Ph*C*H$_2$); 69.1 (C-5); 17.9 (C-6). IR (thin film, cm^{-1}): 1027, 1086, 1217, 1247, 1266, 1357, 1383, 1440, 1455, 1748. HRMS calculated for $C_{28}H_{30}O_6SNa$ 517.16608 [M+Na]$^+$; found 517.16551.

Phenyl 2-*O*-methyl-3,4-di-*O*-benzyl-1-thio-α-L-fucopyranoside (5)



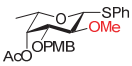
Compound **18** (1.73 g, 6.4 mmol, 1.0 eq) was dissolved in dry DMF (64 mL, 0.1 M) and BnBr (2.18 mL, 19.2 mmol, 3 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.62 g, 15.4 mmol, 2.4 eq) and TBAI (0.47 g, 1.28 mmol, 0.2 eq) were then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (4.77 g, 6.15 mmol, 96 %) as an amorphous white solid. $[\alpha]_D^{25}$ = -21.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.56 (m, 2H, C*H*$_{arom}$); 7.43-7.18 (m, 13H, C*H*$_{arom}$); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.75 (dd, 2H, *J* = 11.6, 18.8 Hz, PhC*H*$_2$); 4.65 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.48 (d, 1H, *J* = 9.6 Hz, H-1); 3.64-3.59 (m, 5H, H-2, H-3, OC*H*$_3$); 3.51-3.47 (m, 2H, H-4, H-5); 1.24 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 138.9, 138.8, 135.2 (C$_{q,arom}$); 128.8, 128.6, 128.3, 128.1, 127.8, 127.6, 127.6, 127.1 (*C*H$_{arom}$); 87.5 (C-1); 84.6 (C-4); 79.0 (C-3); 76.7 (C-2); 74.7 (Ph*C*H$_2$); 74.6 (C-5); 72.9 (Ph*C*H$_2$); 61.3 (O*C*H$_3$); 17.4 (C-6). IR (thin film, cm^{-1}): 1027, 1046, 1069, 1089, 1129, 1163, 1209, 1355, 1379, 1440, 1454, 1480, 1497. HRMS calculated for $C_{27}H_{30}O_4SNa$ 473.17625 [M+Na]$^+$; found 473.17568.

Phenyl 2-*O*-methyl-3-*O*-(4-methoxybenzyl)-1-thio-α/ß-L-fucopyranoside (19)



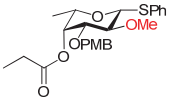
Compound **18** (9.48 g, 35 mmol, 1.0 eq) was dissolved in toluene (500 mL, 0.07 M) and Bu_2SnO (9.58 g, 38.5 mmol, 1.1 eq) was added to the solution. The mixture was refluxed for 2 hours and then cooled to 80 °C. PMBCl (6.2 mL, 45.5 mmol, 1.3 eq) and TBAB (13.54 g, 42 mmol, 1.2 eq) were added to the mixture and it was refluxed for 2 hours. The reaction mixture was then concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (11.8 g, 30.2 mmol, 86%) as a slightly yellow oil. $[\alpha]_D^{25}$ = 16.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.60-7.57 (m, 2H, C*H*$_{arom}$); 7.33-7.25 (m, 5H, C*H*$_{arom}$); 6.93-6.90 (m, 2H, C*H*$_{arom}$); 4.64 (s, 2H, PhC*H*$_2$); 4.48 (d, *J* = 9.6 Hz, H-1); 3.80 (s, 3H, C*H*$_{3,PMB}$); 3.75 (d, 1H, *J* = 2.4 Hz, H-4); 3.54 (s, 3H, OC*H*$_3$); 3.52 (q, 1H, *J* = 6.4 Hz, H-5); 3.46 (dd, 1H, *J* = 3.4, 9.0 Hz, H-3); 3.36 (t, 1H, *J* = 9.4 Hz, H-2); 2.35 (bs, 1H, 4-O*H*); 1.34 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.5, 133.9 (C$_{q,arom}$); 132.0 (*C*H$_{arom}$); 129.9 (C$_{q,arom}$); 129.6, 128.9, 127.4, 114.0 (*C*H$_{arom}$); 87.3 (C-1); 82.5 (C-3); 78.5 (C-2); 74.2 (C-5); 71.9 (Ph*C*H$_2$); 69.5 (C-4); 61.3 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 16.8 (C-6). IR (thin film, cm^{-1}): 1047, 1063, 1069, 1085, 1128, 1173, 1248, 1302, 1367, 1441, 1455, 1464, 1480, 1514, 1585, 1613, 2835, 2870, 2875, 2994, 3493. HRMS calculated for $C_{21}H_{26}O_5SNa$ 413.13986 [M+Na]$^+$; found 413.13908.

Phenyl 2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-acetyl-1-thio-α/ß-L-fucopyranoside (3)



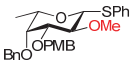
Compound **19** (3.80 g, 9.7 mmol, 1.0 eq) was dissolved in DCM (100 mL, 0.1 M) and Ac_2O (1.84 mL, 19.4 mmol, 2.0 eq) was added to the solution. The mixture was then cooled to 0 °C after which pyridine (1.6 mL, 19.4 mmol, 2.0 eq) and DMAP (0.119 g, 0.97 mmol, 0.1 eq) were added. After stirring for 3 hours the reaction was quenched by addition of MeOH and the resulting mixture was concentrated *in vacuo*. Thereafter the mixture was diluted with Et_2O and the organic layer was subsequently washed with H_2O, 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (4.08 g, 9.4 mmol, 97%) as an amorphous white solid. $[\alpha]_D^{25}$ = -66.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 2H, C*H*$_{arom}$); 7.31-7.22 (m, 5H, C*H*$_{arom}$); 6.89-6.85 (m, 2H, C*H*$_{arom}$); 5.32 (d, 1H, *J* = 3.2 Hz, H-4); 4.67-4.63 (m, 1H, PhC*H*H); 4.52 (d, 1H, *J* = 10.0 Hz, H-1); 4.44 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 3.78 (s, 3H, C*H*$_{3,PMB}$); 3.65 (q, 1H, *J* = 6.4 Hz, H-5); 3.57 (s, 3H, OC*H*$_3$); 3.52 (dd, 1H, *J* = 3.4, 9.4 Hz, H-3); 3.33 (dd, 1H, *J* = 9.2, 9.6 Hz, H-2); 2.15 (s, 3H, C*H*$_3$,Ac); 1.22 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 170.8 (*C*O$_{Ac}$); 159.4, 133.8 (C$_{q,arom}$); 132.1 (*C*H$_{arom}$); 129.9 (C$_{q,arom}$); 129.7, 128.8, 127.5, 113.9 (*C*H$_{arom}$); 87.4 (C-1); 80.9 (C-3); 78.1 (C-2); 73.0 (C-5); 71.5 (Ph*C*H$_2$); 69.8 (C-4); 61.3 (O*C*H$_3$); 55.3 (*C*H$_{3,PMB}$); 21.0 (*C*H$_{3,Ac}$); 16.9 (C-6). IR (thin film, cm^{-1}): 1065, 1128, 1175, 1248, 1371, 1441, 1514, 1613, 1739. HRMS calculated for $C_{23}H_{28}O_6SNa$ 455.1504 $[M+Na]^+$; found 455.14969.

Phenyl 2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-propionyl-1-thio-α/ß-L-fucopyranoside (7)



Compound **19** (3.74 g, 9.6 mmol, 1.0 eq) was dissolved in DCM (100 mL, 0.1 M) and propionic anhydride (2.45 mL, 19.2 mmol, 2.0 eq) was added to the solution. The mixture was then cooled to 0 °C after which pyridine (1.5 mL, 19.2 mmol, 2.0 eq) and DMAP (0.117 g, 0.96 mmol, 0.1 eq) were added. After stirring for 3 hours the reaction was quenched by addition of MeOH and the resulting mixture was concentrated *in vacuo*. Thereafter the mixture was diluted with Et_2O and the organic layer was subsequently washed with H_2O, 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (3.03 g, 6.8 mmol, 71%) as an amorphous white solid. $[\alpha]_D^{25}$ = -54.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 2H, C*H*$_{arom}$); 7.31-7.22 (m, 5H, C*H*$_{arom}$); 6.89-6.84 (m, 2H, C*H*$_{arom}$); 5.35 (dd, 1H, *J* = 1.2, 3.4 Hz, H-4); 4.51 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.48 (d, 1H, *J* = 8.8 Hz, H-1); 4.43 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 3.79 (s, 3H, C*H*$_{3,PMB}$); 3.67 (q, 1H, *J* = 6.2 Hz, H-5); 3.56-3.51 (m, 4H, H-3, OC*H*$_3$); 3.31 (t, 1H, *J* = 9.2 Hz, H-2); 2.43 (q, 2H, *J* = 7.5 Hz, C*H*$_2$CH$_3$); 1.23 (d, 3H, *J* = 6.4 Hz, H-6); 1.16 (t, 3H, *J* = 7.4 Hz, CH$_2$C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 174.5 (*C*O$_{Propionyl}$); 159.4, 133.7 (C$_{q,arom}$); 132.2 (*C*H$_{arom}$); 130.0 (C$_{q,arom}$); 129.8, 128.9, 127.5, 113.9 (*C*H$_{arom}$); 87.3 (C-1); 81.0 (C-3); 78.1 (C-2); 73.2 (C-5); 71.5 (Ph*C*H$_2$); 69.6 (C-4); 61.4 (OC*H*$_3$); 55.4 (*C*H$_{3,PMB}$); 27.7 (*C*H$_2$CH$_3$); 17.0 (C-6); 9.5 (CH$_2$*C*H$_3$). IR (thin film, cm^{-1}): 1065, 1085, 1102, 1128, 1182, 1249, 1302, 1441, 1514, 1613, 1736. HRMS calculated for $C_{24}H_{30}O_6SNa$ 469.1661 $[M+Na]^+$; found 469.16566.

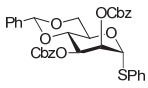
Phenyl 2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-1-thio-α/ß-L-fucopyranoside (8)



Compound **19** (1.73 g, 6.4 mmol, 1.0 eq) was dissolved in dry DMF (64 mL, 0.1 M) and BnBr (2.18 mL, 19.2 mmol, 3.0 eq) was added to the solution. The mixture was cooled to

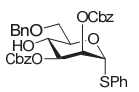
0 °C, and NaH (60%, 0.62 g, 15.4 mmol, 2.4 eq) and TBAI (0.47 g, 1.28 mmol, 0.2 eq) were then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was quenched by addition of H_2O, and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (4.77 g, 6.15 mmol, 96%) as an amorphous white solid. $[\alpha]_D^{25}$ = 6.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 2H, C*H*$_{arom}$); 7.35-7.19 (m, 10H, C*H*$_{arom}$); 6.91-6.86 (m, 2H, C*H*$_{arom}$); 4.98 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.68-4.63 (m, 3H, PhCH*H*, PhC*H*$_2$); 4.48 (d, 1H, *J* = 8.8 Hz, H-1); 3.80 (s, 3H, C*H*$_{3,PMB}$); 3.60-3.56 (m, 5H, H-2, H-3, OC*H*$_3$); 3.49-3.47 (m, 2H, H-4, H-5); 1.23 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 159.3, 138.9, 134.4 (C$_{q,arom}$); 131.6 (*C*H$_{arom}$); 130.7 (C$_{q,arom}$); 129.3, 128.9, 128.8, 128.3, 128.1, 127.6, 127.1, 113.9 (*C*H$_{arom}$); 87.5 (C-1); 84.2 (C-4); 79.0 (C-3); 76.7 (C-2); 74.7 (C-5); 74.6, 72.6 (Ph*C*H$_2$); 61.3 (O*C*H$_3$); 55.4 (*C*H$_{3,PMB}$); 17.4 (C-6). IR (thin film, cm^{-1}): 1069, 1129, 1172, 1248, 1302, 1355, 1440, 1480, 1513. HRMS calculated for $C_{28}H_{32}O_5SNa$ 503.1868 [M+Na]$^+$; found 503.18618.

Phenyl 2,3-di-*O*-benzyloxycarbonyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (26)



Compound **25** (2.59 g, 7.19 mmol, 1.0 eq) was dissolved in DCM (125 mL, 0.06 M) and DMAP (5.06 g, 41.5 mmol, 6.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (2.92 mL, 20.7 mmol, 3.0 eq) was slowly added. The reaction was allowed to stir for 2 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 7:3) gave the title compound (4.43 g, 7.04 mmol, 98%) as a clear oil. $[\alpha]_D^{25}$ = 33.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47 (d, 2H, *J* = 3.2 Hz, C*H*$_{arom}$); 7.36-7.20 (m, 18H, C*H*$_{arom}$); 5.57 (s, 1H, H-1); 5.46 (s, 1H, H-2); 5.17 (s, 2H, PhC*H*$_2$); 5.09 (s, 2H, PhC*H*$_2$); 5.04 (d, 1H, *J* = 9.6 Hz, H-3); 4.52 (dd, 2H, *J* = 11.8, 82.2 Hz, PhC*H*$_2$); 4.37 (d, 1H, *J* = 5.2 Hz, H-5); 4.11 (dd, 1H, *J* = 9.6, 10.0 Hz, H-4); 3.80-3.73 (m, 2H, H-6); 2.95 (bs, 1H, 4-O*H*). ^{13}C-APT NMR (101 MHz) δ: 154.5, 154.4 (*C*O$_{Cbz}$); 137.8, 134.9, 134.7, 133.0 (C$_{q,arom}$); 132.2, 129.2, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.0, 127.8, 127.6 (*C*H$_{arom}$); 85.6 (C-1); 76.1 (C-3); 74.6 (C-2); 73.6 (Ph*C*H$_2$); 72.3 (C-5); 70.3, 70.2 (Ph*C*H$_2$); 69.7 (C-6); 66.7 (C-4). IR (thin film, cm^{-1}): 1002, 1026, 1082, 1098, 1239, 1275, 1441, 1457, 1747, 1751, 3497. HRMS calculated for $C_{35}H_{34}O_9SNa$ 653.18212 [M+Na]$^+$; found 653.18133.

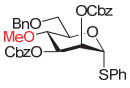
Phenyl 2,3-di-*O*-benzyloxycarbonyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (27)



Compound **26** (4.36 g, 6.94 mmol, 1.0 eq) was dissolved in DCM (70 mL, 0.1 M) and TES-H (11.1 mL, 69.4 mmol, 10.0 eq) was added to the solution. The mixture was cooled to 0 °C and TFA (5.3 mL, 69.4 mmol, 10.0 eq) was slowly added. The reaction was allowed to stir for 30 minutes while warming to rt. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and the organic layer was washed with H_2O and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 7:3) gave the title compound (4.03 g, 6.39 mmol, 92%) as a clear oil. $[\alpha]_D^{25}$ = 33.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47 (d, 2H, *J* = 3.2 Hz, C*H*$_{arom}$); 7.36-7.20 (m, 18H, C*H*$_{arom}$); 5.57 (s, 1H, H-1); 5.46 (s, 1H, H-2); 5.17 (s, 2H, PhC*H*$_2$); 5.09 (s, 2H, PhC*H*$_2$); 5.04 (d, 1H, *J* = 9.6 Hz, H-3); 4.52 (dd, 2H, *J* = 11.8, 82.2 Hz, PhC*H*$_2$); 4.37 (d, 1H, *J* = 5.2 Hz, H-5); 4.11 (dd, 1H, *J* = 9.6, 10.0 Hz, H-4); 3.80-3.73 (m, 2H, H-6); 2.95 (bs, 1H, 4-O*H*). ^{13}C-APT NMR (101 MHz) δ: 154.5, 154.4 (*C*O$_{Cbz}$); 137.8,

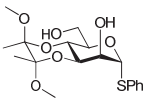
134.9, 134.7, 133.0 ($C_{q,arom}$); 132.2, 129.2, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.0, 127.8, 127.6 (*C*H$_{arom}$); 85.6 (C-1); 76.1 (C-3); 74.6 (C-2); 73.6 (PhCH$_2$); 72.3 (C-5); 70.3, 70.2 (PhCH$_2$); 69.7 (C-6); 66.7 (C-4). IR (thin film, cm^{-1}): 1002, 1026, 1082, 1098, 1239, 1275, 1441, 1457, 1747, 1751, 3497. HRMS calculated for $C_{35}H_{34}O_9SNa$ 653.18212 [M+Na]$^+$; found 653.18133.

Phenyl 2,3-di-*O*-benzyloxycarbonyl-4-*O*-methyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (11)



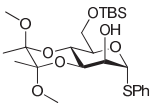
Compound **27** (0.53 g, 0.84 mmol, 1.0 eq) and TTBP (2.09 g, 8.4 mmol, 10.0 eq) were co-evaporated with toluene under inert atmosphere and flame dried (3Å) molecular sieves were added. The mixture was dissolved in DCM (28 ml, 0.03 M) and BF_4OMe_3 (1.24 g, 8.4 mmol, 10.0 eq) was added under a N_2 flow. The solution was stirred at rt for 45 minutes and quenched by addition of NEt_3. The reaction mixture was filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane Et_2O 7:3) gave the title compound (0.38 g, 0.59 mmol, 70%) as a clear oil. $[\alpha]_D^{25}$ = 28.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.50-7.47 (m, 2H, C*H*$_{arom}$); 7.41-7.22 (m, 18H, C*H*$_{arom}$); 5.59 (d, 1H, *J* = 1.6 Hz, H-1); 5.42 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 5.24-5.17 (m, 2H, PhC*H*$_2$); 5.11-5.07 (m, 3H, PhC*H*$_2$, H-3); 4.51 (dd, 2H, *J* = 12.0, 30.8 Hz, PHC*H*$_2$); 3.82-3.69 (m, 3H, H-4, H-6); 3.38 (s, 3H, OC*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 154.5, 154.3 (*C*O$_{Cbz}$); 138.2, 135.1, 134.8, 133.3 ($C_{q,arom}$); 132.1, 129.2, 128.7, 128.7, 128.5, 128.5, 128.4, 127.9, 127.9, 127.7 (*C*H$_{arom}$); 85.5 (C-1); 76.3 (C-3); 75.1 (C-2); 74.7 (C-4); 73.5 (PhCH$_2$); 72.7 (C-5); 70.3, 70.2 (PhCH$_2$); 68.7 (C-6); 60.9 (OCH$_3$). IR (thin film, cm^{-1}): 1000, 1026, 1053, 1065, 1085, 1089, 1100, 1158, 1275, 1441, 1457, 1498, 1751. HRMS calculated for $C_{36}H_{36}O_9SNa$ 667.19777 [M+Na]$^+$; found 667.19710.

Phenyl 3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-*O*-1-thio-α-D-mannopyranoside (21)



Compound **20** (14.0 g, 51.3 mmol, 1.0 eq) was dissolved in MeOH (366 mL, 0.14 M) and trimethyl orthoformate (22.4 mL, 205 mmol, 4.0 eq), 2,3-butanedione (6.75 mL, 76.9 mmol, 1.5 eq) and CSA (595 mg, 2.56 mmol, 0.05 eq) were added to the solution. The mixture was refluxed overnight after which the reaction was quenched by addition of NEt_3 (2.5 mL). The resulting mixture was concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-EtOAc 1:1) gave the title compound (16.8 g, 43.4 mmol, 85%) as an amorphous white solid. Spectroscopic data were in accordance with those previously reported in the literature.[61]

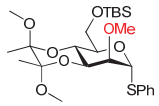
Phenyl 3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-6-O-*tert*-butyldimethylsilyl-1-thio-α-D-mannopyranoside (22)



Compound **21** (3.00 g, 7.76 mmol, 1.0 eq) was dissolved in dry DMF (78 mL, 0.1 M) and TBSCl (1.76 g, 11.6 mmol, 1.5 eq) was added to the solution. The mixture was cooled to 0 °C, and imidazole (1.06 g, 15.5 mmol, 2.0 eq) was then added. The reaction mixture was warmed to rt while stirring for 16 hours. The reaction was quenched by addition of H_2O, and after adding 20 mL of 1 M HCl was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (3.89 g, 7.76 mmol, 100%) as a clear oil. $[\alpha]_D^{25}$ = 246.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.37 (m, 2H, C*H*$_{arom}$); 7.21-7.11 (m, 3H, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 0.4 Hz, H-1); 4.12-4.00 (m, 3H, H-2, H-4, H-5); 3.91 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 3.78 (dd, 1H,

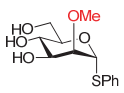
J = 4.4, 11.6 Hz, H-6); 3.70 (dd, 1H, *J* = 2.0, 11.6 Hz, H-6); 3.22 (s, 3H, OC$H_{3,BDA}$); 3.17 (s, 3H, OC$H_{3,BDA}$); 2.76 (bs, 1H, 2-O*H*); 1.25 (s, 3H, C$H_{3,BDA}$); 1.22 (s, 3H, C$H_{3,BDA}$); 0.78 (t, 9H, *J* = 2.8 Hz, C$H_{3,TBDMS}$); -0.05 (t, 3H, *J* = 2.8 Hz, C$H_{3,TBDMS}$) -0.08 (t, 3H, *J* = 2.8 Hz, C$H_{3,TBDMS}$). ^{13}C-APT NMR (101 MHz) δ: 134.5 ($C_{q,arom}$); 131.4, 129.0, 127.3 (CH_{arom}); 100.5, 99.9 ($C_{q,BDA}$); 88.0 (C-1); 72.5 (C-5); 71.2 (C-2); 69.0 (C-3); 63.0 (C-4); 61.6 (C-6); 48.2, 48.0 (OC$H_{3,BDA}$); 26.0 (C$H_{3,TBDMS}$); 18.5 ($C_{q,TBDMS}$); 17.9, 17.7 (C$H_{3,BDA}$); -5.0, -5.4 (C$H_{3,TBDMS}$). IR (thin film, cm^{-1}): 1026, 1050, 1073, 1096, 1115, 1163, 1189, 1252, 1281, 1362, 1378, 1441, 1462, 1472, 1482, 1751, 2858, 2886, 2928, 2951, 3454. HRMS calculated for $C_{24}H_{40}O_7SSiNa$ 523.21562 [M+Na]$^+$; found 523.21539.

Phenyl 2-*O*-methyl-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-6-O-*tert*-butyldimethylsilyl-1-thio-α-D-mannopyranoside (23)



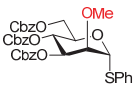
Compound **22** (4.00 g, 8.0 mmol, 1.0 eq) was dissolved in dry DMF (80 mL, 0.1 M) and MeI (0.75 mL, 12 mmol, 1.5 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.64 g, 16 mmol, 2.0 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) gave the title compound (3.78 g, 7.35 mmol, 92%) as a pale oil. $[\alpha]_D^{25}$ = 208.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.53-7.50 (m, 2H, CH_{arom}); 7.31-7.22 (m, 3H, CH_{arom}); 5.61 (d, 1H, *J* = 0.4 Hz, H-1); 4.18-4.16 (m, 1H, H-5); 4.10 (t, 1H, *J* = 10.0 Hz, H-4); 4.00 (dd, 1H, *J* = 2.8, 10.0 Hz, H-3); 3.86-3.84 (m, 2H, H-6); 3.73 (dd, 1H, *J* = 1.4, 2.6 Hz, H-2); 3.43 (s, 3H, OCH_3); 3.31 (s, 3H, OC$H_{3,BDA}$); 3.26 (s, 3H, OC$H_{3,BDA}$); 1.35 (s, 3H, C$H_{3,BDA}$); 1.30 (s, 3H, C$H_{3,BDA}$); 0.87 (s, 9H, C$H_{3,TBDMS}$); 0.05 (s, 3H, C$H_{3,TBDMS}$); 0.03 (s, 3H, C$H_{3,TBDMS}$). ^{13}C-APT NMR (101 MHz) δ: 135.1 ($C_{q,arom}$); 131.3, 130.4, 129.0, 127.3, 126.9 (CH_{arom}); 100.2, 99.6 ($C_{q,BDA}$); 85.2 (C-1); 80.2 (C-2); 72.9 (C-5); 68.9 (C-3); 63.4 (C-4); 61.8 (C-6); 57.8 (OCH_3); 48.1, 48.0 (OC$H_{3,BDA}$); 25.9 (C$H_{3,TBDMS}$); 18.4 ($C_{q,TBDMS}$); 17.9, 17.9 (C$H_{3,BDA}$); -5.1, -5.3 (C$H_{3,TBDMS}$). IR (thin film, cm^{-1}): 1052, 1076, 1115, 1123, 1128, 1132, 1192, 1252, 1375, 1457, 1464, 1472, 2833, 2856, 2929, 2951, 2992. HRMS calculated for 537.23182 $C_{25}H_{34}O_7SSiNa$ [M+Na]$^+$; found 537.23125.

Phenyl 2-*O*-methyl-1-thio-α-D-mannopyranoside (24)



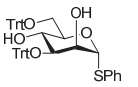
Compound **23** (0.90 g, 1.74 mmol, 1.0 eq) was dissolved in 95% TFA (17 mL, 0.1 M) and stirred for 2 minutes. The solution was then diluted with toluene and concentrated *in vacuo*. Purification by means of column chromatography (DCM-MeOH 19:1) gave the title compound (0.369 g, 1.29 mmol, 74%) as a clear oil. $[\alpha]_D^{25}$ = 145.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.52-7.47 (m, 2H, CH_{arom}); 7.30-7.21 (m, 3H, CH_{arom}); 5.57 (d, 1H, *J* = 0.8 Hz, H-1); 3.97 (t, 1H, *J* = 6.8 Hz, H-4); 3.77 (dd, 1H, *J* = 2.4, 12.0 Hz, H-6); 3.71-3.61 (m, 4H, H-2, H-3, H-5, H-6); 3.38 (OCH_3). ^{13}C-APT NMR (101 MHz) δ: 135.8 ($C_{q,arom}$); 132.9, 130.1, 128.6 (CH_{arom}); 86.4 (C-); 83.5 (C-2); 75.6 (C-4); 73.0 (C-3); 69.0 (C-5); 62.6 (C-6); 58.5 (OCH_3). IR (thin film, cm^{-1}): 1026, 1046, 1085, 1100, 1188, 1203, 1440, 1457, 1481, 1671, 1676, 1680, 1684, 2883, 2887, 2905, 2933, 3394. HRMS calculated for $C_{13}H_{18}O_5SNa$ 309.07726 [M+Na]$^+$; found 309.07665.

Phenyl 2-*O*-methyl-3,4,6-tri-*O*-benzyloxycarbonyl-1-thio-α-D-mannopyranoside (10)



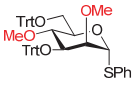
Compound **24** (0.349 g, 1.22 mmol, 1.0 eq) was dissolved in DCM (25 mL, 0.05 M) and DMAP (1.34 g, 11.0 mmol, 9.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (1.03 mL, 7.31 mmol, 6.0 eq) was slowly added. The reaction was allowed to stir for 4 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave the title compound (0.66 g, 0.96 mmol, 79%) as a clear oil. $[\alpha]_D^{25}$ = 85.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.48-7.46 (m, 2H, C*H*$_{arom}$); 7.36-7.22 (m, 18H, C*H*$_{arom}$); 5.56 (s, 1H, H-1); 5.26 (t, 1H, *J* = 10.0 Hz, H-4); 5.16-5.04 (m, 7H, H-3, PhC*H*$_2$); 4.56-4.53 (m, 1H, H-5); 4.39 (dd, 1H, *J* = 6.0, 12.0 Hz, H-6); 4.25 (dd, 1H, *J* = 2.2, 11.8 Hz, H-6). 4.01 (d, 1H, *J* = 1.6 Hz, H-2); 3.36 (s, 3H, OC*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 154.9, 154.3, 154.2 (*C*O$_{Cbz}$); 135.2, 135.0, 134.9, 133.2 (C$_{q,arom}$); 131.9, 129.2, 129.1, 128.7, 128.6, 128.6, 128.5, 128.3, 128.3, 128.2, 128.0 (*C*H$_{arom}$); 84.8 (C-1); 78.9 (C-2); 75.2 (C-3); 70.9 (C-4); 70.3, 70.1, 69.8 (Ph*C*H$_2$); 69.2 (C-5); 66.2 (C-6); 58.7 (O*C*H$_3$). IR (thin film, cm^{-1}): 1025, 1066, 1189, 1243, 1266, 1278, 1382, 1441, 1457, 1751. HRMS calculated for $C_{37}H_{40}NO_{11}S$ 706.23166 $[M+Na]^+$; found 706.23158.

Phenyl 3,6-di-*O*-trityl-1-thio-α-D-mannopyranoside (28)



Compound **20** (4.13 g, 15.2 mmol, 1.0 eq) was dissolved in pyridine (300 mL, 0.05 M) and TrtCl (33.8 g, 121 mmol, 8 eq) was added to the solution. The mixture was warmed to 50 °C and the reaction was allowed to stir for 60 hours. The reaction was then quenched by addition of sat. aq. $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ (3×). The combined organic layers were dried with $MgSO_4$, concentrated *in vacuo* and co-evaporated with toluene to remove traces of pyridine. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (7.65 g, 10.1 mmol, 67%) as a white fluffy solid. $[\alpha]_D^{25}$ = 98.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 6H, C*H*$_{arom}$); 7.46-7.40 (m, 8H, C*H*$_{arom}$); 7.34-7.15 (m, 21H, C*H*$_{arom}$); 5.30 (d, 1H, *J* = 1.6 Hz, H-1); 4.18-4.13 (m, 1H, H-5); 3.99 (dt, 1H, *J* = 3.2, 9.6 Hz, H-4); 3.78 (dd, 1H, *J* = 3.0, 9.0 Hz, H-3); 3.38 (dd, 1H, *J* = 3.2, 10.0 Hz, H-6); 3.33 (dd, 1H, *J* = 5.6, 10.0 H-6); 2.96 (dd, 1H, *J* = 3.4, 4.6 Hz, H-2); 2.43 (d, 1H, *J* = 4.0 Hz, 2-O*H*); 2.06 (d, 1H, *J* = 3.2 Hz, 4-O*H*). ^{13}C-APT NMR (101 MHz) δ: 144.4, 143.9, 134.2 (C$_{q,arom}$); 131.6, 130.5, 129.0, 129.0, 128.9, 128.3, 127.9, 127.7, 127.3, 127.1 (*C*H$_{arom}$); 87.7 (*C*Ph$_3$); 87.2 (C-1); 87.1 (*C*Ph$_3$); 75.3 (C-3); 72.6 (C-5); 70.6 (C-2); 68.3 (C-4); 64.7 (C-6). IR (thin film, cm^{-1}): 1002, 1032, 1219, 1441, 1448, 1491, 3566. HRMS calculated for $C_{50}H_{44}O_5SNa$ 779.28071 $[M+Na]^+$; found 779.28018.

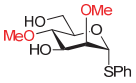
Phenyl 2,4-di-*O*-methyl-3,6-di-*O*-trityl-1-thio-α-D-mannopyranoside (29)



Compound **28** (1.45 g, 1.92 mmol, 1.0 eq) was dissolved in dry DMF (20 mL, 0.1 M) and MeI (0.48 mL, 7.68 mmol, 4.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.31 g, 7.68 mmol, 4.0 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 17:3) gave the title compound (1.36 g, 1.73 mmol, 90%) as a white fluffy solid. $[\alpha]_D^{25}$ = 77.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR

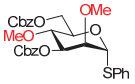
(300 MHz, T = 332K) δ: 7.60-7.55 (m, 6H, C*H*$_{arom}$); 7.49-7.41 (m, 8H, C*H*$_{arom}$); 7.30-7.13 (m, 21H, C*H*$_{arom}$); 5.41 (d, 1H, *J* = 2.4 Hz, H-1); 4.02-3.97 (m, 1H, H-5); 3.84 (dd, 1H, *J* = 2.7, 8.7 Hz, H-3); 3.58 (t, 1H, *J* = 8.9 Hz, H-4); 3.33-3.23 (m, 2H, H-6); 3.18 (s, 6H, OC*H*$_3$); 2.75 (d, 1H, *J* = 2.4 Hz, H-2). ^{13}C-APT NMR (75 MHz) δ: 145.2, 144.5, 135.6 (C$_{q,arom}$); 131.5, 129.7, 129.2, 128.9, 127.9, 127.8, 127.3, 127.1, 127.0 (*C*H$_{arom}$); 87.9, 86.8 (*C*Ph$_3$); 84.3 (C-1); 80.2 (C-2); 77.4 (C-4); 74.1 (C-3); 73.6 (C-5); 63.9 (C-6); 60.2, 56.9 (O*C*H$_3$). IR (thin film, cm^{-1}): 1099, 1232, 1448, 1484. HRMS calculated for $C_{52}H_{48}O_5SNa$ 807.31202 [M+Na]$^+$; found 807.31134.

Phenyl 2,4-di-*O*-methyl-1-thio-α-D-mannopyranoside (30)



Compound **29** (204 mg, 0.26 mmol, 1.0 eq) was dissolved in a mixture of AcOH and H_2O (4:1, 50 mL, 0.005 M) and the solution was warmed to 80 °C. The reaction was allowed to stir for 4 hours after which it was concentrated *in vacuo* and then co-evaporated with toluene. Purification by means of column chromatography (*n*-pentane-acetone 7:3) gave the title compound (68 mg, 0.20 mmol, 78%) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[62]

Phenyl 2,4-di-*O*-methyl-3,6-di-*O*-benzyloxycarbonyl-1-thio-α-D-mannopyranoside (9)



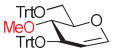
Compound **30** (0.392 g, 1.31 mmol, 1.0 eq) was dissolved in DCM (13 mL, 0.1 M) and DMAP (0.638 g, 5.22 mmol, 4.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (0.55 mL, 3.92 mmol, 3.0 eq) was slowly added. The reaction was allowed to stir for 4 hours after while slowly warming to rt. The reaction was quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (0.742 g, 1.31 mmol, 100%) as a clear oil. $[\alpha]_D^{25}$ = 91.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.49-7.45 (m, 2H, C*H*$_{arom}$); 7.42-7.31 (m, 10H, C*H*$_{arom}$); 7.28-7.22 (m, 3H, C*H*$_{arom}$); 5.55 (d, 1H, *J* = 1.6 Hz, H-1); 5.25-5.18 (m, 2H, PhC*H*$_2$); 5.14 (s, 2H, PhC*H*$_2$); 4.97 (dd, 1H, *J* = 3.6, 9.6 Hz, H-3); 4.47-4.37 (m, 2H, H-6); 4.34-4.30 (m, 1H, H-5); 3.93 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.67 (t, 1H, *J* = 9.6 Hz, H-4); 3.41 (s, 3H, OC*H*$_3$); 3.37 (s, 3H, OC*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 155.1, 154.5 (*C*O$_{Cbz}$); 135.2, 135.2, 133.8 (C$_{q,arom}$); 129.2, 128.7, 128.6, 128.6, 128.4, 128.4, 127.7 (*C*H$_{arom}$); 84.7 (C-1); 79.4 (C-2); 77.9 (C-3); 74.9 (C-4); 70.6 (C-5); 70.0, 69.8 (Ph*C*H$_2$); 66.6 (C-6); 60.8, 58.6 (O*C*H$_3$). IR (thin film, cm^{-1}): 1092, 1178, 1251, 1262, 1361, 1457, 1747. HRMS calculated for $C_{30}H_{36}O_9NS$ 586.21053 [M+Na]$^+$; found 586.21002.

3,6-di-*O*-trityl-D-glucal (52)

D-glucal (2.72 g, 18.6 mmol, 1.0 eq) was dissolved in pyridine (300 mL, 0.05 M) and TrtCl (20.7 g, 75 mmol, 4.0 eq) was added to the solution. The mixture was warmed to 69 °C and the reaction was allowed to stir at this temperature for 40 hours. The reaction was then quenched by addition of sat. aq. $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ (3×). The combined organic layers were washed with sat. aq. $CuSO_4$ (2x), H_2O (2x), dried with $MgSO_4$, concentrated *in vacuo* and co-evaporated with toluene to remove traces of pyridine. The product was then purified with column chromatography to give the title compound (6.61 g, 10.48 mmol, 56%) as a white fluffy solid. $[\alpha]_D^{25}$ = 40.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.36 (m, 6H, C*H*$_{arom}$); 7.32-7.27 (m, 6H, C*H*$_{arom}$); 7.22-7.13 (m, 18H, C*H*$_{arom}$); 6.42-6.40 (m, 1H, H-1); 4.59-4.58 (m, 1H, H-2); 3.98-3.90 (m, 2H, H-5, H-6); 3.74 (s, 1H, H-3);

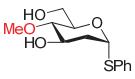
2.76 (d, 1H, *J* = 10.4 Hz, H-6); 2.44 (*s*, 1H, H-4); 1.54 (d, 1H, *J* = 3.2 Hz, 4-O*H*). ^{13}C-APT NMR (101 MHz) δ: 144.7, 144.0 ($C_{q,arom}$); 143.9 (C-1); 129.1, 128.9, 128.7, 128.0, 127.9, 127.3, 127.0 (CH_{arom}); 99.7 (C-2); 87.4, 86.6 (CPh_3); 78.4 (C-5); 67.4 (C-4); 66.9 (C-3); 62.7 (C-6). IR (thin film, cm^{-1}): 1003, 1027, 1039, 1095, 1219, 1450, 1490, 1647, 3439. HRMS calculated for $C_{44}H_{38}O_4Na$ 653.26623 [M+Na]$^+$; found 653.26640.

3,6-di-*O*-trityl-4-*O*-methyl-D-glucal (32)



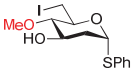
Compound **52** (6.50 g, 10.3 mmol, 1.0 eq) was dissolved in dry DMF (200 mL, 0.05 M) and MeI (1.28 mL, 20.6 mmol, 2.0 eq) was added to the solution. The mixture was cooled to 0 °C, and NaH (60%, 0.62 g, 15.5 mmol, 1.5 eq) was then added. The reaction mixture was warmed to rt while stirring for 3 hours. The reaction was then quenched by addition of H_2O, and the aqueous layer was extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 84:16) gave the title compound (4.11 g, 6.39 mmol, 62%) as a white fluffy solid. $[\alpha]_D^{25}$ = 76.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.47-7.43 (m, 6H, C*H*$_{arom}$); 7.31-7.28 (m, 6H, C*H*$_{arom}$); 7.26-7.13 (m, 18H, C*H*$_{arom}$); 6.51 (d, 1H, *J* = 6.4 Hz, H-1); 4.82 (dt, 1H, *J* = 1.6, 6.4 Hz, H-2); 4.17 (dd, 1H, *J* = 1.6, 9.2 Hz, H-5); 4.08 (dd, 1H, *J* = 9.2, 10.8 Hz, H-6); 3.77-3.75 (m, 1H, H-3); 2.83 (*s*, 3H, OC*H*$_3$); 2.60 (dd, 1H, *J* = 1.6, 10.8 Hz, H-6); 1.69 (d, 1H, *J* = 2.0 Hz, H-4). ^{13}C-APT NMR (101 MHz) δ: 144.8 ($C_{q,arom}$); 144.1 (C-1); 144.0 ($C_{q,arom}$); 129.2, 128.9, 128.7, 128.0, 127.9, 127.1, 127.0 (CH_{arom}); 99.4 (C-2); 87.6, 86.6 (CPh_3); 75.8 (C-4); 74.41 (C-5); 64.0 (C-3); 63.0 (C-6), 57.2 (O*C*H$_3$). IR (thin film, cm^{-1}): 1002, 1026, 1073, 1099, 1155, 1218, 1255, 1411, 1450, 1490, 1597, 1648. HRMS calculated for $C_{45}H_{40}O_4Na$ 667.28188 [M+Na]$^+$; found 667.28178.

Phenyl 2-deoxy-4-*O*-methyl-1-thio-α-D-glucopyranoside (33)



Compound **32** (2.46 g, 3.82 mmol, 1.0 eq) was dissolved in toluene (38 mL, 0.1 M). Thiophenol (1.56 mL, 15.3 mmol, 4.0 eq) and [$Re^VOCl_3(Me_2S)(Ph_3PO)$] (198 mg, 0.306 mmol, 0.08 eq) were added to the solution and the resulting mixture was stirred under N_2 atmosphere for 16 hours. Thereafter the reaction mixture was purified by means of column chromatography (*n*-pentane-acetone 6:4) to give the title compound (0.77 g, 2.87 mmol, 75%, α/ß >20:1) as an amorphous brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.49-7.43 (m, 2H, C*H*$_{arom}$); 7.33-7.24 (m, 3H, C*H*$_{arom}$); 5.61 (d, 1H, *J* = 5.6 Hz, H-1); 4.10-4.03 (m, 2H, H-5, H-3); 3.82-3.75 (m, 2H, H-6); 3.60 (s, 3H, OC*H*$_3$); 3.15 (t, 1H, *J* = 9.2 Hz, H-4); 2.46 (bs, 1H, 3-O*H*); 2.36 (ddd, 1H, *J* = 0.8, 5.2, 13.6 Hz, H-2); 2.18-2.06 (m, 1H, H-2) 1.79 (bs, 1H, 6-O*H*). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ: 131.8, 129.2, 127.6 (CH_{arom}); 84.1 (C-1); 82.1 (C-4); 72.1 (C-5); 69.6 C-3); 62.1 (C-6); 61.0 (O*C*H$_3$); 38.1 (C-2). IR (thin film, cm^{-1}): 1026, 1043, 1181, 1440, 1448, 1481, 3401. HRMS calculated for $C_{13}H_{18}O_4SNa$ 293.08180 [M+Na]$^+$; found 293.08159. (due to the dark colour of the solution of this compound no optical rotation could be measured)

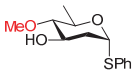
Phenyl 2,6-dideoxy-4-*O*-methyl-6-iodo-1-thio-α-D-glucopyranoside (34)



Compound **33** (0.76 g, 2.82 mmol, 1.0 eq) was dissolved in toluene (28 mL, 0.1 M) and PPh_3 (1.10 g, 4.23 mmol, 1.5 eq), imidazole (0.58 g, 8.46 mmol, 3.0 eq) and I_2 (1.43 g, 5.64 mmol, 2.0 eq) were added to the solution. The resulting mixture was warmed to 69 °C and stirred at this temperature for 1 hour after which it was cooled to rt and quenched with sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were washed with brine,

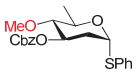
dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (0.66 g, 1.73 mmol, 61%) as an amorphous white solid. $[\alpha]_D^{25}$ = 172.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.50-7.46 (m, 2H, C*H*$_{arom}$); 7.31-7.22 (m, 3H, C*H*$_{arom}$); 5.65 (d, 1H, *J* = 5.6 Hz, H-1); 4.11-4.05 (m, 1H, H-3); 3.83-3.79 (m, 1H, H-5); 3.68 (s, 3H, OC*H*$_3$); 3.50-3.43 (m, 2H, H-6); 3.00 (t, 1H, *J* = 9.0 Hz, H-4); 2.46 (bs, 1H, 3-O*H*); 2.36 (ddd, 1H, *J* = 1.0, 5.0, 13.6 Hz, H-2); 2.18-2.10 (m, 1H, H-2). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ: 134.7 ($C_{q,arom}$); 131.3, 129.1, 127.3 (*C*H$_{arom}$); 85.8 (C-4); 84.0 (C-1); 70.5 (C-3); 69.5 (C-5); 61.4 (O*C*H$_3$); 38.5 (C-2); 8.0 (C-6). IR (thin film, cm^{-1}): 1026, 1035, 1085, 1112, 1183, 1440, 1481, 3411. HRMS calculated for $C_{13}H_{18}IO_3S$ 381.00158 $[M+H]^+$; found 381.00103.

Phenyl 2,6-dideoxy-4-*O*-methyl-1-thio-α-D-glucopyranoside (35)



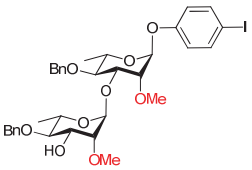
Compound **34** (0.623 g, 1.64 mmol, 1.0 eq) was dissolved in dry DMF (25 mL, 0.06 M) and $NaHCO_3$ (0.44 g, 5.24 mmol, 3.2 eq) was added to the solution. The mixture was purged with N_2 after which Pd/C (5 wt%, 0.70 g, 0.33 mmol, 0.2 eq) was added to the solution. The resulting mixture was purged with H_2 and allowed to stir under H_2 atmosphere for 20 hours. The reaction mixture was then purged with N_2, diluted with Et_2O and filtered over celite. Water was added and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (0.34 g, 1.34 mmol, 82%) as an amorphous white solid. $[\alpha]_D^{25}$ = 284.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.48-7.40 (m, 2H, C*H*$_{arom}$); 7.29-7.22 (m, 3H, C*H*$_{arom}$); 5.56 (d, 1H, *J* = 5.6 Hz, H-1); 4.16-4.12 (m, 1H, H-5); 4.01-3.95 (m, 1H, H-3); 3.60 (s, 3H, OC*H*$_3$); 2.76 (t, 1H, *J* = 9.0 Hz, H-4); 2.35 (ddd, 1H, *J* = 1.2, 5.2, 9.2 Hz, H-2) 2.15-2.07 (m, 1H, H-2); 1.31 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (100 MHz, $CDCl_3$). δ: 135.3 ($C_{q,arom}$); 131.3, 129.0, 127.2 (*C*H$_{arom}$); 88.4 (C-4); 83.9 (C-1); 69.4 (C-3); 68.1 (C-5); 61.0 (O*C*H$_3$); 38.4 (C-2); 18.2 (C-6). IR (thin film, cm^{-1}): 1026, 1036, 1105, 1183, 1440, 1481, 2926, 3440.

Phenyl 2,6-dideoxy-3-*O*-benzyloxycarbonyl-4-*O*-methyl-1-thio-α-D-glucopyranoside (4)



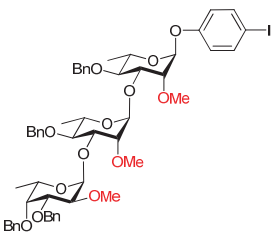
Compound **35** (0.34 g, 1.34 mmol, 1.0 eq) was dissolved in DCM (25 mL, 0.05 M) and DMAP (1.31 g, 10.7 mmol, 8.0 eq) was added to the solution. The mixture was cooled to 0 °C and CbzCl (0.95 mL, 6.70 mmol, 5.0 eq) was slowly added. The reaction was allowed to stir for 20 hours while slowly warming to rt. The reaction was then quenched by addition of 1 M HCl, and the organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 4:1) gave the title compound (0.49 g, 1.26 mmol, 94%) as an amorphous white solid. $[\alpha]_D^{25}$ = 52.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.46-7.34 (m, 7H, C*H*$_{arom}$); 7.31-7.22 (m, 3H, C*H*$_{arom}$); 5.55 (d, 1H, *J* = 5.6 Hz, H-1); 5.23-5.16 (m, 2H, PhC*H*$_2$); 5.09-5.03 (m, 1H, H-3); 4.20 (dq, 1H, *J* = 6.0, 9.2 Hz, H-5); 3.48 (s, 3H, OC*H*$_3$); 2.93 (t, 1H, *J* = 9.0 Hz, H-4); 2.48 (ddd, 1H, *J* = 1.6, 5.2, 13.2 Hz, H-2); 2.19-2.11 (m, 1H, H-2); 1.29 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (100 MHz) δ: 154.5 (*C*O$_{Cbz}$); 135.3, 134.9 ($C_{q,arom}$); 131.4, 129.1, 128.8, 128.6, 127.3 (*C*H$_{arom}$); 84.5 (C-4); 83.1 (C-1); 76.0 (C-3); 69.9 (O*C*H$_2$); 68.2 (C-5); 60.7 (O*C*H$_3$); 36.1 (C-2); 17.9 (C-6). IR (thin film, cm^{-1}): 1061, 1081, 1093, 1113, 1217, 1256, 1292, 1747. HRMS calculated for $C_{21}H_{24}O_5SNa$ 411.12421 $[M+Na]^+$; found 411.12348.

4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (36)



Donor **1** (407 mg, 0.82 mmol, 1.5 eq), Ph_2SO (183 mg, 0.91 mmol, 1.7 eq) and TTBP (511 mg, 2.1 mmol, 3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (16 mL, 0.05 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -70 °C after which Tf_2O (0.15 mL, 0.91 mmol, 1.7 eq) was added to the solution. After stirring for 30 minutes, acceptor **6** (258 mg, 0.55 mmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (1.4 mL, 0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (3 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by means of column chromatography (*n*-pentane-Et_2O 3:1) and all fractions containing product were concentrated *in vacuo*. The resulting residue (416 mg, 0.49 mmol, 89% crude yield) was then dissolved in MeOH (10 mL, 0.05 M) and a catalytic amount of K_2CO_3 was added. The reaction was allowed to stir for 16 hours after which it was diluted with DCM, filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (328 mg, 0.46 mmol, 83% over 2 steps) as a pale oil. $[\alpha]_D^{25}$ = -84.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.63-7.48 (m, 2H, C*H*$_{arom}$); 7.43-7.18 (m, 10H, C*H*$_{arom}$); 6.94-6.68 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.15 (d, *J* = 1.6 Hz, H-1'); 4.90 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.79 (d, 1H *J* = 11.2 Hz, PhCH*H*); 4.72-4.66 (m, 2H, PhC*H*H, PhCH*H*); 4.21 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.00 (dt, 1H, *J* = 3.6, 9.2 Hz, H-3'); 3.87 (dq, 1H, *J* = 6.4, 9.4 Hz, H-5'); 3.81–3.65 (m, 2H, H-2, H-5); 3.61–3.53 (m, 4H, H-4, OC*H*$_3$); 3.47 (dd, 1H, *J* = 1.6, 3.6 Hz, H-2'); 3.29 (t, 1H, *J* = 9.4 Hz, H-4'); 3.20 (s, 3H, OC*H*$_3$); 2.38 (dd, 1H, *J* = 1.6, 9.2 Hz, 3'-O*H*); 1.35 (d, 3H, *J* = 6.4 Hz, 3H); 1.26 (d, 3H, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz) δ: 156.2, 138.6 (C$_{q,arom}$); 138.5 (C*H*$_{arom}$); 138.3 (C$_{q,arom}$); 128.6, 128.5, 128.1, 127.9, 127.8, 127.2, 118.7 (C*H*$_{arom}$); 98.7 (C-1'); 95.1 (C-1); 84.9 (C*I*$_{arom}$); 82.1 (C-4'); 81.0 (C-2'); 80.4 (C-4); 80.2 (C-2); 78.7 (C-3); 75.2, (Ph*C*H$_2$); 71.6 (C-3'); 69.2 (C-5); 68.0 (C-5'); 59.3, 58.7 (O*C*H$_3$); 18.2 (C-6'); 18.1 (C-6). IR (thin film, cm^{-1}): 1029, 1043, 1059, 1098, 1138, 1232, 1454, 1484, 2896, 2933, 3519. HRMS calculated for $C_{34}H_{41}IO_9Na$ 743.16875 $[M+Na]^+$; found 743.16895.

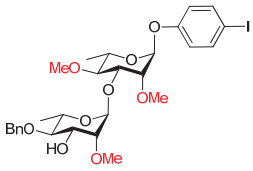
4-iodophenyl 2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3,4-di-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (38)



The title compound was synthesized according to general procedure B using acceptor **36** (70 mg, 97 µmol, 1.0 eq), donor **5** (88 mg, 0.19 mmol, 2.0 eq) and IDCP (137 mg, 0.29 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (76 mg, 71 µmol, 74%, α-β 6:1) as a pale oil. $[\alpha]_D^{25}$ = -88.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57-7.55 (m, 2H, C*H*$_{arom}$); 7.40-7.22 (m, 20H, C*H*$_{arom}$); 6.85-6.82 (m, 2H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.23-5.19 (m, 2H, H-1", PhC*H*H); 5.15 (d, 1H, *J* = 1.2 Hz, H-1'); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.85-4.80

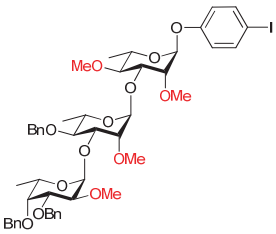
(m, 2H, PhC*H*H, PhC*H*H); 4.73 (d, 1H, *J* = 12.4 Hz, PhCH*H*); 4.67-4.63 (m, 2H, PhCH*H*, PhCH*H*); 4.54 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.17 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.09-4.02 (m, 2H, H-3', H-5"); 3.98-3.89 (m, 2H, H-3", H-5'); 3.82 (dd, 1H, *J* = 3.6, 10.0 Hz, H-2"); 3.75-3.66 (m, 4H, H-2, H-2', H-4", H-5); 3.55-3.44 (m, 5H, H-4, H-4', OCH_3); 3.39 (s, 3H, OCH_3); 3.21 (s, 3H, OCH_3); 1.33 (d, 3H, *J* = 6.4 Hz, H-6'); 1.24 (d, 3H, *J* = 6.0 Hz, H-6); 1.08 (d, 3H, *J* = 6.4 Hz, H-6"). ^{13}C-APT NMR (101 MHz) δ: 156.3, 139.2, 139.1, 138.8 ($C_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.3 ($C_{q,arom}$); 128.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 127.5, 127.4, 118.7 (*C*H$_{arom}$); 100.1 (C-1"); 98.9 (C-1'); 94.8 (C-1); 84.9 (*C*I$_{arom}$); 80.7 (C-3'); 80.2 (C-2'); 79.9 (C-2); 79.8 (C-4); 79.6 (C-3); 78.9 (C-3"); 78.6 (C-2"); 77.8 (C-4"); 75.4, 75.2, 75.0, 72.9 (Ph*C*H$_2$); 69.1 (C-5); 68.7 (C-5'); 67.0 (C-5); 59.1, 59.1, 57.8 (OCH_3); 18.4 (C-6); 18.1 (C-6'); 17.1 (C-6"). IR (thin film, cm^{-1}): 1042, 1098, 1129, 1178, 1195, 1232, 1355, 1454, 1484, 2929, 2976, 3030. HRMS calculated for $C_{55}H_{65}IO_{13}Na$ 1083.33621 [M+Na]$^+$; found 1083.33613.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (37)



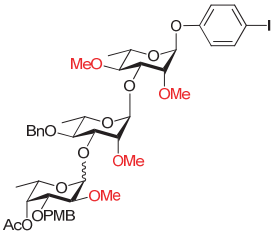
Donor **1** (0.742 g, 1.5 mmol, 1.5 eq), Ph_2SO (0.394 g, 1.95 mmol, 2.0 eq) and TTBP (0.932 g, 3.75 mmol, 3.8 eq) were dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges. The mixture was then dissolved in DCM (20 mL, 0.08 M) and flame-dried 3Å molecular sieves were added. The solution was then cooled to -65 °C after which Tf_2O (0.33 mL, 1.95 mmol, 2.0 eq) was added to the solution. After stirring for 30 minutes, acceptor **2** (0.394 g, 1.0 mmol, 1.0 eq), which was also dried by co-evaporation with toluene (3x) followed by 3 vacuum/nitrogen purges, was dissolved in DCM (2.5 mL, 0.4 M) and slowly added to the solution. After TLC analysis indicated the consumption of the acceptor (3 hours) the reaction was quenched by addition of NEt_3. The reaction mixture was then diluted with DCM, filtered over celite, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by means of column chromatography (*n*-pentane-Et_2O 3:1) and all fractions containing product were concentrated *in vacuo*. The resulting residue (0.756 g, 0.97 mmol, 97% crude yield) was then dissolved in MeOH (20 mL, 0.05 M) and a catalytic amount of K_2CO_3 was added. The reaction was allowed to stir for 16 hours after which it was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (0.549 g, 0.85 mmol, 85% over 2 steps) as a pale oil. $[\alpha]_D^{25}$ = -103.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.55 (m, 2H, C*H*$_{arom}$); 7.40-7.26 (m, 5H, C*H*$_{arom}$); 6.85-6.82 (m, 2H, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 1.6 Hz, H-1); 5.22 (d, 1H, *J* = 1.2 Hz, H-1'); 4.79 (dd, 2H, *J* = 11.2, 89.6 Hz, Ph*C*H$_2$); 4.10 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.00 (dt, 1H, *J* = 4.0, 9.2 Hz, H-3'); 3.89-3.82 (m, 1H, H-5'); 3.65 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.63-3.56 (m, 2H, H-2', H-5); 3.54 (s, 3H, OCH_3); 3.52 (s, 3H, OCH_3); 3.51 (s, 3H, OCH_3); 3.31 (t, 1H, *J* = 9.4 Hz, H-4'); 3.24 (t, 1H, *J* = 9.6 Hz, H-4); 2.46 (dd, 1H, *J* = 5.2, 9.2 Hz, 3'-O*H*); 1.36 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2, 138.5 ($C_{q,arom}$); 138.5, 128.5, 128.1, 127.9, 118.7 (*C*H$_{arom}$); 98.4 (C-1'); 95.2 (C-1); 84.9 (*C*I$_{arom}$); 82.4 (C-4); 82.1 (C-4'); 81.2 (C-2'); 80.1 (C-2); 78.2 (C-3); 75.3 (Ph*C*H$_2$); 69.1 (C-3'); 67.9 (C-5); 61.2, 59.4, 58.8 (OCH_3); 18.2 (C-6'); 17.9 (C-6). IR (thin film, cm^{-1}): 1001, 1008, 1028, 1041, 1098, 1139, 1233, 1264, 1483. HRMS calculated for $C_{28}H_{37}IO_9Na$ 667.13800 [M+Na]$^+$; found 667.13744.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-3,4-di-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (39)



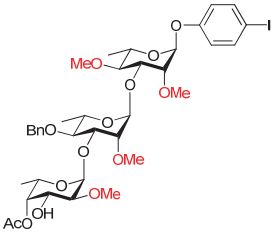
The title compound was synthesized according to general procedure B using acceptor **37** (59 mg, 92 µmol, 1.0 eq), donor **5** (82 mg, 0.18 mmol, 2.0 eq) and IDCP (129 mg, 0.27 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (89 mg, 90 µmol, 99%, α/β 6:1) as a pale oil. $[\alpha]_D^{25}$ = -95.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.58-7.54 (m, 2H, C*H*$_{arom}$); 7.40-7.25 (m, 15H, C*H*$_{arom}$); 6.84-6.81 (m, 2H, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.20 (m, 2H, H-1", PhC*H*H); 5.14 (d, 1H, *J* = 1.6 Hz, H-1'); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.85 (d, 1H, *J* = 12.0 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 12.4 Hz, PhCH*H*); 4.67 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.55 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.11 (q, 1H, *J* = 6.4 Hz, H-5"); 4.05-3.91 (m, 4H, H-3, H-3', H-3", H-5'); 3.82 (dd, 1H, *J* = 3.8, 10.2 Hz, H-2"); 3.72-3.69 (m, 3H, H-2, H-2', H-4"); 3.60-3.45 (m, 11H, H-4', H-5, OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.20 (t, 1H, *J* = 9.6 Hz, H-4); 1.32 (d, 3H, *J* = 6.0 Hz, H-6'); 1.24 (d, 3H, *J* = 6.4 Hz, H-6); 1.14 (d, 3H, *J* = 6.4 Hz, H-6"). ^{13}C-APT NMR (101 MHz) δ: 156.3, 139.2, 139.1 138.7 (C$_{q,arom}$); 138.5, 128.6, 128.5, 128.4, 128.4, 127.9, 127.8, 127.6, 127.5, 127.5, 118.7 (*C*H$_{arom}$); 100.1 (C-1"); 98.8 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 81.9 (C-4); 80.9 (C-2'); 80.7 (C-3'); 80.0 (C-2); 80.0 (C-3); 79.7 (C-4'); 79.0 (C-3"); 78.6 (C-2"); 77.7 (C-4"); 75.2, 75.0, 73.0 (Ph*C*H$_2$); 69.1 (C-5); 68.8 (C-5'); 66.9 (C-5"); 61.4, 59.2, 59.1, 58.0 (O*C*H$_3$); 18.4 (C-6'); 17.9 (C-6); 17.1 (C-6"). IR (thin film, cm^{-1}): 1042, 1072, 1099, 1175, 1193, 1232, 1357, 1379, 1454, 1484, 2830, 2932, 2974. HRMS calculated for $C_{49}H_{61}IO_{13}Na$ 1007.30545 $[M+Na]^+$; found 1007.30503.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-acetyl-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (40)



The title compound was synthesized according to general procedure B using acceptor **37** (161 mg, 0.25 mmol, 1.0 eq), donor **3** (216 mg, 0.50 mmol, 2.0 eq) and IDCP (352 mg, 0.75 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (163 mg, 0.17 mmol, 74%, α/β 6:1) as a pale oil. The mixture was used in the next step without further purification or analysis.

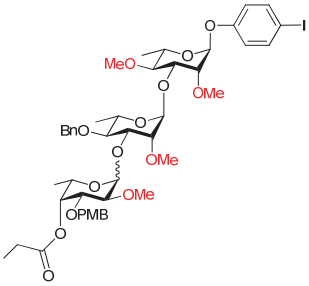
4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (43)



Compound **40** (163 mg, 0.17 mmol, 1.0 eq) was dissolved in DCM/H_2O (16:1, 1.7 mL, 0.1 M). After stirring for a few minutes DDQ (46 mg, 0.20 mmol, 1.2 eq) was added to the solution. The reaction was stirred vigorously for 4 hours after which it was quenched by addition of sat. aq. $NaHCO_3$. The organic layer was then washed sat. aq. $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (113

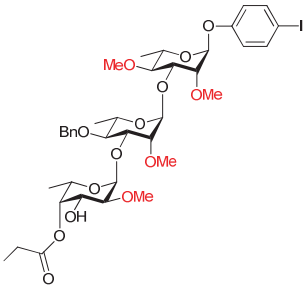
mg, 0.13 mmol, 79%) as a pale oil. $[\alpha]_D^{25}$ = -124.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.38-7.27 (m, 5H, C*H*$_{arom}$); 6.84 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.29 (d, 1H, *J* = 2.4 Hz, H-4''); 5.24 (d, 1H, *J* = 3.6 Hz, H-1''); 5.19 (d, 1H, *J* = 1.2 Hz, H-1'); 5.13 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.59 (d, 1H, *J* = 11.6 hz, PhCH*H*); 4.35 (q, 1H, *J* = 6.8 Hz, H-5''); 4.25 (dd, 1H, *J* = 3.4, 10.2 Hz, H-3''); 4.07-4.00 (m, 2H, H-3, H-3'); 3.96-3.92 (m, 1H, H-5'); 3.74-3.72 (m, 2H, H-2, H-2'); 3.62-3.57 (m, 1H, H-5); 3.54-3.45 (m, 11H, H-2'', H-4', OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.22 (t, 1H, *J* = 9.6 Hz, H-4); 2.35 (bs, 1H, 3''-O*H*); 2.19 (s, 3H, C*H*$_{3,Ac}$); 1.32 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.0 Hz, H-6); 1.15 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 171.3 (*C*O$_{Ac}$); 156.3, 139.1 (C$_{q,arom}$); 138.5, 128.4, 127.6, 127.5, 118.7 (*C*H$_{arom}$); 99.2 (C-1''); 98.5 (C-1'); 94.8 (C-1); 84.9 (*C*I$_{arom}$); 82.0 (C-3' and C-4); 80.7 (C-2); 80.1 (C-2'); 79.8 (C-3); 79.4 (C-4'); 78.5 (C-2''); 75.1 (Ph*C*H$_2$); 73.0 (C-4''); 69.1 (C-5); 68.8 (C-5'); 68.1 (C-3''); 65.3 (C-5''); 61.3, 59.1, 58.2, 57.8 (O*C*H$_3$); 21.0 (*C*H$_{3,Ac}$); 18.4 (C-6'); 17.9 (C-6); 16.6 (C-6''). IR (thin film, cm^{-1}): 1042, 1098, 1128, 1232, 1448, 1484, 1740, 3490. HRMS calculated for $C_{37}H_{51}IO_{14}Na$ 869.22212 $[M+Na]^+$; found 869.22114.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-propionyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (42)



The title compound was synthesized according to general procedure B using acceptor **37** (66 mg, 102 µmol, 1.0 eq), donor **7** (91 mg, 0.20 mmol, 2.0 eq) and IDCP (144 mg, 0.31 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 6:4) gave the title compound (84 mg, 86 µmol, 84%, α/β 6:1) as a pale oil. The mixture was used in the next step without further purification or analysis.

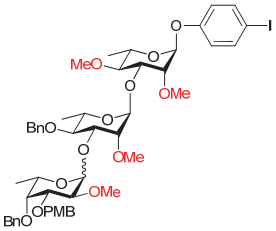
4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-4-*O*-propionyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (45)



Compound **42** (180 mg, 0.18 mmol, 1.0 eq) was dissolved in DCM/H_2O (19:1, 2.0 mL, 0.1 M). After stirring for a few minutes DDQ (50 mg, 0.22 mmol, 1.2 eq) was added to the solution. The reaction was stirred vigorously for 1 hour after which it was quenched by addition of sat. aq. $NaHCO_3$. The organic layer was then washed sat. aq. $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:4) gave the title compound (121 mg, 0.14 mmol, 77%) as a pale oil. $[\alpha]_D^{25}$ = -119.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.38-7.26 (m, 5H, C*H*$_{arom}$); 6.84 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.6 Hz, H-1); 5.30 (d, 1H, *J* = 2.4 Hz, H-4''); 5.24 (d, 1H, *J* = 3.6 Hz, H-1''); 5.19 (d, 1H, *J* = 1.6 Hz, H-1'); 5.13 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.59 (d, 1H, *J* = 11.6 hz, PhCH*H*); 4.35 (q, 1H, *J* = 6.8 Hz, H-5''); 4.25 (dd, 1H, *J* = 3.6, 10.0 Hz, H-3''); 4.07-4.00 (m, 2H, H-3, H-3'); 3.96-3.92 (m, 1H, H-5'); 3.74-3.71 (m, 2H, H-2, H-2'); 3.62-3.45 (m,

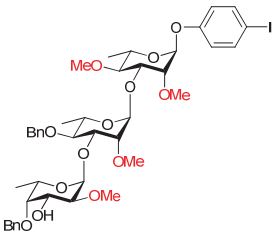
12H, H-2", H-4', H-5, OCH_3); 3.31 (s, 3H, OCH_3); 3.22 (t, 1H, *J* = 9.6 Hz, H-4); 2.47 (dq, 2H, *J* = 1.4, 7.5 Hz, CH_2CH$_3$); 2.35 (bs, 1H, 3"-O*H*); 1.32 (d, 3H, *J* = 6.0 Hz, H-6'); 1.25 (d, 3H, *J* = 6.4 Hz, H-6); 1.20 (t, 3H, *J* = 7.6 Hz, CH$_2$CH_3); 1.14 (d, 3H, *J* = 6.8 Hz, H-6"). ^{13}C-APT NMR (101 MHz) δ: 174.8 (*C*O$_{propionyl}$); 156.3, 139.0 (C$_{q,arom}$); 138.5, 128.3, 127.6, 127.5, 118.7 (*C*H$_{arom}$); 99.2 (C-1"); 98.5 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 82.0 (C-4); 81.4 (C-3'); 80.7 (C-2); 80.1 (C-2'); 79.7 (C-3); 79.4 (C-4'); 78.5 (C-2"); 75.1 (Ph*C*H$_2$); 72.8 (C-4"); 69.1 (C-5); 68.8 (C-5'); 68.1 (C-3"); 65.3 (C-5"); 61.3, 59.1, 58.3, 57.8 (O*C*H$_3$); 27.7 (*C*H$_2$CH$_3$); 18.3 (C-6'); 17.9 (C-6); 16.5 (C-6") 9.4 (CH$_2$*C*H$_3$). IR (thin film, cm^{-1}): 1042, 1098, 1128, 1232, 1484, 1739, 3494. HRMS calculated for $C_{38}H_{53}IO_{14}Na$ 883.23777 [M+Na]$^+$; found 883.23735.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-methoxybenzyl)-4-*O*-benzyl-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (41)



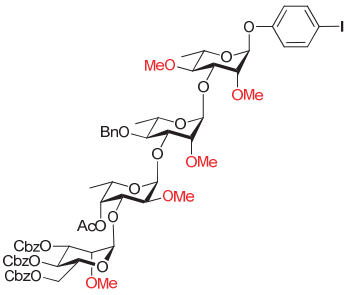
The title compound was synthesized according to general procedure B using acceptor **37** (129 mg, 0.20 mmol, 1.0 eq), donor **8** (192 mg, 0.40 mmol, 2.0 eq) and IDCP (281 mg, 0.60 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et$_2$O 1:1) gave the title compound (190 mg, 0.19 mmol, 96%, α-β 6:1) as a pale oil. The mixture was used in the next step without further purification or analysis.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-4-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (44)



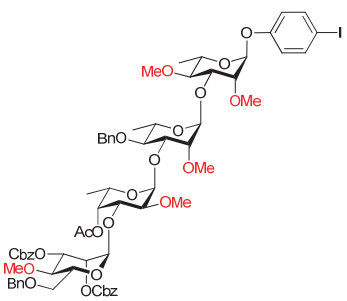
Compound **41** (190 mg, 0.19 mmol, 1.0 eq) was dissolved in DCM/H$_2$O (19:1, 1.9 mL, 0.1 M). After stirring for a few minutes DDQ (53 mg, 0.23 mmol, 1.2 eq) was added to the solution. The reaction was stirred vigorously for 4 hours after which it was quenched by addition of sat. aq. NaHCO$_3$. The organic layer was then washed sat. aq. NaHCO$_3$, dried with MgSO$_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et$_2$O 3:7) gave the title compound (121 mg, 0.14 mmol, 70%) as a pale oil. [α]$_D^{25}$ = -133.8 ° (c = 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.42-7.23 (m, 10H, C*H*$_{arom}$); 6.85-6.81 (m, 2H, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.6 H-1); 5.22 (d, 1H, *J* = 3.6 Hz, H-1"); 5.16-5.12 (m, 2H, H-1', PhC*H*H); 4.81 (dd, 2H, *J* = 11.6, 60.8 Hz, PhC*H*$_2$); 4.59 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.22-4.12 (m, 2H, H-3", H-5"); 4.05-3.99 (m, 2H, H-3, H-3'); 3.96-3.92 (m, 1H, H-5'); 3.74-3.67 (m, 3H, H-2, H-2', H-4"); 3.62-3.46 (m, 12H, H-2", H-4', H-5, OCH_3); 3.29 (s, 3H, OCH_3); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.35 (d, 1H, *J* = 4.8 Hz, 3"-O*H*); 1.31 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.4 Hz, H-6); 1.19 (d, 3H, *J* = 6.4 Hz, H-6"). ^{13}C-APT NMR (101 MHz) δ: 156.3, 139.2 (C$_{q,arom}$); 138.5, 128.5, 128.5, 128.3, 128.0, 127.5, 127.5, 118.7 *C*H$_{arom}$); 99.2 (C-1"); 98.7 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 81.9 (C-4); 80.8 (C-3'); 80.1 (C-2' and C-2); 79.5, 79.4 (C-4' and C-4"); 78.9 (C-2"); 75.7, 75.0 (Ph*C*H$_2$); 70.6 (C-3"); 69.1 (C-5); 68.8 (C-5'); 66.7 (C-5"); 61.4, 59.1, 58.2, 57.9 (O*C*H$_3$); 18.4 (C-6'); 17.9 (C-6); 17.1 (C-6"). IR (thin film, cm^{-1}): 1040, 1073, 1098, 1128, 1232, 1484, 3479. HRMS calculated for $C_{42}H_{55}IO_{13}Na$ 917.25850 [M+Na]$^+$; found 917.25767.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3,4,6-tri-*O*-benzyloxycarbonyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (46)



The title compound was synthesized according to general procedure A using acceptor **43** (72 mg, 85 µmol, 1.0 eq) and donor **10** (117 mg, 0.17 mmol, 2.0 eq). Column chromatography (*n*-pentane-Et_2O 3:7) gave the title compound (103 mg, 72 µmol, 96%) as a pale oil. $[\alpha]_D^{25}$ = -62.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.45-7.21 (m, 20H, C*H*$_{arom}$); 6.86-6.82 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.28 (d, 1H, *J* = 2.8 Hz, H-4''); 5.23-5.05 (m, 11H, H-1', H-1'', H-1''', H-4''', PhC*H*$_2$, PhC*H*H); 4.93 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3'''); 4.58 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.35-4.29 (m, 3H, H-5'', H-6'''); 4.25 (dd, 1H, *J* = 3.6, 10.0 Hz, H-3''); 4.21-4.16 (m, 1H, H-5'''); 4.05 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.01 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3'); 3.98-3.89 (m, 1H, H-5'); 3.73-3.71 (m, 2H, H-2, H-2'''); 3.69 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2'); 3.64-3.58 (m, 1H, H-5); 3.55-3.47 (m, 8H, H-2'', H-4', OC*H*$_3$); 3.40 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.25-3.19 (m, 4H, H-4, OC*H*$_3$); 2.18 (s, 3H, C*H*$_{3,Ac}$); 1.33 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.0 Hz, H-6); 1.09 (d, 3H, *J* = 6.4 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 170.9 (*C*O$_{Ac}$); 156.3 (C$_{q,arom}$); 155.0, 154.4, 154.3 (*C*O$_{Cbz}$); 139.1 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 135.4, 135.2, 135.1 (C$_{q,arom}$); 128.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 127.4, 127.4, 118.7 (*C*H$_{arom}$); 99.4 (C-1''); 98.8 (C-1'''); 98.4 (C-1'); 94.8 (C-1); 84.9 (*C*I$_{arom}$); 81.9 (C-4); 81.6 (C-3'); 80.6 (C-2'); 80.1 (C-2); 79.8 (C-3); 79.3 (C-4'); 78.6 (C-2''); 77.8 (C-2'''); 75.1 (Ph*C*H$_2$); 75.0 (C-3''); 73.8 (C-3'''); 72.9 (C-4''); 70.4 (C-4'''); 70.2, 69.8, 69.8 (Ph*C*H$_2$); 69.1 (C-5); 68.9 (C-5'''); 68.8 (C-5'); 66.4 (C-6'''); 65.3 (C-5''); 61.3, 59.1, 59.0, 58.5, 57.7 (O*C*H$_3$); 20.9 (*C*H$_{3,Ac}$); 18.3 (C-6'); 17.9 (C-6); 16.3 (C-6''). IR (thin film, cm^{-1}): 1020, 1043, 1098, 1129, 1176, 1236, 1385, 1455, 1484, 1747, 2833, 2929. HRMS calculated for $C_{68}H_{81}IO_{25}Na$ 1447.40038 $[M+Na]^+$; found 1447.40038.

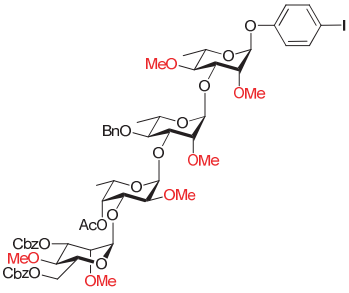
4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,3-di-*O*-benzyloxycarbonyl-4-*O*-methyl-6-*O*-benzyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (47)



The title compound was synthesized according to general procedure A using acceptor **43** (81 mg, 63 µmol, 1.0 eq) and donor **11** (53 mg, 0.12 mmol, 2.0 eq). Column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (55 mg, 40 µmol, 64%) as a pale oil. $[\alpha]_D^{25}$ = -72.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.38-7.22 (m, 20H, C*H*$_{arom}$); 6.83 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 2.0 Hz, H-1); 5.28 (d, 1H, *J* = 1.2 Hz, H-1'''); 5.26 (d, 1H, *J* = 3.6 Hz, H-4''); 5.20-5.15 (m, 5H, H-1', H-1'', H-2''', PhC*H*$_2$); 5.13-5.08 (m, 3H, PhC*H*$_2$, PhC*H*H); 4.99 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3'''); 4.72 (d, 1H, *J* = 12.0 Hz, PhC*H*H); 4.56-4.50 (m, 2H, PhCH*H*, PhCH*H*); 4.33-4.26 (m, 2H, H-3'', H-5''); 4.07-3.98

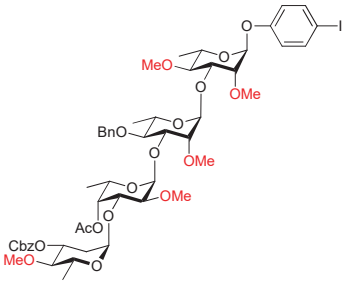
(m, 3H, H-3, H-3', H-5'''); 3.96-3.89 (m, 1H, H-5'); 3.80 (dd, 1H, *J* = 4.4, 11.2 Hz, H-6'''); 3.73-3.67 (m, 4H, H-2, H-2', H-4''', H-6'''); 3.63-3.47 (m, 9H, H-2'', H-4', H-5, OC*H*$_3$); 3.42 (s, 3H, OC*H*$_3$); 3.37 (s, 3H, OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 1.33 (d, 3H, *J* = 6.4 Hz, H-6'); 1.25 (d, 3H, *J* = 6.0 Hz, H-6); 1.10 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 171.1 (*C*O$_{Ac}$); 156.3 (C$_{q,arom}$); 154.6, 154.5 (*C*O$_{Cbz}$); 139.1 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 138.5, 135.3 (C$_{q,arom}$); 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 127.9, 127.9, 127.6, 127.5, 118.7 (*C*H$_{arom}$); 99.7 (C-1''); 98.6 (C-1'''); 98.5 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 82.0 (C-4); 81.6 (C-3'); 80.7 (C-2'); 80.1 (C-2); 79.7 (C-3); 79.4 (C-4;); 78.8 (C-2''); 75.8 (C-3'''); 75.4 (Ph*C*H$_2$); 74.2 (C-4'''); 73.6 (C-2'''); 73.6 (Ph*C*H$_2$); 73.0 (C-4''); 72.9 (C-3''); 72.1 (C-5'''); 70.1, 69.9 (Ph*C*H$_2$); 69.1 (C-5); 68.8 (C-5'); 65.3 (C-5''); 61.3, 60.8, 59.1, 58.9, 57.8 (O*C*H$_3$); 20.9 (*C*H$_{3,Ac}$); 18.3 (C-6'); 17.9 (C-6); 16.3 (C-6''). IR (thin film, cm^{-1}): 1044, 1097, 1127, 1216, 1234, 1273 1483, 1751. HRMS calculated for $C_{67}H_{81}IO_{23}Na$ 1403.41110 [M+Na]$^+$; found 1403.41046.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,4-di-*O*-methyl-3,6-di-*O*-benzyloxycarbonyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (48)



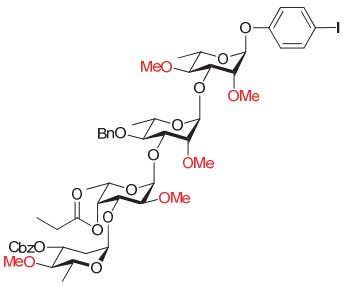
The title compound was synthesized according to general procedure A using acceptor **43** (63 mg, 74 µmol, 1.0 eq) and donor **9** (85 mg, 0.15 mmol, 2.0 eq). Column chromatography (*n*-pentane-Et$_2$O 3:7) gave the title compound (97 mg, 74 µmol, 100%) as a pale oil. [α]$_D^{25}$ = -79.4 ° (c = 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz) δ: 7.59-7.55 (m, 2H, C*H*$_{arom}$); 7.39-7.21 (m, 15H, C*H*$_{arom}$); 6.86-6.82 (m, 2H, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.6 Hz, H-1); 5.27 (dd, 1H, *J* = 0.8, 3.6 Hz, H-4''); 5.22-5.11 (m, 8H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.87 (dd, 1H, *J* = 3.4, 9.8 Hz, H-3'''); 4.57 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.47 (dd, 1H, *J* = 2.0, 11.6 Hz, H-6'''); 4.37-4.30 (m, 2H, H-5'', H-6'''); 4.24 (dd, 1H, *J* = 3.4, 10.2 Hz, H-3''); 4.05 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.02-3.98 (m, 2H, H-3', H-5'''); 3.94-3.91 (m, 1H, H-5'); 3.72 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.69 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2'); 3.65 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2'''); 3.63-3.56 (m, 2H, H-4''', H-5); 3.54-3.49 (m, 8H, H-2'', H-4', OC*H*$_3$); 3.44 (s, 3H, OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.24-3.21 (m, 4H, H-4, OC*H*$_3$); 2.19 (s, 3H, C*H*$_{3,Ac}$); 1.33 (d, 3H, *J* = 6.0 Hz, H-6'); 1.25 (d, 3H, *J* = 6.0 Hz, H-6); 1.10 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 170.9 (*C*O$_{Ac}$); 156.3 (C$_{q,arom}$); 155.3, 154.7 (*C*O$_{Cbz}$); 139.2 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 135.4 (C$_{q,arom}$); 128.7, 128.6, 128.6, 128.6, 128.4, 128.3, 128.2, 127.4, 127.4, 118.7 (*C*H$_{arom}$); 99.5 (C-1''); 98.6 (C-1'''); 98.5 (C-1'); 94.8 (C-1); 84.9 (*C*I$_{arom}$); 82.0 (C-4); 81.6 (C-3'); 80.7 (C-2'); 80.1 (C-2); 79.8 (C-3); 79.4 (C-4'); 78.7 (C-2''); 78.3 (C-2'''); 77.5 (C-3'''); 75.2 (Ph*C*H$_2$); 74.4 (C-4'''); 73.5 (C-3''); 73.0 (C-4''); 70.2 (C-5'''); 69.7, 69.7 (Ph*C*H$_2$); 69.1 (C-5); 68.8 (C-5'); 66.9 (C-6'''); 65.3 (C-5''); 61.3, 60.6, 59.1, 59.0, 58.5, 57.8 (O*C*H$_3$); 20.9 (*C*H$_{3,Ac}$); 18.3 (C-6'); 17.9 (C-6); 16.3 (C-6''). IR (thin film, cm^{-1}): 1019, 1043, 1098, 1128, 1176, 1236, 1249, 1455, 1484, 1746, 2932. HRMS calculated for $C_{61}H_{77}IO_{23}Na$ 1327.37962 [M+Na]$^+$; found 1327.37925.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (49)



The title compound was synthesized according to general procedure B, but with DCM as solvent instead of Et_2O/DCE (1.2 mL, 0.05 M), using acceptor **43** (51 mg, 60 µmol, 1.0 eq), donor X (47 mg, 0.12 mmol, 2.0 eq) and IDCP (84 mg, 0.18 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (190 mg, 0.19 mmol, 90%, α/β 4:1) as a pale oil. $[\alpha]_D^{25}$ = -68.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.38-7.25 (m, 10H, C*H*$_{arom}$); 6.83 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.6 Hz, H-1); 5.23 (d, 1H, *J* = 2.8 Hz, H-4''); 5.20-5.11 (m, 6H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.98-4.92 (m, 1H, H-3'''); 4.56 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.33 (q, 1H, *J* = 6.4 Hz, H-5''); 4.18 (dd, 1H, *J* = 3.6, 10.4 Hz, H-3''); 4.07-4.00 (m, 2H, H-3, H-3'); 3.95-3.85 (m, 2H, H-5', H-5'''); 3.72-3.69 (m, 2H, H-2, H-2'); 3.61-3.44 (m, 15H, H-2'', H-4', H-5, OC*H*$_3$); 3.27 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.4 Hz, H-4); 2.87 (t, 1H, *J* = 9.4 Hz, H-4'''); 2.30 (dd, 1H, *J* = 4.8, 12.6 Hz, H-2'''); 2.20 (s, 3H, C*H*$_{3,Ac}$); 1.71 (dt, 1H, *J* = 3.0, 12.4 Hz, H-2'''); 1.36-1.21 (m, 9H, H-6, H-6', H-6'''); 1.12 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 171.0 (*C*O$_{Ac}$); 156.3 (C$_{q,arom}$); 154.6 (*C*O$_{Cbz}$); 139.2 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 135.4 (C$_{q,arom}$); 128.7, 128.6, 128.4, 128.3, 127.6, 127.5, 118.7 (*C*H$_{arom}$); 99.8 (C-1''); 98.7 (C-1'''); 98.4 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 84.2 (C-4'''); 82.0 (C-4); 81.4 (C-3'); 80.8 (C-2'); 80.1 (C-2); 79.8 (C-3); 79.5 (C-4'); 78.7 (C-2''); 75.4 (C-3'''); 75.2 (Ph*C*H$_2$); 73.3 (C-4''); 73.2 (C-3''); 69.7 (Ph*C*H$_2$); 69.1 (C-5); 68.8 (C-5'); 67.4 (C-5'''); 65.5 (C-5''); 61.3, 60.3, 59.1, 58.9, 57.8 (O*C*H$_3$); 35.7 (C-2'''); 21.0 (*C*H$_{3,Ac}$); 18.3 (C-6'); 18.1 (C-6'''); 17.9 (C-6); 16.5 (C-6''). IR (thin film,cm^{-1}): 1040, 1099, 1125, 1139, 1255, 1484, 1749, 2911, 2929. HRMS calculated for $C_{52}H_{69}IO_{19}Na$ 1147.33682 [M+Na]$^+$; found 1147.33699.

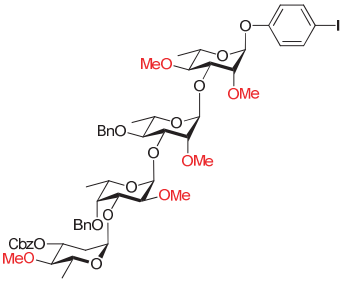
4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-propionyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (51)



The title compound was synthesized according to general procedure B, but with DCM as solvent instead of Et_2O/DCE (2.4 mL, 0.05 M), using acceptor **45** (104 mg, 0.12 mmol, 1.0 eq), donor **4** (94 mg, 0.24 mmol, 2.0 eq) and IDCP (170 mg, 0.36 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 4:6) gave the title compound (123 mg, 0.11 mmol, 89%, α/β 4:1) as a pale oil. $[\alpha]_D^{25}$ = -63.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.38-7.25 (m, 10H, C*H*$_{arom}$); 6.83 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.28 (d, 1H, *J* = 2.8 Hz, H-4''); 5.24 (dd, 1H, *J* = 1.2, 3.6 Hz, H-4''); 5.22-5.13 (m, 6H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.96-4.90 (m, 1H, H-3'''); 4.56 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.33 (q, 1H, *J* = 6.4 Hz, H-5''); 4.18 (dd, 1H, *J* = 3.6, 10.4 Hz, H-3''); 4.07-4.00 (m, 2H, H-3, H-3'); 3.95-3.85 (m, 2H, H-5', H-5'''); 3.72-3.69 (m, 2H, H-

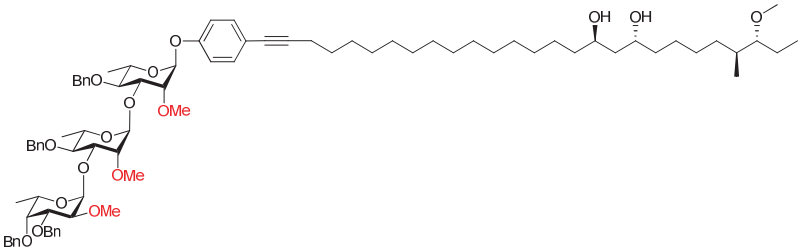
2, H-2'); 3.61-3.57 (m, 1H, H-5); 3.56-3.44 (m, 14H, H-2'', H-4', OC*H*$_3$); 3.27 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.87 (t, 1H, *J* = 9.2 Hz, H-4'''); 2.54-2.42 (m, 2H, C*H*$_2$CH$_3$); 2.29 (ddd, 1H, *J* = 1.4, 5.2, 12.6 Hz, H-2'''); 1.74-1.67 (m, 1H, H-2'''); 1.34-1.29 (m, 6H, H-6', H-6'''); 1.26-1.21 (m, 6H, CH$_2$C*H*$_3$, H-6); 1.11 (d, 3H, *J* = 6.8 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*O$_{propionyl}$); 156.3 (C$_{q,arom}$); 154.6 (*C*O$_{Cbz}$); 139.2 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 135.4 (C$_{q,arom}$); 128.7, 128.6, 128.4, 128.3, 127.7, 127.5, 118.7 (*C*H$_{arom}$); 99.9 (C-1''); 98.7 (C-1'''); 98.5 (C-1'); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 84.1 (C-4'''); 82.0 (C-4); 81.4 (C-3'); 80.8 (C-2'); 80.1 (C-2); 79.7 (C-3); 78.7 (C-2''); 75.3 (C-3'''); 75.2 (Ph*C*H$_2$); 73.5 (C-3''); 73.1 (C-4''); 69.7 (Ph*C*H$_2$); 69.1 (C-5); 68.8 (C-5'); 67.8 (C-5'''); 65.6 (C-5''); 61.4, 60.1, 59.1, 59.0, 57.9 (O*C*H$_3$); 35.7 (C-2'''); 27.8 (*C*H$_2$CH$_3$); 18.3 (C-6'); 18.1 (C-6'''); 17.9 (C-6); 16.5 (C-6''); 9.7 (CH$_2$*C*H$_3$). IR (thin film, cm^{-1}): 1016, 1043, 1099, 1128, 1256, 1485, 1744, 2928. HRMS calculated for $C_{53}H_{71}IO_{19}Na$ 1161.35264 [M+Na]$^+$; found 1161.35290.

4-iodophenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (50)



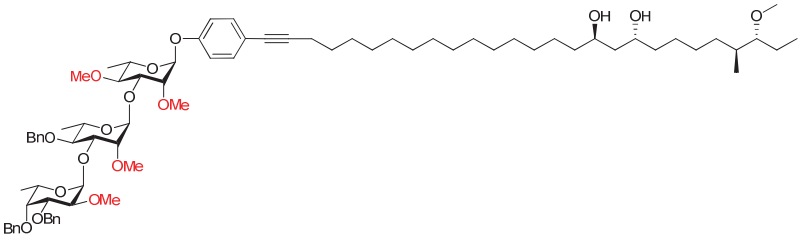
The title compound was synthesized according to general procedure B, but with DCM as solvent instead of Et$_2$O/DCE (2.6 mL, 0.05 M), using acceptor **44** (113 mg, 0.13 mmol, 1.0 eq), donor **4** (98 mg, 0.26 mmol, 2.0 eq) and IDCP (178 mg, 0.38 mmol, 3.0 eq). Column chromatography (*n*-pentane-Et$_2$O 1:1) gave the title compound (77 mg, 66 μmol, 52%) as a pale oil. $[\alpha]_D^{25}$ = -55.4 ° (c = 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz) δ: 7.57 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 7.45-7.24 (m, 15H, C*H*$_{arom}$); 6.83 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.45 (d, 1H, *J* = 1.6 Hz, H-1); 5.24 (d, 1H, *J* = 2.8 Hz, H-1'''); 5.20-5.11 (m, 5H, H-1', H-1'', PhC*H*$_2$, PhC*H*H); 5.06 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.57 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.23-4.15 (m, 2H, H-3'', H-5''); 4.05-3.98 (m, 2H, H-3, H-3'); 3.95-3.86 (m, H-5', H-5'''); 3.75-3.71 (m, 3H, H-2, H-2', H-2''); 3.62-3.55 (m, 2H, H-4'', H-5); 3.53-3.46 (m, 13H, H-4', OC*H*$_3$); 3.25 (s, 3H, OC*H*$_3$); 3.20 (t, 1H, *J* = 9.6 Hz, H-4); 2.93 (t, 1H, *J* = 9.2 Hz, H-4'''); 2.42 (dd, 1H, *J* = 5.2, 12.0 Hz, H-2'''); 1.78 (dt, 1H, *J* = 3.6, 12.0 Hz, H-2'''); 1.34-1.31 (m, 6H, H-6', H-6'''); 1.24 (d, 3H, *J* = 6.4 Hz, H-6); 1.17 (d, 3H, *J* = 6.4 Hz, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.3 (C$_{q,arom}$); 154.5 (*C*O$_{Cbz}$); 139.3, 138.6 (C$_{q,arom}$); 138.5 (*C*H$_{arom}$); 135.4 (C$_{qarom}$); 128.7, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 127.5, 127.4, 118.7 (*C*H$_{arom}$); 99.9 (C-1''); 98.6 (C-1'); 98.4 (C-1'''); 94.9 (C-1); 84.9 (*C*I$_{arom}$); 84.5 (C-4'''); 81.8 (C-4); 81.4 (C-3'); 80.8 (C-2'); 80.1 (C-3); 80.0 (C-2); 79.9 (C-4''); 79.4 (C-4'); 79.1 (C-2''); 76.0 (C-3'''); 75.6 (C-3''); 75.4, 75.1, 69.8 (Ph*C*H$_2$); 69.1 (C-5); 68.8 (C-5'); 68.0 (C-5'''); 67.1 (C-5''); 61.4, 60.8, 59.1, 58.6, 57.9 (O*C*H$_3$); 35.6 (C-2'''); 18.4 (C-6'); 18.3 (C-6'''); 17.9 (C-6); 17.1 (C-6''). IR (thin film, cm^{-1}): 1040, 1098, 1126, 1173, 1192, 1255, 1382, 1455, 1484, 1747, 2933. HRMS calculated for $C_{57}H_{73}IO_{18}Na$ 1195.37338 [M+Na]$^+$; found 1195.37337.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-3,4-di-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl))-4-*O*-benzyl-α-L-rhamnopyranoside (53)



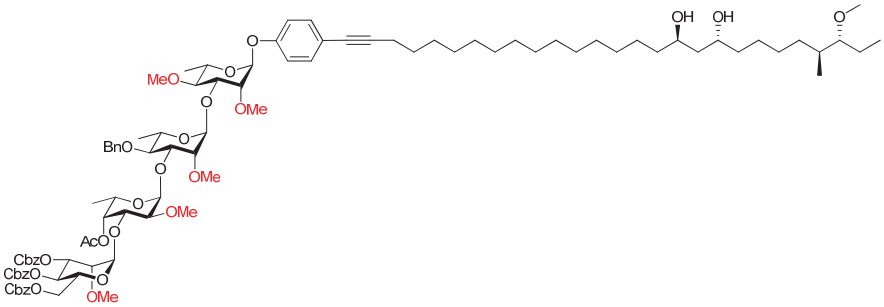
The title compound was synthesized according to general procedure C using **38** (30 mg, 28.3 µmol, 1.0 eq) and phthiocerol (15 mg, 34.0 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 3:7) yielded the title compound (31 mg, 22.4 µmol, 79%) as a yellow oil. $[\alpha]_D^{25}$ = -86.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.22 (m, 22H, C*H*$_{arom}$); 6.97-6.94 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 2.0 Hz, H-1); 5.23-5.19 (m, 2H, H-1'', PhC*H*H); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.85-4.80 (m, 2H, PhC*H*H, PhC*H*H); 4.73 (d, 1H, *J* = 12.4 Hz, PhCH*H*); 4.67-4.63 (m, 2H, PhCH*H*); 4.54 (d, 1H, *J* = 10.8 Hz, PhCH*H*); 4.17 (dd, 1H, *J* = 2.8, 9.6 Hz, H-3); 4.08-4.03 (m, 2H, H-3', H-5''); 3.98-3.91 (m, 4H, H-3'', H-5', C*H*$_{Phth}$); 3.82 (dd, 1H, *J* = 3.6, 10.0 Hz, H-2''); 3.74-3.66 (m, 4H, H-2, H-2', H-4'', H-5); 3.55-3.44 (m, 5H, H-4, H-4', OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.21 (s, 3H, OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.32 (bs, 2H O*H*); 1.56-1.23 (m, 47H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 1.11-1.07 (m, 5H, H-6'', C*H*$_{2,Phth}$); 0.93-0.89 (m, 3H, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.7, 139.3, 139.1, 138.8, 138.3 (C$_{q,arom}$); 133.0 128.5, 128.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 127.5, 127.4 (C*H*$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.1 (C-1''); 98.9 (C-1'); 94.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.7 (C-3'); 80.3 (C-2'); 80.1 (C$_{q,alkyne}$); 80.0 (C-2); 79.9 (C-4); 79.7 (C-3); 78.9 (C-3''); 78.6 (C-2''); 77.8 (C-4''); 75.3, 75.2, 75.0, 72.9 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.7 (C-5'); 67.0 (C-5); 59.1, 59.0 57.9, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.3 (C-6); 18.1 (C-6'); 17.1 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1098, 1233, 1454, 1507, 2853, 2926, 3411. HRMS calculated for $C_{84}H_{120}O_{16}Na$ 1407.84686 $[M+Na]^+$; found 1408.84643.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-3,4-di-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (54)



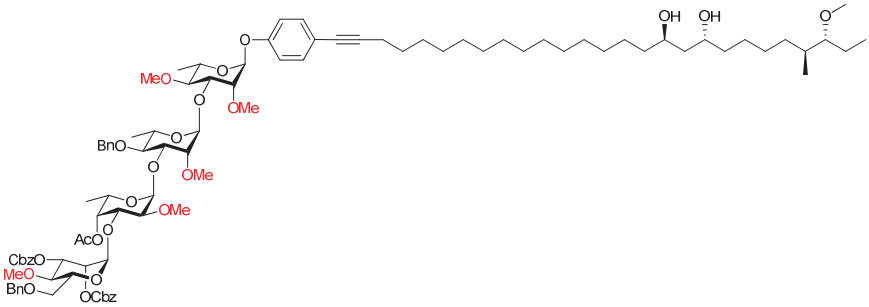
The title compound was synthesized according to general procedure C using **39** (27 mg, 27.3 µmol, 1.0 eq) and phthiocerol (15 mg, 32.8 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the title compound (28 mg, 21.4 µmol, 78%) as a yellow oil. $[\alpha]_D^{25}$ = -83.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.25 (m, 17H, C*H*$_{arom}$); 6.96-6.93 (m, 2H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.19 (m, 2H, H-1", PhC*H*H); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.85 (d, 1H, *J* = 12.4 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 12.4 Hz, PhCH*H*); 4.67 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.55 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.11 (q, 1H, *J* = 6.8 Hz, H-5"); 4.06-3.91 (m, 6H, H-3, H-3', H-3", H-5', C*H*$_{Phth}$); 3.82 (dd, 1H, *J* = 3.6, 10.0 Hz, H-2"); 3.72-3.69 (m, 3H, H-2, H-2', H-4"); 3.60-3.45 (m, 11H, H-4', H-5, OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.20 (t, 1H, *J* = 9.6 Hz, H-4); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.32 (bs, 2H, O*H*$_{Phth}$); 1.62-1.23 (m, 47H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 1.11-1.07 (m, 5H, H-6'', C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.7, 139.2, 139.1 138.7 (C$_{q,arom}$); 133.0, 128.6, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.6, 127.5, 127.5 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.1 (C-1"); 98.7 (C-1'); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 81.9 (C-4); 80.9 (C-2'); 80.6 (C-3'); 80.1 (C$_{q,alkyne}$); 80.1 (C-2); 80.0 (C-3); 79.7 (C-4'); 79.0 (C-3"); 78.6 (C-2"); 77.7 (C-4"); 75.2, 75.0, 73.0 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 66.9 (C-5"); 61.4, 59.2, 59.1, 58.0, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.4 (C-6); 17.9 (C-6'); 17.1 (C-6"); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1099, 1233, 1357, 1454, 1507, 2853, 2926, 3453. HRMS calculated for $C_{78}H_{117}O_{16}$ 1309.83361 $[M+H]^+$; found 1309.83422.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3,4,6-tri-*O*-benzyloxycarbonyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (55)



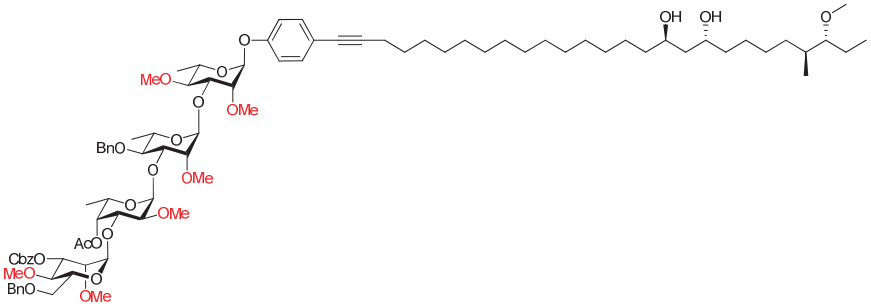
The title compound was synthesized according to general procedure C using **46** (40 mg, 27.7 µmol, 1.0 eq) and phthiocerol (15 mg, 33.2 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:9) yielded the title compound (41 mg, 23.4 µmol, 85%) as a yellow oil. $[\alpha]_D^{25}$ = -53.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.21 (m, 22H, C*H*$_{arom}$); 6.98-6.95 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.27 (d, 1H, *J* = 2.8 Hz, H-4''); 5.23-5.05 (m, 11H, H-1', H-1'', H-1''', H-4''', PhC*H*$_2$, PhC*H*H); 4.93 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3'''); 4.58 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.35-4.29 (m, 3H, H-5'', H-6'''); 4.25 (dd, 1H, *J* = 3.6, 10.4 Hz, H-3''); 4.21-4.16 (m, 1H, H-5'''); 4.07 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.00 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3'); 3.95-3.91 (m, 3H, H-5', C*H*$_{Phth}$); 3.73-3.71 (m, 2H, H-2, H-2'''); 3.69 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 3.64-3.60 (m, 1H, H-5); 3.54-3.48 (m, 8H, H-2'', H-4', OC*H*$_3$); 3.40 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.23-3.18 (m, 4H, H-4, OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.32 (bs, 2H, O*H*$_{Phth}$); 2.18 (s, 3H, C*H*$_{3,Ac}$); 1.62-1.23 (m, 47H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 1.11-1.07 (m, 5H, H-6'', C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 170.9 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 155.1, 154.5, 154.4 (*C*O$_{Cbz}$); 139.2, 135.4, 135.2, 135.1 (C$_{q,arom}$); 133.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.4, 127.4 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.5 (C-1''); 98.8 (C-1'''); 98.5 (C-1'); 94.7 (C-1); 89.6 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.0 (C-4); 81.7 (C-3'); 80.7 (C-2'); 80.2 (C-2); 80.1 (C$_{q,alkyne}$); 79.9 (C-3); 79.4 (C-4'); 78.7 (C-2''); 77.8 (C-2'''); 75.2 (Ph*C*H$_2$); 75.0 (C-3''); 73.8 (C-3''); 72.9 (C-4''); 70.5 (C-4'''); 70.2, 69.8, 69.8 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.1 (C-5); 68.9 (C-5'''); 68.8 (C-5'); 66.4 (C-6'''); 65.4 (C-5''); 61.3, 59.1, 59.0, 58.5, 57.7, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5 (*C*H$_{2,Phth}$); 20.9 (*C*H$_{3,Ac}$); 19.5 (*C*H$_{2,Phth}$); 18.3 (C-6); 18.0 (C-6'); 16.3 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1098, 1128, 1235, 1457, 1507, 1747, 2853, 2927, 3440. HRMS calculated for $C_{97}H_{136}O_{28}Na$ 1771.91103 $[M+Na]^+$; found 1171.91207.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,3-di-*O*-benzyloxycarbonyl-4-*O*-methyl-6-*O*-benzyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (56)



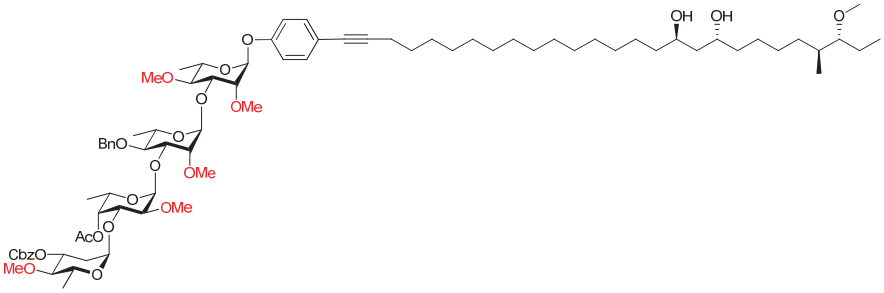
The title compound was synthesized according to general procedure C using **47** (32 mg, 23.3 µmol, 1.0 eq) and phthiocerol (13 mg, 28.0 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the title compound (26 mg, 15.2 µmol, 65%) as a yellow oil. $[\alpha]_D^{25}$ = -82.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.22 (m, 22H, C*H*$_{arom}$); 6.98-6.94 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.2 Hz, H-1); 5.28 (d, 1H, *J* = 1.6 Hz, H-1'''); 5.26 (d, 1H, *J* = 2.8 Hz, H-4''); 5.20-5.15 (m, 5H, H-1', H-1'', H-2''', PhC*H*$_2$); 5.13-5.08 (m, 3H, PhC*H*$_2$, PhC*H*H); 4.99 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3'''); 4.72 (d, 1H, *J* = 12.0 Hz, PhC*H*H); 4.56-4.50 (m, 2H, PhCH*H*, PhCH*H*); 4.32-4.26 (m, 2H, H-3'', H-5''); 4.07 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.01-3.91 (m, 5H, H-3', H-5', H-5''', C*H*$_{Phth}$); 3.80 (dd, 1H, *J* = 4.4, 11.2 Hz, H-6'''); 3.73-3.68 (m, 4H, H-2, H-2', H-4''', H-6'''); 3.64-3.47 (m, 9H, H-2'', H-4', H-5, OC*H*$_3$); 3.42 (s, 3H, OC*H*$_3$); 3.37 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.32 (bs, 2H, O*H*$_{Phth}$); 2.18 (s, 3H, C*H*$_{3,Ac}$); 1.62-1.23 (m, 47H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 1.11-1.07 (m, 5H, H-6'', C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.2 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 171.1 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 154.6, 154.5 (*C*O$_{Cbz}$); 139.1, 138.5, 135.3, 135.0 (C$_{q,arom}$); 133.0, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 127.9, 127.9, 127.6, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.7 (C-1''); 98.6 (C-1'''); 98.4 (C-1'); 94.8 (C-1); 89.6 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.1 (C-4); 81.8 (C-3'); 80.7 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-2); 79.8 (C-3); 79.4 (C-4;); 78.8 (C-2''); 75.8 (C-3'''); 75.4 (PhCH$_2$); 74.2 (C-4'''); 73.6 (C-2'''); 73.5 (Ph*C*H$_2$); 73.0 (C-4''); 72.9 (C-3''); 72.1 (C-5'''); 70.1, 69.9 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 65.3 (C-5''); 61.3, 60.7, 59.1, 58.9, 57.8, 57.5 (OCH$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5 (*C*H$_{2,Phth}$); 20.9 (*C*H$_{3,Ac}$); 19.5 (*C*H$_{2,Phth}$); 18.3 (C-6); 17.9 (C-6'); 16.3 (C-6''); 15.0, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1098, 1235, 1274, 1382, 1455, 1507, 1750, 2853, 2926, 3411. HRMS calculated for $C_{96}H_{136}O_{26}Na$ 1727.92120 $[M+Na]^+$; found 1727.92198.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,4-di-*O*-methyl-3,6-di-*O*-benzyloxycarbonyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (57)



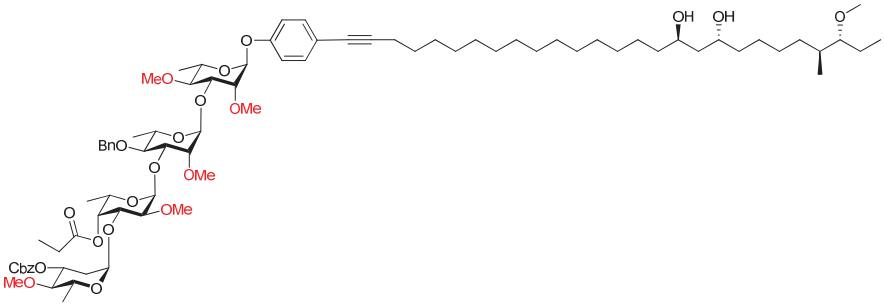
The title compound was synthesized according to general procedure C using **48** (23 mg, 17.6 µmol, 1.0 eq) and phthiocerol (10 mg, 21.1 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:9) yielded the title compound (21 mg, 12.9 µmol, 73%) as a yellow oil. $[\alpha]_D^{25}$ = -64.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.21 (m, 17H, C*H*$_{arom}$); 6.98-6.95 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.26 (d, 1H, *J* = 2.8 Hz, H-4''); 5.21-5.11 (m, 8H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.87 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3'''); 4.57 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.47 (dd, 1H, *J* = 1.8, 11.6 Hz, H-6'''); 4.37-4.31 (m, 2H, H-5'', H-6'''); 4.24 (dd, 1H, *J* = 3.6, 10.0 Hz, H-3''); 4.05 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.02-3.94 (m, 4H, H-3', H-5''', C*H*$_{Phth}$); 3.94-3.91 (m, 1H, H-5'); 3.72 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.69 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2'); 3.65 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'''); 3.63-3.58 (m, 2H, H-4''', H-5); 3.53-3.50 (m, 8H, H-2'', H-4', OC*H*$_3$); 3.41 (s, 3H, OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.24-3.21 (m, 4H, H-4, OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.39-2.26 (4H, C*H*$_{2,Phth}$, O*H*$_{Phth}$); 2.19 (s, 3H, C*H*$_{3,Ac}$); 1.62-1.23 (m, 47H, H-6, H-6', C*H*$_{Phth}$, C*H*$_{2,Phth}$); 1.11-1.07 (m, 5H, H-6'', C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.2 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 170.9 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 155.3, 154.7 (*C*O$_{Cbz}$); 139.2, 135.4 (C$_{q,arom}$); 138.5, 128.7, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 127.4 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.6 (C-1''); 98.6 (C-1'''); 98.5 (C-1'); 94.7 (C-1); 89.6 (*C*H$_{Phth}$); 82.0 (C-4); 81.7 (C-3'); 80.7 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-2); 79.8 (C-3); 79.4 (C-4'); 78.7 (C-2''); 78.3 (C-2'''); 77.5 (C-3'''); 75.2 (Ph*C*H$_2$); 74.4 (C-4'''); 73.5 (C-3''); 73.0 (C-4''); 70.2 (C-5'''); 69.8, 69.7 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 66.9 (C-6'''); 65.3 (C-5''); 61.3, 60.7, 59.1, 59.0, 58.6, 57.8, 57.5 (O*C*H$_3$); 42.4, 37.7 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 32.8, 29.8, 29.8, 29.7, 29.3, 29.1, 29.0, 27.7, 26.3, 25.9, 22.5 (*C*H$_{2,Phth}$); 20.9 (*C*H$_{3,Ac}$); 19.5 (*C*H$_{2,Phth}$); 18.3 (C-6); 17.9 (C-6'); 16.3 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1096, 1128, 1251, 1457, 1507, 1747, 2853, 2926, 3433. HRMS calculated for $C_{90}H_{132}O_{26}Na$ 1651.88990 $[M+Na]^+$; found 1651.89174.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (58)



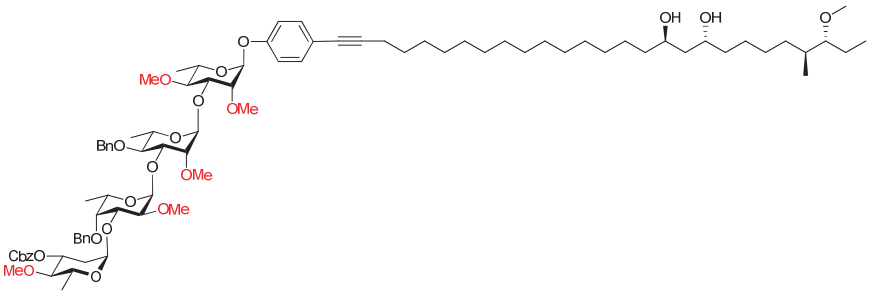
The title compound was synthesized according to general procedure C using **49** (35 mg, 30.8 µmol, 1.0 eq) and phthiocerol (17 mg, 37.0 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:9) yielded the title compound (36 mg, 24.8 µmol, 81%) as a yellow oil. $[\alpha]_D^{25}$ = -71.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.23 (m, 12H, C*H*$_{arom}$); 6.97-6.94 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.23 (d, 1H, *J* = 2.8 Hz, H-4''); 5.20-5.11 (m, 6H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.98-4.92 (m, 1H, H-3'''); 4.56 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.33 (q, 1H, *J* = 6.8 Hz, H-5''); 4.18 (dd, 1H, *J* = 3.8, 10.2 Hz, H-3''); 4.08-4.00 (m, 2H, H-3, H-3'); 3.95-3.85 (m, 4H, H-5', H-5''', C*H*$_{Phth}$); 3.72-3.69 (m, 2H, H-2, H-2'); 3.61-3.46 (m, 15H, H-2'', H-4', H-5, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.27 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.89-2.85 (m, 2H, H-4''', C*H*$_{Phth}$); 2.45-2.25 (m, 5H, H-2''', C*H*$_{2,Phth}$, O*H*$_{Phth}$); 2.20 (s, 3H, C*H*$_{3,Ac}$); 1.71-1.24 (m, 53H, H-2''', H-6, H-6', H-6''', C*H*$_{2,Phth}$); 1.11-1.07 (m, 5H, C*H*$_{2,Phth}$, H-6''); 0.91 (t, 3H, *J* = 7.2 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 171.0 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 154.6 (*C*O$_{Cbz}$); 139.2, 135.4 (C$_{q,arom}$); 133.0, 128.7, 128.6, 128.4, 128.3, 127.6, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 98.7 (C-1'''); 98.4 (C-1'); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.2 (C-4'''); 82.0 (C-4); 81.5 (C-3'); 80.8 (C-2'); 80.1 (C$_{q,alkyne}$); 80.1 (C-2); 79.8 (C-3); 79.5 (C-4'); 78.7 (C-2''); 75.4 (C-3'''); 75.2 (Ph*C*H$_2$); 73.4 (C-4''); 73.2 (C-3''); 69.7 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 67.6 (C-5'''); 65.5 (C-5''); 61.3, 60.3, 59.1, 58.9, 57.8, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 35.7 (C-2'''); 34.9 (*C*H$_{Phth}$); 32.7, 29.8, 29.8, 29.7, 29.3, 29.1, 28.9, 27.7, 26.3, 25.9, 22.5 (*C*H$_{2,Phth}$); 21.0 (*C*H$_{3,Ac}$); 19.5 (*C*H$_{2,Phth}$); 18.3 (C-6'); 18.1 (C-6'''); 17.9 (C-6); 16.5 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1098, 1235, 1256, 1507, 1744, 2853, 2928, 3449. HRMS calculated for $C_{81}H_{124}O_{22}Na$ 1471.84765 $[M+Na]^+$; found 1471.84802.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-propionyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (59)



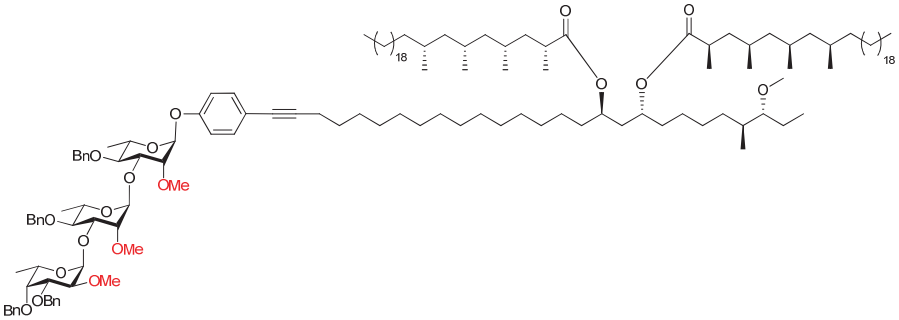
The title compound was synthesized according to general procedure C using **51** (35 mg, 30.9 µmol, 1.0 eq) and phthiocerol (17 mg, 37.1 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the title compound (37 mg, 25.3 µmol, 82%) as a yellow oil. $[\alpha]_D^{25}$ = -60.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.23 (m, 12H, C*H*$_{arom}$); 6.98-6.94 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.24 (dd, 1H, *J* = 2.8, 3.6 Hz, H-4''); 5.20-5.13 (m, 5H, H-1', H-1'', PhC*H*$_2$, PhC*H*H); 5.11 (d, 1H, *J* = 2.8 Hz, H-1'''); 4.96-4.90 (m, 1H, H-3'''); 4.56 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.33 (q, 1H, *J* = 7.2 Hz, H-5''); 4.18 (dd, 1H, *J* = 3.6, 9.6 Hz, H-3''); 4.07-4.00 (m, 2H, H-3, H-3'); 3.95-3.85 (m, 4H, H-5', H-5''', C*H*$_{Phth}$); 3.72-3.69 (m, 2H, H-2, H-2'); 3.61-3.57 (m, 1H, H-5); 3.54-3.45 (m, 14H, H-2'', H-4', OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$); 3.27 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.90-2.85 (m, 2H, H-4''', C*H*$_{Phth}$); 2.54-2.38 (m, 7H, H-2''', COC*H*$_2$CH$_3$, C*H*$_{2,Phth}$, O*H*$_{Phth}$); 1.77-1.07 (m, 53H, H-2''', H-6, H-6', H-6'', H-6''', COCH$_2$C*H*$_3$, C*H*$_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C*H*$_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C*H*$_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 174.4 (*C*O$_{propionyl}$); 155.7 (C$_{q,arom}$); 154.6 (*C*O$_{Cbz}$); 139.2, 135.4 (C$_{q,arom}$); 133.0, 128.7, 128.6, 128.4, 128.3, 128.3, 127.6, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 98.7 (C-1'''); 98.4 (C-1'); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.1 (C-4'''); 82.0 (C-4); 81.4 (C-3'); 80.8 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-2); 79.8 (C-3); 79.5 (C-4'); 78.7 (C-2''); 75.3 (C-3'''); 75.2 (Ph*C*H$_2$); 73.5 (C-3''); 73.1 (C-4''); 69.6 (Ph*C*H$_2$); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 67.5 (C-5'''); 65.6 (C-5''); 61.3, 60.1, 59.1, 59.0, 57.9, 57.5 (O*C*H$_3$); 42.4, 37.6 (*C*H$_{2,Phth}$); 35.7 (C-2'''); 34.9 (*C*H$_{Phth}$); 32.7, 29.8, 29.8, 29.7, 29.3, 29.1, 28.9 (*C*H$_{2,Phth}$); 27.8 (*C*H$_{2,Propionyl}$); 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.3 (C-6'); 18.1 (C-6'''); 17.9 (C-6); 16.5 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$), 9.7 (*C*H$_{3,Propionyl}$). IR (thin film, cm^{-1}): 1043, 1099, 1256, 1382, 1457, 1507, 1744, 2855, 2928, 3454. HRMS calculated for $C_{82}H_{126}O_{22}Na$ 1485.86330 [M+Na]$^+$; found 1485.86337.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (60)



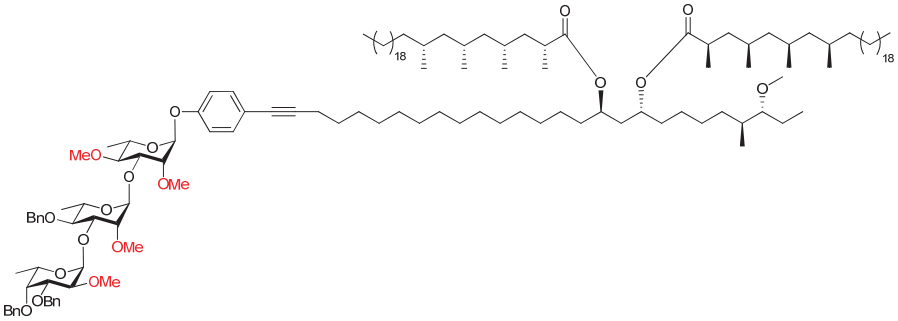
The title compound was synthesized according to general procedure C using **50** (39 mg, 34.1 µmol, 1.0 eq) and phthiocerol (19 mg, 40.9 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the title compound (51 mg, 34.1 µmol, 100%) as a yellow oil. $[\alpha]_D^{25}$ = -53.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.26 (m, 17H, C*H*$_{arom}$); 6.83 (dd, 2H, *J* = 1.8, 7.0 Hz, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.24 (d, 1H, *J* = 2.8 Hz, H-1'''); 5.18-5.11 (m, 6H, H-1', H-1'', H-3''' PhCH_2, PhC*H*H); 5.06 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.64 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.57 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.23-4.17 (m, 2H, H-3'', H-5''); 4.06-3.86 (m, 6H, H-3, H-3', H-5', H-5''', C*H*$_{Phth}$); 3.75-3.71 (m, 3H, H-2, H-2', H-2''); 3.62-3.55 (m, 2H, H-4'', H-5); 3.52-3.46 (m, 13H, H-4', OCH_3); 3.34 (s, 3H, OCH_3); 3.25 (s, 3H, OCH_3); 3.20 (t, 1H, *J* = 9.6 Hz, H-4); 2.93 (t, 1H, *J* = 9.2 Hz, H-4'''); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.42 (dd, 1H, *J* = 5.2, 12.0 Hz, H-2'''); 2.42-2.36 (m, 5H, H-2''', C$H_{2,Phth}$, O*H*$_{Phth}$); 1.79-1.62 (m, 3H, H-2''', C$H_{2,Phth}$); 1.59-1.10 (m, 53H, H-2''', H-6, H-6', H-6'', H-6''', C$H_{2,Phth}$); 0.91 (t, 3H, *J* = 7.4 Hz, C$H_{3,Phth}$); 0.83 (d, 3H, *J* = 6.8 Hz, C$H_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 155.7 (C$_{q,arom}$); 154.5 (*C*O$_{Cbz}$); 139.3, 138.6, 135.4 (C$_{q,arom}$); 128.7, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 127.4 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 98.6 (C-1'); 98.3 (C-1'''); 94.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.5 (C-4'''); 81.9 (C-4); 81.4 (C-3'); 80.8 (C-2'); 80.1 (C-3); 80.1 (C-2); 79.9 (C-4''); 79.4 (C-4'); 79.1 (C-2''); 76.0 (C-3'''); 75.6 (C-3''); 75.4, 75.1, 69.7 (Ph*C*H_2); 69.6, 69.6 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 68.0 (C-5'''); 67.1 (C-5''); 61.4, 60.8, 59.0, 58.6, 57.9; 57.5 (OCH_3); 42.4, 37.6 (*C*H$_{2,Phth}$); 35.6 (C-2'''); 34.9 (*C*H$_{Phth}$); 32.7, 29.8, 29.8, 29.7, 29.3, 29.1, 28.9, 27.7, 26.3, 25.9, 22.5, 19.5 (*C*H$_{2,Phth}$); 18.4 (C-6'); 18.2 (C-6'''); 17.9 (C-6); 17.0 (C-6''); 14.9, 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1040, 1099, 1455, 1507, 1749, 2853, 2928, 3436. HRMS calculated for $C_{86}H_{128}O_{21}Na$ 1519.88403 $[M+Na]^+$; found 1519.88543.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-3,4-di-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl))-4-*O*-benzyl-α-L-rhamnopyranoside (61)



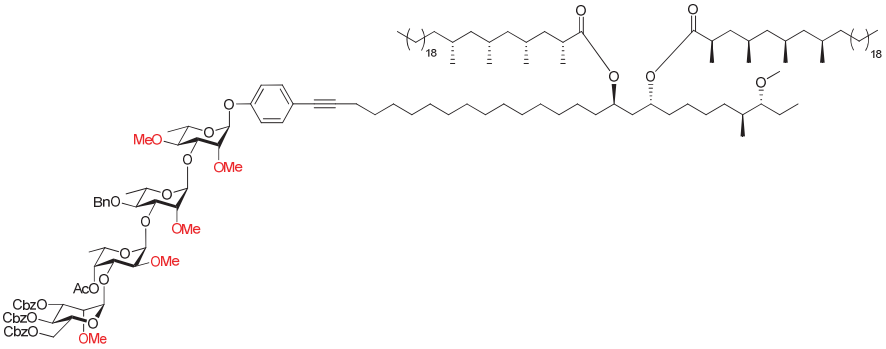
The title compound was synthesized according to general procedure D using **53** (30 mg, 21.7 µmol, 1.0 eq), mycocerosic acid (31 mg, 65.0 µmol, 3.0 eq), DIC (20 µL, 130 µmol, 6.0 eq) and DMAP (24 mg, 195 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 7:3) yielded the title compound (30 mg, 14.3 µmol, 66%) as a waxy solid. $[\alpha]_D^{25}$ = -82.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.22 (m, 22H, C*H*$_{arom}$); 6.95 (d, 2H, *J* = 8.8 Hz, CH$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.23-5.19 (m, 2H, H-1'', PhC*H*H); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.89-4.80 (m, 4H, PhC*H*H, PhC*H*H, C*H*$_{Phth}$); 4.73 (d, 1H, *J* = 12.0 Hz, PhCH*H*); 4.67-4.63 (m, 2H, PhCH*H,* PhCH*H*); 4.54 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.19 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.09-4.03 (m, 2H, H-3', H-5''); 3.98-3.89 (m, 2H, H-3'', H-5'); 3.82 (dd, 1H, *J* = 3.6, 10.4 Hz, H-2''); 3.77-3.66 (m, 4H, H-2, H-2', H-4'', H-5); 3.56-3.44 (m, 5H, H-4, H-4', OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.21 (s, 3H, OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.57-2.48 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 1.75-0.81 (m, 220H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.7, 139.3, 139.1, 138.8 (C$_{q,arom}$); 133.0 128.8, 128.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 127.5, 127.4 (C*H*$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.1 (C-1''); 98.9 (C-1'); 94.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.7 (C-3'); 80.3 (C-2'); 80.1 (C$_{q,alkyne}$); 80.0 (C-2); 79.9 (C-4); 79.7 (C-3); 78.9 (C-3''); 78.6 (C-2''); 77.9 (C-4''); 75.4, 75.2, 75.0, 72.9 (PhC*H*$_2$); 70.4 (*C*H$_{Phth}$); 69.0 (C-5); 68.7 (C-5'); 67.0 (C-5); 59.1, 59.0 57.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.4 (*C*H$_{2,Phth}$); 30.2 (*C*H$_{Myc}$); 30.1, 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'); 18.1 (C-6); 17.1 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1099, 1175, 1233, 1378, 1457, 1507, 1733, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-3,4-di-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (62)



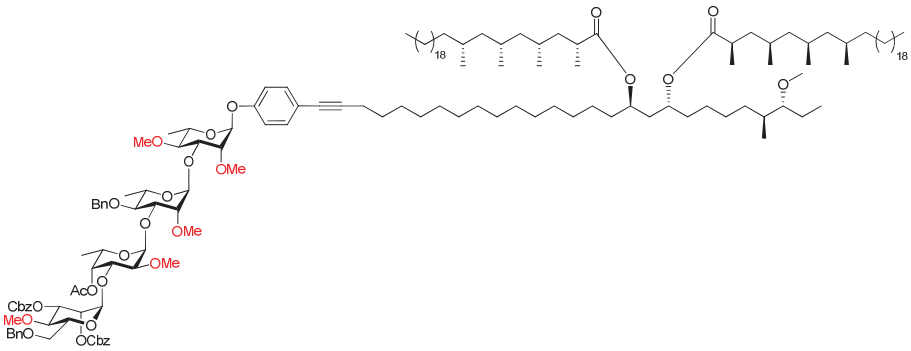
The title compound was synthesized according to general procedure D using **54** (26 mg, 19.9 µmol, 1.0 eq), mycocerosic acid (29 mg, 59.6 µmol, 3.0 eq), DIC (18 µL, 119 µmol, 6.0 eq) and DMAP (22 mg, 179 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 7:3) yielded the title compound (30 mg, 13.4 µmol, 68%) as a waxy solid. $[\alpha]_D^{25}$ = -57.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.25 (m, 17H, C*H*$_{arom}$); 6.95 (d, 2H, *J* = 8.8 Hz, CH$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.10 (m, 2H, H-1'', PhC*H*H); 5.15 (d, 1H, *J* = 1.6 Hz, H-1'); 5.00 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.87-4.69 (m, 3H, PhC*H*H, C*H*$_{Phth}$); 4.67 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.55 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.11 (q, 1H, *J* = 6.8 Hz, H-5''); 4.06-3.91 (m, 4H, H-3, H-3', H-3'', H-5'); 3.82 (dd, 1H, *J* = 3.6, 10.4 Hz, H-2''); 3.72-3.69 (m, 3H, H-2, H-2', H-4''); 3.62-3.55 (m, 1H, H-5); 3.53-3.45 (m, 10H, H-4', OC*H*$_3$); 3.39 (s, 3H, OC*H*$_3$); 3.32 (s, 3H, OC*H*$_3$); 3.20 (t, 1H, *J* = 9.6 Hz, H-4); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.57-2.48 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 1.75-0.81 (m, 218H, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$, H-6, H-6', H-6''). ^{13}C-APT NMR (101 MHz) δ: 176.1, 176.1 (*C*O$_{Myc}$); 155.7, 139.3, 139.1 138.7 (C$_{q,arom}$); 133.0, 128.6, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.6, 127.5, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.1 (C-1''); 98.8 (C-1'); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 81.9 (C-4); 80.9 (C-2'); 80.7 (C-3'); 80.1 (C-2); 80.1 (C-3); 79.7 (C-4'); 79.0 (C-3''); 78.6 (C-2''); 77.7 (C-4''); 75.2, 75.0, 73.0 (PhC*H*$_2$); 70.4 (*C*H$_{Phth}$); 69.0 (C-5); 68.8 (C-5'); 66.9 (C-5''); 61.4, 59.2, 59.1, 58.0, 57.5 (OC*H*$_3$); 45.6, 45.4 (C*H*$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.3 (*C*H$_{2,Phth}$); 30.2 (*C*H$_{Myc}$); 30.1, 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.4 (C-6'); 17.9 (C-6); 17.1 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1100, 1175, 1233, 1378, 1507, 1733, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3,4,6-tri-*O*-benzyloxycarbonyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (62)



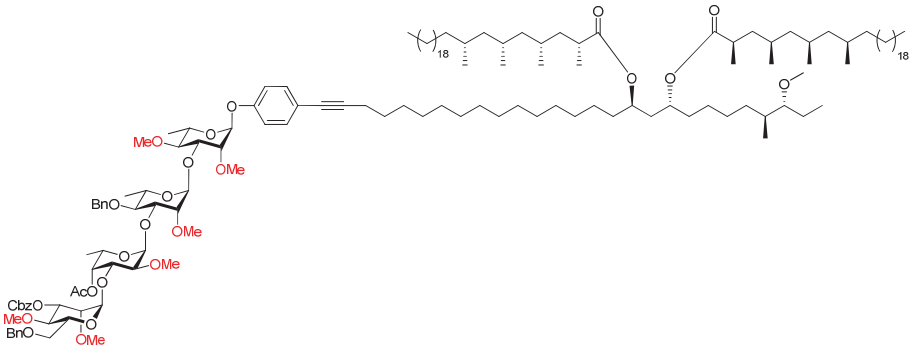
The title compound was synthesized according to general procedure D using **55** (34 mg, 19.4 µmol, 1.0 eq), mycocerosic acid (28 mg, 58.3 µmol, 3.0 eq), DIC (18 µL, 117 µmol, 6.0 eq) and DMAP (21 mg, 175 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 6:4) yielded the title compound (28 mg, 10.5 µmol, 54%) as a waxy solid. $[\alpha]_D^{25}$ = -48.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.21 (m, 22H, C*H*$_{arom}$); 6.98-6.95 (m, 2H, C*H*$_{arom}$); 5.50 (d, 1H, *J* = 1.6 Hz, H-1); 5.27 (d, 1H, *J* = 2.8 Hz, H-4''); 5.23-5.05 (m, 11H, H-1', H-1'', H-1''', H-4''', PhC*H*$_2$, PhC*H*H); 4.93 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3'''); 4.89-4.80 (m, 2H, C*H*$_{Phth}$); 4.58 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.35-4.29 (m, 3H, H-5'', H-6'''); 4.25 (dd, 1H, *J* = 3.6, 10.0 Hz, H-3''); 4.20-4.16 (m, 1H, H-5'''); 4.07 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.00 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3'); 3.95-3.91 (m, 3H, H-5', C*H*$_{Phth}$); 3.73-3.71 (m, 2H, H-2, H-2'''); 3.69 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'); 3.64-3.60 (m, 1H, H-5); 3.54-3.48 (m, 8H, H-2'', H-4', OC*H*$_3$); 3.40 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.23-3.18 (m, 4H, H-4, OC*H*$_3$); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H C*H*$_{Myc}$); 2.38 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 2.18 (s, 3H, C*H*$_{3,Ac}$); 1.75-0.81 (m, 198H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 170.9 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 155.1, 154.5, 154.4 (*C*O$_{Cbz}$); 139.2, 135.4, 135.2, 135.1 (C$_{q,arom}$); 133.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.4 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.5 (C-1''); 98.8 (C-1'''); 98.5 (C-1'); 94.7 (C-1); 89.6 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.0 (C-4); 81.7 (C-3'); 80.7 (C-2'); 80.2 (C-2); 80.1 (C$_{q,alkyne}$); 79.9 (C-3); 79.4 (C-4'); 78.7 (C-2''); 77.8 (C-2'''); 75.2 (Ph*C*H$_2$); 75.0 (C-3''); 73.8 (C-3''); 72.9 (C-4''); 70.5 (C-4'''); 70.4 (*C*H$_{Phth}$); 70.2, 69.8, 69.8 (Ph*C*H$_2$); 69.0 (C-5); 69.0 (C-5'''); 68.8 (C-5'); 66.4 (C-6'''); 65.4 (C-5''); 61.3, 59.2, 59.0, 58.5, 57.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'); 18.0 (C-6); 16.3 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1019, 1045, 1099, 1129, 1175, 1235, 1378, 1457, 1507, 1744, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,3-di-*O*-benzyloxycarbonyl-4-*O*-methyl-6-*O*-benzyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside



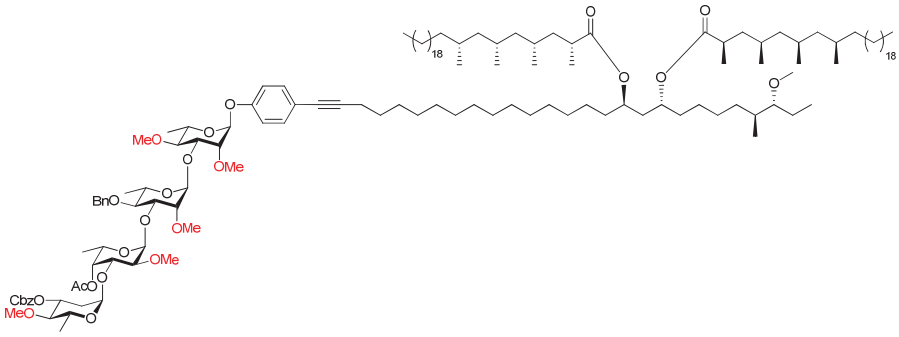
The title compound was synthesized according to general procedure D using **56** (26 mg, 15.2 µmol, 1.0 eq), mycocerosic acid (22 mg, 45.7 µmol, 3.0 eq), DIC (14 µL, 91.4 µmol, 6.0 eq) and DMAP (17 mg, 137 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 6:4) yielded the title compound (26 mg, 9.88 µmol, 65%) as a waxy solid. $[\alpha]_D^{25}$ = -47.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.22 (m, 22H, C*H*$_{arom}$); 6.98-6.94 (m, 2H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.28 (d, 1H, *J* = 2.0 Hz, H-1'''); 5.26 (d, 1H, *J* = 3.6 Hz, H-4''); 5.20-5.15 (m, 5H, H-1', H-1'', H-2''', PhC*H*$_2$); 5.13-5.08 (m, 3H, PhC*H*$_2$, PhC*H*H); 4.99 (dd, 1H, *J* = 3.0, 9.8 Hz, H-3'''); 4.88-4.80 (m, 2H, C*H*$_{Phth}$); 4.72 (d, 1H, *J* = 12.0 Hz, PhC*H*H); 4.56-4.50 (m, 2H, PhCH*H*, PhCH*H*); 4.32-4.26 (m, 2H, H-3'', H-5''); 4.07 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3); 4.02-3.91 (m, 3H, H-3', H-5', H-5'''); 3.80 (dd, 1H, *J* = 4.0, 11.2 Hz, H-6'''); 3.73-3.68 (m, 4H, H-2, H-2', H-4''', H-6'''); 3.63-3.47 (m, 9H, H-2'', H-4', H-5, OC*H*$_3$); 3.42 (s, 3H, OC*H*$_3$); 3.37 (s, 3H, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.4 Hz, H-4); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.21 (s, 3H, C*H*$_{3,Ac}$); 1.75-0.81 (m, 198H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 171.1 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 154.6, 154.5 (*C*O$_{Cbz}$); 139.1, 138.5, 135.3, 135.0 (C$_{q,arom}$); 133.0, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 127.9, 127.9, 127.6, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.7 (C-1''); 98.6 (C-1'''); 98.4 (C-1'); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 82.1 (C-4); 81.8 (C-3'); 80.7 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-2); 79.8 (C-3); 79.4 (C-4;); 78.8 (C-2''); 75.8 (C-3'''); 75.4 (Ph*C*H$_2$); 74.2 (C-4'''); 73.7 (C-2'''); 73.6 (Ph*C*H$_2$); 73.0 (C-4''); 72.9 (C-3''); 72.1 (C-5'''); 70.4 (*C*H$_{Phth}$); 70.1, 69.9 (Ph*C*H$_2$); 69.0 (C-5); 68.8 (C-5'); 65.3 (C-5''); 61.3, 60.7, 59.1, 58.9, 57.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9 (*C*H$_{3,Ac}$); 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'); 17.9 (C-6); 16.3 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1045, 1099, 1173, 1235, 1275, 1378, 1507, 1749, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,4-di-*O*-methyl-3,6-di-*O*-benzyloxycarbonyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (65)



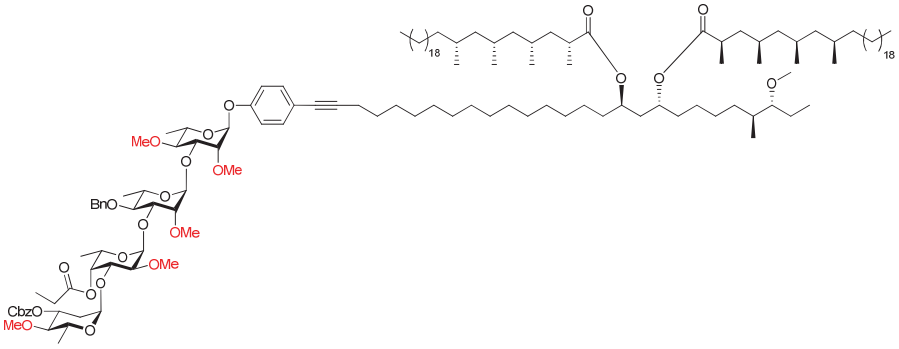
The title compound was synthesized according to general procedure D using **57** (20 mg, 12.3 µmol, 1.0 eq), mycocerosic acid (18 mg, 36.8 µmol, 3.0 eq), DIC (11 µL, 73.6 µmol, 6.0 eq) and DMAP (14 mg, 110 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the title compound (16 mg, 6.37 µmol, 52%) as a waxy solid. $[\alpha]_D^{25}$ = -86.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.21 (m, 17H, C*H*$_{arom}$); 6.96 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.26 (d, 1H, *J* = 3.2 Hz, H-4''); 5.20-5.11 (m, 8H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.88-4.83 (m, 3H, H-3''', C*H*$_{Phth}$); 4.57 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.47 (dd, 1H, *J* = 1.8, 11.8 Hz, H-6'''); 4.37-4.31 (m, 2H, H-5'', H-6'''); 4.24 (dd, 1H, *J* = 3.4, 10.2 Hz, H-3''); 4.06 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 4.02-3.94 (m, 2H, H-3', H-5'''); 3.94-3.91 (m, 1H, H-5'); 3.72 (dd, 1H, *J* = 2.0, 3.2 Hz, H-2); 3.69 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2'); 3.65 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2'''); 3.66-3.58 (m, 2H, H-4''', H-5); 3.53-3.50 (m, 8H, H-2'', H-4', OC*H*$_3$); 3.41 (s, 6H, OC*H*$_3$); 3.34 (s, 3H, OC*H*$_3$);); 3.33 (s, 3H, OC*H*$_3$); 3.24-3.18 (m, 4H, H-4, OC*H*$_3$); 2.86-2.82 (m, 1H, C*H*$_{Phth}$); 2.55-2.50 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.19 (s, 3H, C*H*$_{3,Ac}$); 1.75-0.81 (m, 222H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, (*C*O$_{Myc}$); 171.0 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 155.3, 154.7 (*C*O$_{Cbz}$); 139.2, 135.4 (C$_{q,arom}$); 133.0, 128.7, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 127.5, 127.4 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.6 (C-1''); 98.6 (C-1'''); 98.5 (C-1'); 94.7 (C-1); 89.6 (*C*H$_{Phth}$); 82.1 (C-4); 81.7 (C-3'); 80.7 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-2); 79.9 (C-3); 79.4 (C-4'); 78.7 (C-2''); 78.3 (C-2'''); 77.5 (C-3'''); 75.2 (Ph*C*H$_2$); 74.4 (C-4'''); 73.5 (C-3''); 73.0 (C-4''); 70.4 (*C*H$_{Phth}$); 70.2 (C-5'''); 69.8, 69.7 (Ph*C*H$_2$); 69.0 (C-5); 68.8 (C-5'); 66.9 (C-6'''); 65.3 (C-5''); 61.3, 60.7, 59.1, 59.0, 58.6, 57.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9 (*C*H$_{3,Ac}$); 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'); 18.0 (C-6); 16.3 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1098, 1129, 1175, 1252, 1378, 1457, 1507, 1740, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (66)



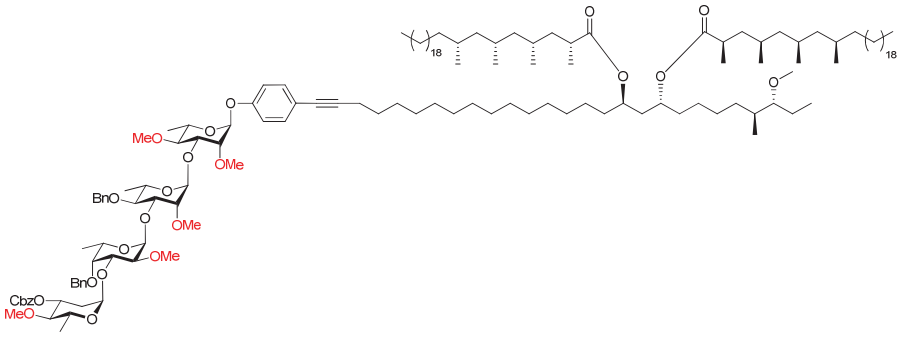
The title compound was synthesized according to general procedure D using **58** (29 mg, 20.3 µmol, 1.0 eq), mycocerosic acid (29 mg, 60.8 µmol, 3.0 eq), DIC (19 µL, 122 µmol, 6.0 eq) and DMAP (22 mg, 183 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 6:4) yielded the title compound (25 mg, 10.5 µmol, 52%) as a waxy solid. $[\alpha]_D^{25}$ = -41.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.39-7.23 (m, 12H, C*H*$_{arom}$); 6.96 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.49 (*s*, 1H, H-1); 5.23 (d, 1H, *J* = 3.2 Hz, H-4''); 5.20-5.11 (m, 6H, H-1', H-1'', H-1''', PhC*H*$_2$, PhC*H*H); 4.97-4.92 (m, 1H, H-3'''); 4.89-4.80 (m, 2H, C*H*$_{Phth}$); 4.56 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.33 (q, 1H, *J* = 7.2 Hz, H-5''); 4.18 (dd, 1H, *J* = 3.4, 10.2 Hz, H-3''); 4.06 (dd, 1H, *J* = 2.8, 9.2 Hz, H-3''); 4.06 (dd, 1H, *J* = 2.8, 9.2 Hz, H-3); 4.02 (dd, 1H, *J* = 3.0, 9.2 Hz, H-3'); 3.95-3.85 (m, 2H, H-5', H-5'''); 3.72-3.70 (m, 2H, H-2, H-2'); 3.63-3.46 (m, 15H, H-2'', H-4', H-5, OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.27 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.89-2.85 (m, 2H, H-4''', C*H*$_{Phth}$); 2.54-2.51 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.30 (dd, 1H, *J* = 4.4, 12.2 Hz, H-2'''); 2.20 (s, 3H, C*H*$_{3,Ac}$); 1.75-0.81 (m, 206H, H-2''', H-6, H-6', H-6'', H-6''', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2 (*C*O$_{Myc}$); 171.0 (*C*O$_{Ac}$); 155.7 (C$_{q,arom}$); 154.6 (*C*O$_{Cbz}$); 139.2, 135.4 (C$_{q,arom}$); 133.0, 128.7, 128.6, 128.4, 128.3, 127.6, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 98.7 (C-1'''); 98.5 (C-1'); 94.7 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.2 (C-4'''); 82.1 (C-4); 81.5 (C-3'); 80.8 (C-2'); 80.1 (C$_{q,alkyne}$); 80.1 (C-2); 79.9 (C-3); 79.5 (C-4'); 78.7 (C-2''); 75.4 (C-3'''); 75.2 (Ph*C*H$_2$); 73.4 (C-4''); 73.2 (C-3''); 70.4 (*C*H$_{Phth}$); 69.7 (Ph*C*H$_2$); 69.0 (C-5); 68.8 (C-5'); 67.7 (C-5'''); 65.5 (C-5''); 61.3, 60.3, 59.1, 58.9, 57.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 35.7 (C-2'''); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 21.0 (*C*H$_{3,Ac}$); 20.9, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'); 18.1 (C-6'''); 17.9 (C-6); 16.5 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1100, 1175, 1235, 1258, 1378, 1457, 1507, 1736, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-propionyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (67)



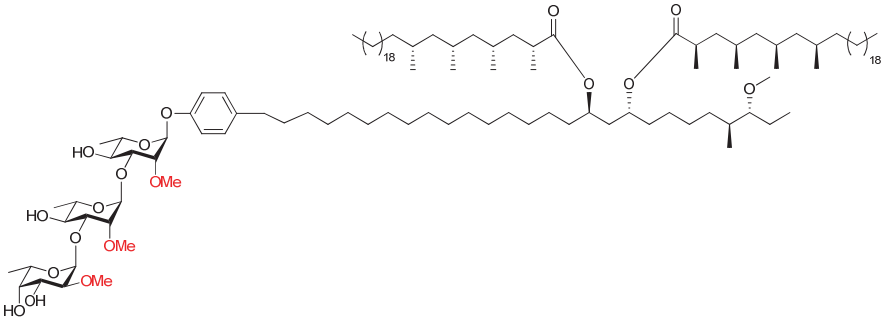
The title compound was synthesized according to general procedure D using **59** (29 mg, 19.6 µmol, 1.0 eq), mycocerosic acid (28 mg, 58.8 µmol, 3.0 eq), DIC (18 µL, 118 µmol, 6.0 eq) and DMAP (22 mg, 176 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 6:4) yielded the title compound (28 mg, 11.7 µmol, 60%) as a waxy solid. $[\alpha]_D^{25}$ = -41.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.38-7.26 (m, 12H, C*H*$_{arom}$); 6.96 (d, 2H, *J* = 8.8 Hz, CH_{arom}); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.24 (d, 1H, *J* = 2.8 Hz, H-4''); 5.24 (dd, 1H, *J* = 2.8, 3.6 Hz, H-4''); 5.20-5.13 (m, 5H, H-1', H-1'', PhC*H*$_2$, PhC*H*H); 5.10 (d, 1H, *J* = 2.8 Hz, H-1'''); 4.96-4.83 (m, 3H, H-3''', C*H*$_{Phth}$); 4.56 (d, 1H, *J* = 11.2 Hz, PhCH*H*); 4.33 (q, 1H, *J* = 7.6 Hz, H-5''); 4.18 (dd, 1H, *J* = 3.4, 10.2 Hz, H-3''); 4.08-4.00 (m, 2H, H-3, H-3'); 3.95-3.85 (m, 2H, H-5', H-5'''); 3.72-3.69 (m, 2H, H-2, H-2'); 3.63-3.59 (m, 1H, H-5); 3.54-3.45 (m, 14H, H-2'', H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.27 (s, 3H, OC*H*$_3$); 3.21 (t, 1H, *J* = 9.6 Hz, H-4); 2.89-2.84 (m, 2H, H-4''', C*H*$_{Phth}$); 2.54-2.42 (m, 4H, C*H*$_{Myc}$, COC*H*$_2$CH$_3$); 2.35 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 2.29 (dd, 1H, *J* = 5.2, 11.6 Hz, H-2'''); 1.75-0.81 (m, 193H, H-2''', H-6, H-6', H-6'', H-6''', COCH$_2$C*H*$_3$, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc}$, C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 174.4 (*C*O$_{propionyl}$); 155.7 (C$_{q,arom}$); 154.6 (*C*O$_{Cbz}$); 139.2, 135.4 (C$_{q,arom}$); 133.0, 128.7, 128.6, 128.4, 128.3, 128.3, 127.6, 127.5 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 98.7 (C-1'''); 98.5 (C-1'); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.1 (C-4'''); 82.1 (C-4); 81.5 (C-3'); 80.8 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-2); 79.8 (C-3); 79.5 (C-4'); 78.7 (C-2''); 75.3 (C-3'''); 75.2 (Ph*C*H$_2$); 73.5 (C-3''); 73.1 (C-4''); 70.4 (*C*H$_{Phth}$); 69.7 (Ph*C*H$_2$); 69.0 (C-5); 68.8 (C-5'); 67.6 (C-5'''); 65.6 (C-5''); 61.3, 60.1, 59.1, 59.0, 57.9, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 35.8 (C-2'''); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.9 (*C*H$_{2,Propionyl}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$);18.3 (C-6'); 18.1 (C-6'''); 17.9 (C-6); 16.5 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$); 9.7 (*C*H$_{3,Propionyl}$). IR (thin film, cm^{-1}): 1043, 1100, 1129, 1175, 1256, 1379, 1464, 1507, 1736, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(3-*O*-benzyloxycarbonyl-4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (68)



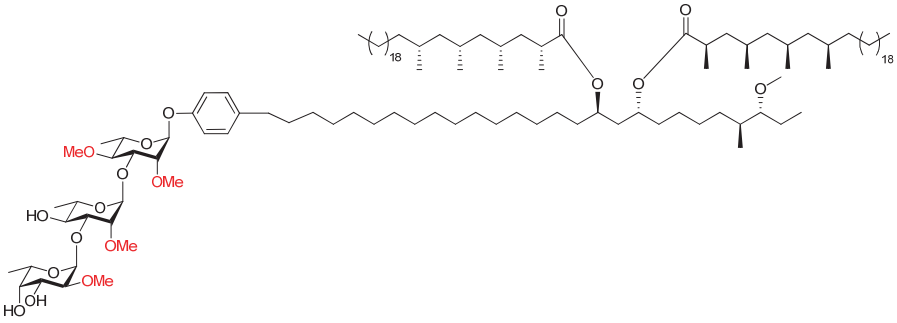
The title compound was synthesized according to general procedure D using **60** (37 mg, 24.3 µmol, 1.0 eq), mycocerosic acid (35 mg, 72.9 µmol, 3.0 eq), DIC (23 µL, 146 µmol, 6.0 eq) and DMAP (27 mg, 219 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 6:4) yielded the title compound (38 mg, 15.3 µmol, 63%) as a waxy solid. $[\alpha]_D^{25}$ = -35.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.45-7.26 (m, 17H, C*H*$_{arom}$); 6.95 (d, 2H, *J* = 9.2 Hz, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.24 (d, 1H, *J* = 2.4 Hz, H-1'''); 5.18-5.11 (m, 6H, H-1', H-1'', H-3''', PhC*H*$_2$, PhC*H*H); 5.06 (d, 1H, *J* = 11.6 Hz, PhC*H*H); 4.89-4.80 (m, 2H, C*H*$_{Phth}$); 4.64 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.57 (d, 1H, *J* = 11.6 Hz, PhCH*H*); 4.23-4.17 (m, 2H, H-3'', H-5''); 4.06-3.86 (m, 4H, H-3, H-3', H-5', H-5'''); 3.75-3.71 (m, 3H, H-2, H-2', H-2''); 3.62-3.57 (m, 2H, H-4'', H-5); 3.52-3.42 (m, 13H, H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.24 (s, 3H, OC*H*$_3$); 3.20 (t, 1H, *J* = 9.6 Hz, H-4); 2.93 (t, 1H, *J* = 9.2 Hz, H-4'''); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.54-2.51 (m, 2H, C*H*$_{Myc}$); 2.42-2.36 (m, 3H, H-2''', C*H*$_{2,Phth}$); 1.75-0.81 (m, 206H, H-2''', H-6, H-6', H-6'', H-6''', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 155.7 (C$_{q,arom}$); 154.5 (*C*O$_{Cbz}$); 139.4, 138.6, 135.4 (C$_{q,arom}$); 128.7, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 127.4 (*C*H$_{arom}$); 118.1 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 98.6 (C-1'); 98.4 (C-1'''); 94.8 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 84.5 (C-4'''); 81.9 (C-4); 81.4 (C-3'); 80.9 (C-2'); 80.2 (C$_{q,alkyne}$); 80.1 (C-3); 80.1 (C-2); 79.9 (C-4''); 79.4 (C-4'); 79.2 (C-2''); 76.0 (C-3'''); 75.7 (C-3''); 75.4, 75.1 (Ph*C*H$_2$); 70.4 (*C*H$_{Phth}$); 69.8 (Ph*C*H$_2$); 69.0 (C-5); 68.8 (C-5'); 68.0 (C-5'''); 67.1 (C-5''); 61.4, 60.9, 59.0, 58.6, 57.9; 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8 (*C*H$_{2,Myc}$); 35.6 (C-2'''); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,Phth}$); 18.6 (*C*H$_{3,Myc}$); 18.4 (C-6'); 18.3 (C-6'''); 17.9 (C-6); 17.1 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1040, 1100, 1128, 1175, 1256, 1507, 1734, 2853, 2923. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (69)



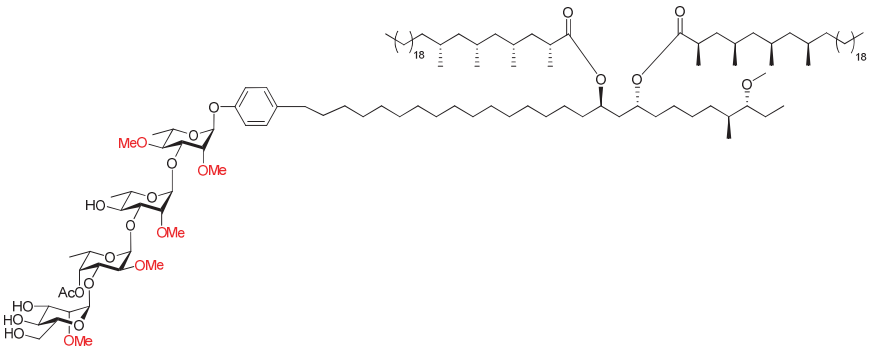
Compound **61** (28 mg, 12.1 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (20 mg, 10.2 µmol, 84%) as a pale oil. $[\alpha]_D^{25}$ = -42.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.99 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.2 Hz, H-1); 5.21 (d, 1H, *J* = 1.2 Hz, H-1'); 5.15 (d, 1H, *J* = 3.6 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.22 (q, 1H, *J* = 6.4 Hz, H-5''); 4.08-4.03 (m, 2H, H-3, H-3''); 3.94-3.87 (m, 1H, H-5'); 3.83 (d, 1H, *J* = 2.4 Hz, H-4''); 3.81-3.75 (m, 4H, H-2, H-3', H-5', O*H*); 3.72-3.63 (m, 3H, H-2', H-4, H-4'); 3.55-3.44 (m, 10H, H-2'', OCH_3); 3.33 (s, 3H, OCH_3); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.57-2.50 (m, 5H, C*H*$_{2,Phth}$, C*H*$_{Myc}$, O*H*); 1.77-0.80 (m, 222H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2, 176.2 (*C*O$_{Myc}$); 154.7, 137.1 (C$_{q,arom}$); 129.5, 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 99.3 (C-1'); 95.0 (C-1); 86.8 (*C*H$_{Phth}$); 83.1 (C-3'); 80.3 (C-2 and C-2'); 80.3 (C-3); 79.5 (C-2''); 72.0 (C-4''); 71.7 (C-4'); 71.6 (C-4); 70.4 (*C*H$_{Phth}$); 69.9 (C-3''); 69.2 (C-5); 69.1 (C-5'); 66.7 (C-5''); 59.4, 58.7, 58.7, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6) 17.9 (C-6'); 16.5 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1036, 1098, 1129, 1173, 1378, 1464, 1508, 1734, 2853, 2923, 3427. HRMS calculated for $C_{120}H_{225}O_{18}$ 1955.67196 $[M+H]^+$; found 1955.67197.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-O-(2-*O*-methyl-α-L-fucopyranosyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (70)



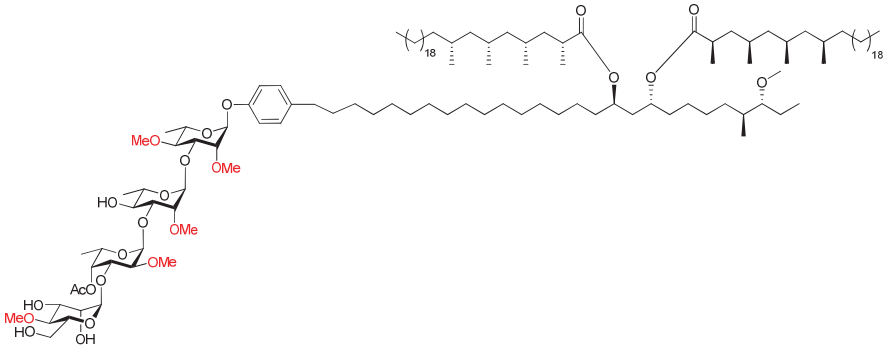
Compound **62** (28 mg, 12.5 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (15 mg, 7.6 µmol, 61%) as a pale oil. $[\alpha]_D^{25}$ = -55.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.09 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.2 Hz, H-1); 5.19 (d, 1H, *J* = 1.2 Hz, H-1'); 5.14 (d, 1H, *J* = 4.0 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.25 (q, 1H, *J* = 6.4 Hz, H-5''); 4.12 (dd, 1H, *J*= 3.4, 9.8 Hz, H-3); 4.06 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3''); 3.91-3.86 (m, 1H, H-5'); 3.83 (d, 1H, *J* = 2.8 Hz, H-4''); 3.78 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3'); 3.73-3.61 (m, 3H, H-2, H-2', H-4', H-5); 3.56-3.45 (m, 13H, H-2'', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.23 (t, 1H, *J* = 9.6 Hz, H-4); 2.88-2.84 (m, 1H, C*H*$_{Phth}$); 2.72 (bs, 1H, O*H*); 2.56-2.48 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.41 (bs, 1H, O*H*); 1.77-0.81 (m, 221H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 154.6, 137.0 (C$_{q,arom}$); 129.4, 116.2 (*C*H$_{arom}$); 99.8 (C-1''); 99.4 (C-1'); 95.1 (C-1); 86.8 (*C*H$_{Phth}$); 83.0 (C-3'); 82.4 (C-4); 80.6, 80.5 (C-2 and C-2'); 79.5 (C-2''); 79.3 (C-3) 72.0 (C-4''); 71.7 (C-4'); 70.4 (*C*H$_{Phth}$); 69.9 (C-3''); 69.1 (C-5); 68.9 (C-5'); 66.5 (C-5''); 61.2, 59.4, 58.7, 58.7, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.5, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.0 (C-6) 18.0 (C-6'); 16.5 (C-6''); 14.8 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1100, 1132, 1173, 1229, 1378, 1461, 1510, 1734, 2853, 2923, 3421. HRMS calculated for $C_{121}H_{227}O_{18}Na$ 1969.68761 $[M+H]^+$; found 1969.68743.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (71)



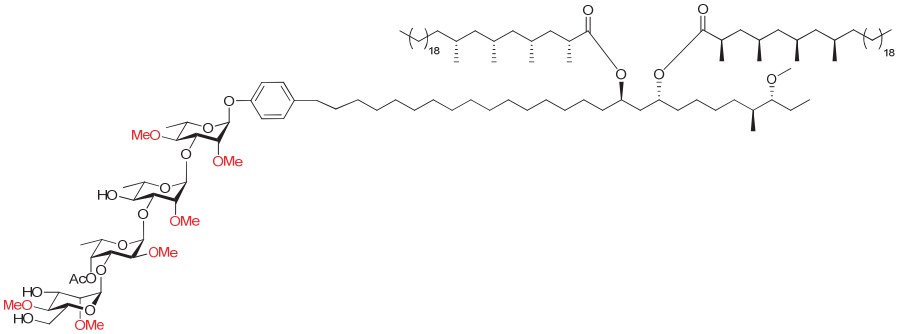
Compound **63** (22 mg, 8.2 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (16 mg, 7.3 µmol, 89%) as a pale oil. $[\alpha]_D^{25}$ = -37.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz) δ: 7.09 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 9.0 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.5 Hz, H-1); 5.26 (d, 1H, *J* = 2.5 Hz, H-4''); 5.21-5.20 (m, 2H, H-1', H-1'''); 5.12 (d, 1H, *J* = 3.5 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.3 Hz, C*H*$_{Phth}$); 4.31 (q, 1H, *J* = 6.5 Hz, H-5''); 4.22 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3'''); 4.12 (dd, 1H, *J* = 3.3, 9.8 Hz, H-3); 3.92-3.85 (m, 2H, H-5', H-6'''); 3.83-3.77 (m, 2H, H-3', H-6'''); 3.73-3.44 (m, 24H, H-2, H-2', H-2'', H-2''', H-3''', H-4', H-4''', H-5, H-5''', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.27 (t, 1H, *J* = 9.5 Hz, H-4); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.56-2.48 (m, 4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.17 (s, 3H, C*H*$_{3,Ac}$); 1.76-0.81 (m, 185H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (125 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 170.9 (*C*O$_{Ac}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 100.5 (C-1''); 99.3 (C-1'); 98.3 (C-1'''); 95.1 (C-1); 86.8 (*C*H$_{Phth}$); 83.5 (C-3'); 82.4 (C-4); 80.7 (C-2'); 80.5 (C-2); 80.2 (C-2'''); 79.7 (C-2''); 79.2 (C-3); 74.3 (C-3''); 73.4 (C-4''); 72.5 (C-5'''); 71.7 (C-4'); 71.4 (C-3'''); 70.4 (*C*H$_{Phth}$); 69.4 (C-4'''); 69.0 (C-5'); 68.9 (C-5); 65.9 (C-5''); 62.8 (C-6'''); 61.2, 59.8, 59.1, 58.9, 58.7, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 35.0 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.4 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 21.0 (*C*H$_{3,Ac}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.0 (C-6) 18.0 (C-6'); 16.4 (C-6''); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1040, 1073, 1100, 1135, 1173, 1233, 1378, 1464, 1510, 1734, 2853, 2923, 3429. HRMS calculated for $C_{130}H_{240}O_{24}$ 2187.76665 $[M+H]^+$; found 2187.76668.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-*O*-methyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (72)



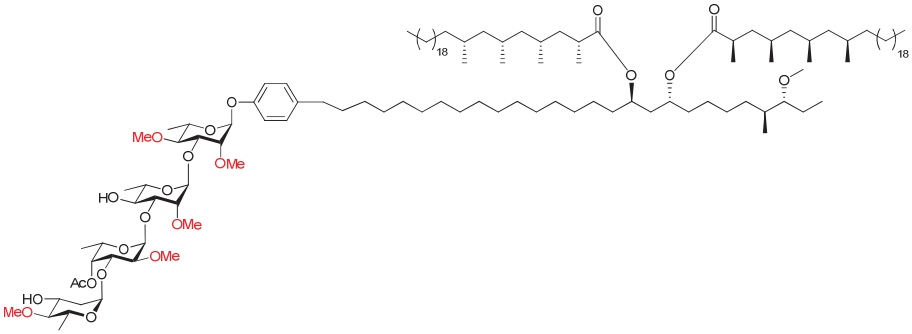
Compound **64** (23 mg, 8.7 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (15 mg, 6.9 µmol, 78%) as a pale oil. $[\alpha]_D^{25}$ = -37.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz) δ: 7.09 (d, 2H, *J* = 9.0 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.5 Hz, H-1); 5.23 (d, 1H, *J* = 3.0 Hz, H-4''); 5.20 (s, 1H, H-1'); 5.13-5.12 (m, 2H, H-1'', H-1'''); 4.84 (quint, 2H, *J* = 6.5 Hz, C*H*$_{Phth}$); 4.29 (q, 1H, *J* = 6.6 Hz, H-5''); 4.21 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3''); 4.11 (dd, 1H, *J* = 3.3, 9.8 Hz, H-3); 4.00-3.95 (m, 2H, H-2''', O*H*); 3.91-3.85 (m, 2H, H-5', H-6'''); 3.79-3.77 (m, 3H, H-3', H-3''', H-6'''); 3.71-3.62 (m, 5H, H-2, H-2', H-4, H-5, H-5'''); 3.59-3.46 (m, 14H, H-2'', H-4''', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.22 (t, 1H, *J* = 9.8 Hz, H-4); 3.04 (bs 1H, O*H*); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.56-2.50 (4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.15 (s, 3H, C*H*$_{3,Ac}$); 1.76-0.81 (m, 186H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (125 MHz) δ: 176.1 (*C*O$_{Myc}$); 170.8 (*C*O$_{Ac}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 101.5 (C-1''); 100.3 (C-1'''); 99.1 (C-1'); 95.1 (C-1); 86.8 (*C*H$_{Phth}$); 83.3 (C-3'); 82.4 (C-4); 80.6 (C-2); 80.5 (C-2'); 79.5 (C-2''); 79.3 (C-3); 77.0 (C-4'''); 74.0 (C-3''); 73.3 (C-4''); 72.4 (C-5'''); 71.5 (C-4'); 71.2 (C-3'''); 71.1 (C-2'''); 70.4 (*C*H$_{Phth}$); 69.4 (C-4'''); 69.1 (C-5'); 68.8 (C-5); 65.9 (C-5''); 62.0 (C-6'''); 61.2, 60.6, 59.6, 59.1, 58.4, 57.5 (O*C*H$_3$); 45.7, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 35.0 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.4 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 21.0 (*C*H$_{3,Ac}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.1 (C-6) 18.0 (C-6'); 16.4 (C-6''); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1099, 1129, 1175, 1235, 1378, 1461, 1510, 1736, 2853, 2923, 3410. HRMS calculated for $C_{130}H_{240}O_{24}$ 2187.76665 $[M+H]^+$; found 2187.76633.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2,4-di-*O*-methyl-α-D-mannopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (73)



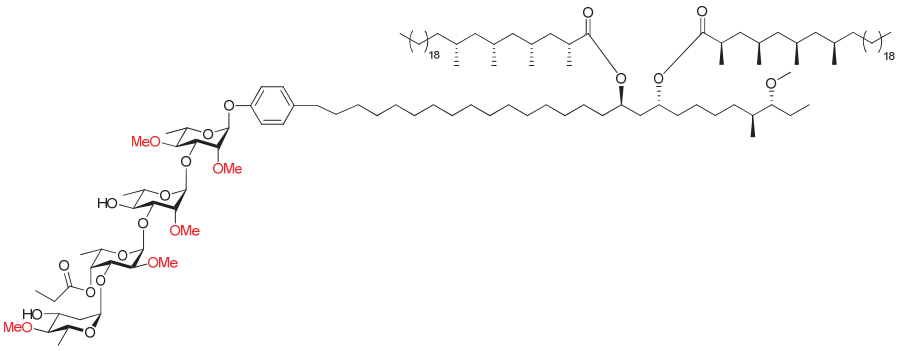
Compound **65** (13 mg, 5.2 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (10 mg, 4.5 µmol, 88%) as a pale oil. $[\alpha]_D^{25}$ = -41.0 ° (c = 0.5, $CHCl_3$). ^{1}H-NMR (500 MHz) δ: 7.09 (d, 2H, *J* = 9.0 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.5 Hz, H-1); 5.24 (d, 1H, *J* = 2.5 Hz, H-4''); 5.19 (d, 1H, *J* = 1.0 Hz, H-1'''); 5.16 (d, 1H, *J* = 1.5 Hz, H-1'); 5.12 (d, 1H, *J* = 4.0 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.5 Hz, C*H*$_{Phth}$); 4.29 (q, 1H, *J* = 6.8 Hz, H-5''); 4.19 (dd, 1H, *J* = 3.5, 10.0 Hz, H-3''); 4.12 (dd, 1H, *J* = 3.0, 9.5 Hz, H-3); 3.99-3.86 (m, 2H, H-5', H-6''');; 3.91-3.85 (m, 2H, H-5', H-6'''); 3.79-3.61 (m, 8H, H-2, H-2', H-3', H-3''', H-4', H-5, H-5''', H-6'''); 3.59-3.52 (m, 16H, H-2'', OC*H*$_3$); 3.48-3.47 (m, 4H, H-2''', OC*H*$_3$); 3.23 (t, 1H, *J* = 9.5 Hz, H-4); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.56-2.50 (4H, C*H*$_{2,Phth}$, C*H*$_{Myc}$); 2.39 (bs, 1H, OH); 2.22 (t, 1H, *J* = 7.8 Hz, O*H*); 2.15 (s, 3H, C*H*$_{3,Ac}$); 1.75-0.81 (m, 224H, H-6, H-6', H-6'', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc}$, C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (125 MHz) δ: 176.1 (*C*O$_{Myc}$); 170.7 (*C*O$_{Ac}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 100.6 (C-1''); 99.4 (C-1'); 98.4 (C-1'''); 95.1 (C-1); 86.8 (*C*H$_{Phth}$); 83.5 (C-3'); 82.4 (C-4); 80.7 (C-2'); 80.7 (C-2'''); 80.5 (C-2); 79.7 (C-2''); 79.2 (C-3); 78.0 (C-4'''); 74.6 (C-3''); 73.2 (C-4''); 72.2 (C-3'''); 71.8 (C-4'); 71.1 (C-5'''); 70.4 (*C*H$_{Phth}$); 69.4 (C-4'''); 69.0 (C-5'); 68.9 (C-5); 66.0 (C-5''); 62.4 (C-6'''); 61.2, 60.6, 59.8, 59.1, 58.9, 58.7, 57.5 (O*C*H$_3$); 45.7, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 35.0 (*C*H$_{Phth}$); 34.9, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.4 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 21.0 (*C*H$_{3,Ac}$); 20.9, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.0 (C-6) 18.0 (C-6'); 16.4 (C-6''); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1096, 1173, 1233, 1378, 1464, 1510, 1734, 2853, 2923, 3424. HRMS calculated for $C_{131}H_{243}O_{24}$ 2201.78230 $[M+H]^+$; found 2201.78198.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-acetyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (74)



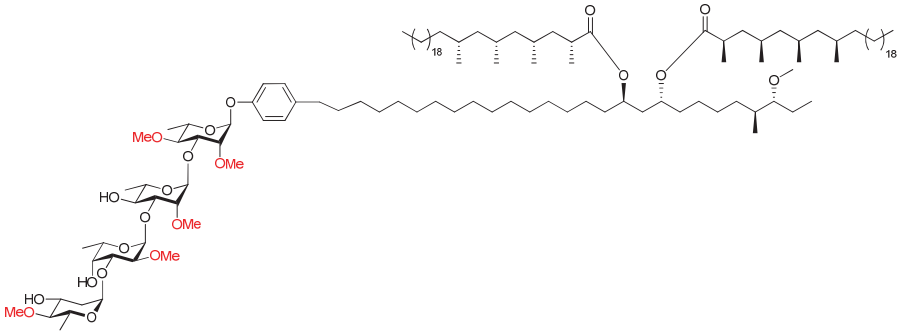
Compound **66** (18 mg, 7.6 μmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (14 mg, 6.5 μmol, 86%) as a pale oil. $[\alpha]_D^{25}$ = -38.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz) δ: 7.09 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.18-5.17 (m, 2H, H-1', H-4''); 5.09-5.08 (m, 2H, H-1'', H-1'''); 4.84 (quint, 2H, *J* = 6.5 Hz, C*H*$_{Phth}$); 4.29 (q, 1H, *J* = 6.8 Hz, H-5''); 4.16-4.11 (m, 2H, H-3, H-3''); 3.88-3.82 (m, 2H, H-3''', H-5'); 3.79-3.74 (m, 3H, H-3', H-5'''); 3.71-3.68 (m, 2H, H-2, H-5); 3.63-3.62 (m, 2H, H-2', H-4'); 3.57-3.47 (m, 16H, H-2'', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.23 (t, 1H, *J* = 9.5 Hz, H-4); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.70 (t, 1H, *J* = 9.0 Hz, H-4'''); 2.55-2.50 (m, 4H, C*H*$_{Myc,}$ C*H*$_{2,Phth}$); 2.16-2.12 (m, 4H, H-2''', C*H*$_{3,Ac}$); 1.76-0.81 (m, 197H, H-2''', H-6, H-6', H-6'', H-6''', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (125 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 170.7 (*C*O$_{Ac}$); 154.6, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 101.0 (C-1''); 99.5 (C-1'); 99.4 (C-1'''); 95.2 (C-1); 88.1 (C-4'''); 86.8 (*C*H$_{Phth}$); 83.6 (C-3'); 82.5 (C-4); 80.7 (C-2'); 80.5 (C-2); 79.7 (C-2''); 79.0 (C-3); 74.1 (C-3''); 73.7 (C-4''); 71.7 (C-4'); 70.4 (*C*H$_{Phth}$); 69.1 (C-5'); 68.9 (C-5); 68.0 (C-3'''); 67.7 (C-5'''); 66.1 (C-5''); 61.2, 60.4, 60.0, 59.1, 58.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 37.7, 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.5 (*C*H$_{2,Phth}$); 30.2 (*C*H$_{Myc}$); 30.1, 29.9, 29.9, 29.8, 29.7, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 21.0 (*C*H$_{3,Ac}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'''); 18.0 (C-6) 18.0 (C-6'); 16.5 (C-6''); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1132, 1173, 1233, 1378, 1464, 1510, 1734, 2853, 2923, 3440. HRMS calculated for $C_{130}H_{240}O_{22}Na$ 2177.75877 [M+Na]$^+$; found 2177.75981.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-4-*O*-propionyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (75)



Compound **67** (20 mg, 8.4 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (15 mg, 6.9 µmol, 83%) as a pale oil. $[\alpha]_D^{25}$ = -37.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz) δ: 7.09 (d, 2H, *J* = 9.0 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.5 Hz, H-1); 5.19-5.18 (m, 2H, H-1', H-4''); 5.09-5.08 (m, 2H, H-1'', H-1'''); 4.84 (quint, 2H, *J* = 6.5 Hz, C*H*$_{Phth}$); 4.29 (q, 1H, *J* = 6.8 Hz, H-5''); 4.16-4.11 (m, 2H, H-3, H-3''); 3.88-3.81 (m, 2H, H-3''', H-5'); 3.77-3.73 (m, 3H, H-3', H-5'''); 3.71-3.68 (m, 2H, H-2, H-5); 3.65-3.62 (m, 2H, H-2', H-4'); 3.57-3.47 (m, 16H, H-2'', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.23 (t, 1H, *J* = 9.8 Hz, H-4); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.70 (t, 1H, *J* = 9.3 Hz, H-4'''); 2.55-2.50 (m, 4H, C*H*$_{Myc,}$ C*H*$_{2,Phth}$); 2.44 (dq, 2H, *J* = 2.2, 7.5 Hz, COC*H*$_2$CH$_3$); 2.34 (bs, 1H, O*H*); 2.13 (dd, 1H, *J* = 5.0, 12.0 Hz, H-2''); 1.76-0.81 (m, 197H, H-2''', H-6, H-6', H-6'', H-6''', COCH$_2$C*H*$_3$, C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (125 MHz) δ: 176.2, 176.1 (*C*O$_{Myc}$); 174.2 (*C*O$_{Propionyl}$); 154.6, 137.0 (C$_{q,arom}$); 129.4, 116.3 (*C*H$_{arom}$); 101.0 (C-1''); 99.5 (C-1'); 99.4 (C-1'''); 95.2 (C-1); 88.0 (C-4'''); 86.8 (*C*H$_{Phth}$); 83.6 (C-3'); 82.5 (C-4); 80.7 (C-2'); 80.5 (C-2); 79.7 (C-2''); 79.0 (C-3); 74.4 (C-3''); 73.4 (C-4''); 71.8 (C-4'); 70.4 (*C*H$_{Phth}$); 69.1 (C-5'); 68.9 (C-5); 67.9 (C-3'''); 67.6 (C-5'''); 66.1 (C-5''); 61.2, 60.2, 60.0, 59.1, 58.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 37.8, 36.8, 35.3 (*C*H$_{2,Myc}$); 34.9 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.8 (CO*C*H$_2$CH$_3$); 27.6 (*C*H$_{2,Phth}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.3 (C-6'''); 18.0 (C-6) 18.0 (C-6'); 16.5 (C-6''); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$); 9.7 (COCH$_2$*C*H$_3$). IR (thin film, cm^{-1}): 1042, 1100, 1132, 1175, 1231, 1378, 1462, 1510, 1736, 2853, 2923, 3464. HRMS calculated for $C_{130}H_{240}O_{24}Na$ 2191.77442 [M+Na]$^+$; found 2191.77772.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-9,11-diyl bismycocerosate)phenyl 2,4-di-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(2-*O*-methyl-3-*O*-(4-*O*-methyl-2,6-dideoxy-α-D-glucopyranosyl)-α-L-fucopyranosyl) -α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (76)



Compound **68** (31 mg, 12.8 µmol, 1.0 eq) was hydrogenated using general procedure E to give the title compound (27 mg, 12.8 µmol, 100%) as a pale oil. $[\alpha]_D^{25}$ = -31.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz) δ: 7.09 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 6.97 (d, 2H, *J* = 8.5 Hz, C*H*$_{arom}$); 5.46 (d, 1H, *J* = 1.5 Hz, H-1); 5.17-5.16 (m, 2H, H-1', H-1'''); 5.06 (d, 1H, *J* = 4.0 Hz, H-1''); 4.84 (quint, 2H, *J* = 6.5 Hz, C*H*$_{Phth}$); 4.29 (q, 1H, *J* = 6.8 Hz, H-5''); 4.11 (dd, 1H, *J* = 3.3, 9.8 Hz, H-3''); 4.03 (dd, 1H, *J* = 3.0, 10.0 Hz, H-3); 4.00-3.95 (m, 1H, H-3'''); 3.88-3.83 (m, 1H, H-5'); 3.79-3.60 (m, 9H, H-2, H-2', H-3', H-4', H-4'', H-5, H-5''', O*H*); 3.60-3.45 (m, 16H, H-2'', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.23 (t, 1H, *J* = 9.8 Hz, H-4); 2.87-2.84 (m, 1H, C*H*$_{Phth}$); 2.74 (t, 1H, *J* = 9.3 Hz, H-4'''); 2.55-2.50 (m, 4H, C*H*$_{Myc,}$ C*H*$_{2,Phth}$); 2.36 (bs, 1H, O*H*); 2.24-2.18 (m, 2H, H-2''', O*H*); 1.76-0.81 (m, 209H, H-2''', H-6, H-6', H-6'', H-6''', C*H*$_{Phth}$, C*H*$_{2,Phth}$, C*H*$_{3,Phth}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (125 MHz) δ: 176.1 (*C*O$_{Myc}$); 154.6, 137.0 (C$_{q,arom}$); 129.4, 116.3 (*C*H$_{arom}$); 101.0 (C-1''); 99.6 (C-1'); 99.3 (C-1'''); 95.2 (C-1); 88.0 (C-4'''); 86.8 (*C*H$_{Phth}$); 83.5 (C-3'); 82.4 (C-4); 80.8 (C-2'); 80.5 (C-2); 79.0 (C-3); 78.9 (C-2''); 77.2 (C-3''); 72.4 (C-4''); 71.8 (C-4'); 70.4 (*C*H$_{Phth}$); 69.1 (C-5'); 68.9 (C-3'''); 68.7 (C-5); 68.1 (C-5'''); 66.4 (C-5''); 61.2, 61.2, 60.0, 59.2, 58.8, 57.5 (O*C*H$_3$); 45.6, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,Phth}$); 37.9, 37.9 (*C*H$_{Myc}$); 36.8, 35.3 (*C*H$_{2,Myc}$); 35.0 (*C*H$_{Phth}$); 34.8, 32.8 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Myc}$); 31.9, 30.2 (*C*H$_{2,Phth}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.6 (*C*H$_{2,Phth}$); 27.4 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,Phth}$); 22.8 (*C*H$_{2,Myc}$); 22.5 (*C*H$_{2,Phth}$); 20.9, 20.6, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.4 (C-6'''); 18.0 (C-6) 18.0 (C-6'); 16.4 (C-6''); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Myc}$); 10.3 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1036, 1100, 1132, 1175, 1232, 1378, 1464, 1510, 1734, 2853, 2923, 3446. HRMS calculated for $C_{128}H_{240}O_{24}Na$ 2135.74820 [M+Na]$^+$; found 2135.74993.

References:

1. Buhler, V. B. & Pollak, A. Human Infection with Atypical Acid-Fast Organisms: Report of Two Cases with Pathologic Findings. *Am. J. Clin. Pathol.* **23**, 363–374 (1953).
2. Shitrit, D. *et al.* Differentiation of Mycobacterium kansasii infection from Mycobacterium tuberculosis infection: comparison of clinical features, radiological appearance, and outcome. *Eur. J. Clin. Microbiol. Infect. Dis.* **26**, 679–684 (2007).
3. Matveychuk, A., Fuks, L., Priess, R., Hahim, I. & Shitrit, D. Clinical and radiological features of Mycobacterium kansasii and other NTM infections. *Respir. Med.* **106**, 1472–1477 (2012).
4. Gommans, E. P. A. T. *et al.* Risk factors for mortality in patients with pulmonary infections with non-tuberculous mycobacteria: A retrospective cohort study. *Respir. Med.* **109**, 137–145 (2015).
5. Hernández-Garduño, E., Rodrigues, M. & Elwood, R. K. The incidence of pulmonary non-tuberculous mycobacteria in British Columbia, Canada. *Int. J. Tuberc. Lung Dis.* **13**, 1086–93 (2009).
6. van Ingen, J. *et al.* Clinical relevance of non-tuberculous mycobacteria isolated in the Nijmegen-Arnhem region, The Netherlands. *Thorax* **64**, 502–506 (2009).
7. Prevots, D. R. & Marras, T. K. Epidemiology of Human Pulmonary Infection with Nontuberculous Mycobacteria. *Clin. Chest Med.* **36**, 13–34 (2015).
8. Falkinham, J. O. Nontuberculous mycobacteria in the environment. *Clin. Chest Med.* **23**, 529–51 (2002).
9. von Reyn, C. F. *et al.* Isolation of Mycobacterium avium complex from water in the United States, Finland, Zaire, and Kenya. *J. Clin. Microbiol.* **31**, 3227–3230 (1993).
10. Saleem, N., Saba, R., Maddika, S. & Weinstein, M. Mycobacterium kansasii Infection in a Patient Receiving Biologic Therapy—Not All Reactive Interferon Gamma Release Assays Are Tuberculosis. *Am. J. Med. Sci.* **353**, 394–397 (2017).
11. Steadham, J. E. High-catalase strains of Mycobacterium kansasii isolated from water in Texas. *J. Clin. Microbiol.* **11**, 496–498 (1980).
12. Prevots, D. R. & Marras, T. K. Epidemiology of Human Pulmonary Infection with Nontuberculous Mycobacteria. *Clin. Chest Med.* **36**, 13–34 (2015).
13. Jankute, M. *et al.* The role of hydrophobicity in tuberculosis evolution and pathogenicity. *Sci. Rep.* **7**, 1–10 (2017).
14. Falkinham, J. O. Mycobacterial Aerosols and Respiratory Disease. *Emerg. Infect. Dis.* **9**, 763–767 (2003).
15. Smith, D. W., Randall, H. M., Gastambide-Odier, M. M. & Koevoet, A. L. The Characterization of Mycobacterial Strains by the Composition of their Lipid Extracts. *Ann. N. Y. Acad. Sci.* **69**, 145–157 (1957).
16. Smith, D. W., Randall, H. M., MacLennan, A. P. & Lederer, E. Mycosides: A new class of type-specific glycolipids of mycobacteria. *Nature* **186**, 887–888 (1960).
17. Gastambide-Odier, M. & Villé, C. [Deoxysugars isolated from mycoside A: identification of acetyl derivatives of methyl 2,4-DI-O-methyl-rhamnopyranoside, 2-O-methyl-rhamofuranoside, 3-O-methyl-rhamnofuranoside, 2-O-methyl-fucopyranoside and 3-O-methyl-fucofuranoside]. *Bull. Soc. Chim. Biol. (Paris).* **52**, 679–93 (1970).
18. Gastambide-Odier, M., Sarda, P. & Lederer, E. Structure des aglycones des mycosides A et B. *Tetrahedron Lett.* **6**, 3135–3143 (1965).
19. Gastambide-Odier, M. & Sarda, P. Contribution à l'étude de la structure et de la biosynthèse de glycolipides spécifiques isolés de mycobactéries: les mycosides A et B. *Pneumonol. Pneumonol.* **142**, 241–255 (1970).

20. Smith, D. W. & Randall, H. M. Mycosides of mycobacteria. *Am. Rev. Respir. Dis.* **92**, 34–41 (1965).

21. GILLERON, M., VENISSE, A., RIVIÈRE, M., SERVIN, P. & PUZO, G. Carbohydrate epitope structural elucidation by 1H-NMR spectroscopy of a new Mycobacterium kansasii phenolic glycolipid antigen. *Eur. J. Biochem.* **193**, 449–457 (1990).

22. GILLERON, M. *et al.* Structural and immunological properties of the phenolic glycolids from Mycobacterium gastri and Mycobacterium kansasii. *Eur. J. Biochem.* **189**, 167–173 (1990).

23. Watanabe, M., Aoyagi, Y., Ohta, A. & Minnikin, D. E. Structures of phenolic glycolipids from Mycobacterium kansasii. *Eur. J. Biochem.* **248**, 93–98 (1997).

24. Fournief, J.-J., Rivieres, M., Papas, F. & Puzou, G. THE JOURNAL OF BIOLOGICAL CHEMISTRY Structural Elucidation of the Major Phenolic Glycolipid from Mycobacterium kansasii 11. PRESENCE OF A NOVEL DIDEOXYHEXOSE* X+(1-3)2-0-Me-4-O-Ac-Fucp(1-3) .2-0-Me-Rhap(l-3)2,4-di-O-Me-Rhapl-pbenolglycol. **262**, 3180–3184 (1987).

25. Rivière, M., Fournié, J. J. & Puzo, G. A novel mannose containing phenolic glycolipid from Mycobacterium kansasii. *J. Biol. Chem.* **262**, 14879–14884 (1987).

26. Fournie, J. J., Riviere, M., Papa, F. & Puzo, G. Structural elucidation of the major phenolic glycolipid from Mycobacterium kansasii. II. Presence of a novel dideoxyhexose. *J. Biol. Chem.* **262**, 3180–3184 (1987).

27. FOURNIE, J. -J, RIVIERE, M. & PUZO, G. Absolute configuration of the unique 2,6-dideoxy-4-O-methyl-arabino-hexopyranose of the major phenolic glycolipid antigen from Mycobacterium kansasii. *Eur. J. Biochem.* **168**, 181–183 (1987).

28. Vercellone, A., Rivière, M., Fournié, J. J. & Puzo, G. Structural analogy between the major phenolic glycolipid antigens from two Myobacteria species: kansasii and gastri. *Chem. Phys. Lipids* **48**, 129–134 (1988).

29. Papa, F., Vaquero, M. & David, H. L. Chromatographic and serologic identity of the specific phenolglycolipids PGL-K1 from Mycobacterium kansasii and PGL-G1 from M. Gastri. *Ann. Inst. Pasteur. Microbiol.* **139**, 149–157 (1988).

30. Gurjar, M. K. & Reddy, K. R. Synthesis of tri-saccharide segments of a phenolic glycolipid of Mycobacterium kansasii. *Carbohydr. Res.* **226**, 233–238 (1992).

31. Zegelaar-Jaarsveld, K., van der Marel, G. A. & van Boom, J. H. Iodonium ion assisted synthesis of a common inner core trisaccharide fragment corresponding to the cell-wall phenolic glycolipid of Mycobacterium kansasii. *Tetrahedron* **48**, 10133–10148 (1992).

32. Zegelaar-Jaarsveld, K., Duynstee, H. I., van der Marel, G. A. & van Boom, J. H. Iodonium ion-assisted synthesis of tetrameric fragments corresponding to the cell wall phenolic glycolipids of Mycobacterium kansasii serovars II and IV. *Tetrahedron* **52**, 3575–3592 (1996).

33. Zegelaar-Jaarsveld, K., Smits, S. A. W., van Straten, N. C. R., van der Marel, G. A. & van Boom, J. H. Iodonium ion-assisted synthesis of a tetrameric fragment corresponding to the cell wall phenolic glycolipids of Mycobacterium kansasii serovar I. *Tetrahedron* **52**, 3593–3608 (1996).

34. Elsaidi, H. R. H. & Lowary, T. L. Effect of phenolic glycolipids from Mycobacterium kansasii on proinflammatory cytokine release. A structure - activity relationship study. *Chem. Sci.* **6**, 3161–3172 (2015).

35. Zheng, R. B. *et al.* Insights into Interactions of Mycobacteria with the Host Innate Immune System from a Novel Array of Synthetic Mycobacterial Glycans. *ACS Chem. Biol.* **12**, 2990–3002 (2017).

36. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie Int. Ed.* **51**, 11774–11777 (2012).

37. Barroso, S., Geerdink, D., Ter Horst, B., Casas-Arce, E. & Minnaard, A. J. Total synthesis of the phenolic glycolipid mycoside B and the glycosylated p-hydroxybenzoic acid methyl ester HBAD-I, virulence markers of mycobacterium tuberculosis. *European J. Org. Chem.* 4642–4654 (2013)

doi:10.1002/ejoc.201300437.

38. Kim, K. S. & Suk, D. H. Remote Participation of Protecting Groups at Remote Positions of Donors in Glycosylations. *Trends Glycosci. Glycotechnol.* **23**, 53–66 (2011).

39. Baek, J. Y., Lee, B.-Y., Jo, M. G. & Kim, K. S. β-Directing Effect of Electron-Withdrawing Groups at O -3, O -4, and O -6 Positions and α-Directing Effect by Remote Participation of 3- O -Acyl and 6- O -Acetyl Groups of Donors in Mannopyranosylations. *J. Am. Chem. Soc.* **132**, 7229–7229 (2010).

40. Komarova, B. S., Tsvetkov, Y. E. & Nifantiev, N. E. Design of α-Selective Glycopyranosyl Donors Relying on Remote Anchimeric Assistance. *Chem. Rec.* **16**, 488–506 (2016).

41. Cheshev, P. E., Khatuntseva, E. A., Tsvetkov, Y. E., Shashkov, A. S. & Nifantiev, N. E. Synthesis of Aminoethyl Glycosides of the Ganglioside GM 1 and Asialo-GM 1 Oligosaccharide Chains. *Russ. J. Bioorganic Chem.* **30**, 60–70 (2004).

42. Volbeda, A. G. *et al.* Chemoselective Cleavage of p-Methoxybenzyl and 2-Naphthylmethyl Ethers Using a Catalytic Amount of HCl in Hexafluoro-2-propanol. *J. Org. Chem.* **80**, 8796–8806 (2015).

43. Montchamp, J. L., Tian, F., Hart, M. E. & Frost, J. W. Butane 2,3-bisacetal protection of vicinal diequatorial diols. *J. Org. Chem.* **61**, 3897–3899 (1996).

44. Nakamura, H. *et al.* Total synthesis of (-)-caprazamycin a. *Angew. Chemie - Int. Ed.* **54**, 3136–3139 (2015).

45. Saksena, R., Adamo, R. & Kováč, P. Studies toward a conjugate vaccine for anthrax. Synthesis and characterization of anthrose [4,6-dideoxy-4-(3-hydroxy-3-methylbutanamido)-2-O-methyl-D-glucopyranose] and its methyl glycosides. *Carbohydr. Res.* **340**, 1591–1600 (2005).

46. Aoyama, T. & Shioiri, T. Trimethylsilyldiazomethane: a convenient reagent for the preparation of (E)-1-trimethylsilyl-1-alkenes. *Tetrahedron Lett.* **29**, 6295–6296 (1988).

47. Arnarp, J. & Lonngren, J. Alkylation of Carbohydrates with Alkyl Trifluoromethansesulfonates. *Acta Chem. Scand* **32**, 465–467 (1978).

48. Williams, D. R., Plummer, S. V. & Patnaik, S. Formal Synthesis of Leucascandrolide A. *Angew. Chemie Int. Ed.* **42**, 3934–3938 (2003).

49. Lichtenthaler, F. W., Oberthür, M. & Peters, S. Directed and efficient syntheses of β(1→4)-linked galacto-oligosaccharides. *European J. Org. Chem.* 3849–3869 (2001) doi:10.1002/1099-0690(200110)2001:20<3849::AID-EJOC3849>3.0.CO;2-Q.

50. Sato, K. I. *et al.* Novel synthetic approaches to manβ1-4GLCNAc and LeX units from N-acetyllactosamine. *J. Carbohydr. Chem.* **17**, 703–727 (1998).

51. David, S., Thieffry, A. & Veyrières, A. A mild procedure for the regiospecific benzylation and allylation of polyhydroxy-compounds via their stannylene derivatives in non-polar solvents. *J. Chem. Soc., Perkin Trans. 1* 1796–1801 (1981) doi:10.1039/P19810001796.

52. Jiang, L. & Chan, T.-H. Regioselective Acylation of Hexopyranosides with Pivaloyl Chloride. *J. Org. Chem.* **63**, 6035–6038 (1998).

53. Roslund, M. U. *et al.* Acyl Group Migration and Cleavage in Selectively Protected β- <scp>d</scp> -Galactopyranosides as Studied by NMR Spectroscopy and Kinetic Calculations. *J. Am. Chem. Soc.* **130**, 8769–8772 (2008).

54. Koto, S., Morishima, N., Yoshida, T., Uchino, M. & Zen, S. Ditritylation of Methyl and Benzyl α-D-Gluco-, -Manno-, and -Galactopyranosides and Preparation of Their Partially Benzylated Derivatives. *Bull. Chem. Soc. Jpn.* **56**, 1171–1175 (1983).

55. Tanaka, H., Yoshizawa, A. & Takahashi, T. Direct and stereoselective synthesis of β-linked 2,6-deoxyoligosaccharides. *Angew. Chemie - Int. Ed.* **46**, 2505–2507 (2007).

56. Bolitt, V., Mioskowski, C., Lee, S. G. & Falck, J. R. Direct preparation of 2-deoxy-D-glucopyranosides from glucals without Ferrier rearrangement. *J. Org. Chem.* **55**, 5812–5813 (1990).

57. Sherry, B. D., Loy, R. N. & Toste, F. D. Rhenium (V) -Catalyzed Synthesis of 2-Deoxy- r -glycosides. 4510–4511 (2004).

58. Karageorgi, S. Total synthesis of Mycobacterium kansasii oligosaccharides.

59. Jakas, A. *et al.* Synthesis of anthrose lipidic derivative as mimic of B. anthracis BclA glycoprotein for use in ELISA-like binding assays. *J. Carbohydr. Chem.* **35**, 69–85 (2016).

60. Hansen, T. *et al.* Defining the SN1 Side of Glycosylation Reactions: Stereoselectivity of Glycopyranosyl Cations. *ACS Cent. Sci.* **5**, 781–788 (2019).

61. Crich, D., Cai, W. & Dai, Z. Highly diastereoselective α-mannopyranosylation in the absence of participating protecting groups. *J. Org. Chem.* **65**, 1291–1297 (2000).

62. Elferink, H. *et al.* The Glycosylation Mechanisms of 6,3-Uronic Acid Lactones. *Angew. Chemie - Int. Ed.* **58**, 8746–8751 (2019).

Chapter 7

Aglycone analogues of Phenolic Glycolipids

Introduction

When a pathogen enters the host, exogenous glycolipids can be recognized by pattern recognition receptors (PRRs) of the innate immune system which can respond to a multitude of pathogen-associated molecular patterns (PAMPs).[1] The PRRs most associated with glycolipids include, but are not limited to, C-type lectin receptors (CLRs) and Toll-like receptors (TLRs). Recognition of PAMPs leads to the production of cytokines which recruit more immune cells to mount an effective inflammatory response. At a later stage antigens can be presented to the adaptive immune system through major histocompatibility complex (MHC) proteins on the surface of antigen presenting cells (APCs) such as dendritic cells, macrophages and B cells. This presentation may induce an immunological memory which is highly specific towards a single pathogen. The cluster of differentiation 1 (CD1) family of transmembrane glycoproteins, related to the class I MHC molecules, is expressed on the surface of various APCs and is capable of presenting lipids, and thereby also glycolipids, to the adaptive immune system. CD1b is thought to have the biggest hydrophobic grooves of the CD1 family and is therefore the most relevant for the presentation of long mycobacterial lipids (C_{25}-C_{80}).[2–4] It is thought that glycolipids expressed on the surface of pathogenic mycobacteria, such as *Mycobacterium tuberculosis*

and *M. leprae,* play a large role in their ability to dampen or evade the host immune response.[5–8] These pathogens are known to be able to remain dormant, hiding in cells of the host immune system for years before developing active disease.[9–12] Therefore much research has been performed to elucidate the exact structures of the relevant molecules and their interaction with (receptors of) the host immune system to unravel their exact mode of action, with the ultimate goal of finding a therapeutic target or vaccine candidate.[13]

To fully understand the structural determinants for binding to immune receptors, not only natural products but also analogues of natural products have been synthesized. The human immune system is able to differentiate between many endogenous and countless exogenous carbohydrates and with structural analogues it has been established that even small changes to the glycan may lead to a complete loss of recognition of glycolipids. Replacing the glucose of glucose monomycolate (GMM) with a mannose, galactose, arabinose or trehalose for instance, results in a complete loss of recognition by CD1b restricted T-cells, as does changing the position of the lipid tail on the carbohydrate.[3,14,15] The role of structural elements of the aglycone of glycolipids, such as chain length, *C*-methyl branches and distal cyclopropanes, methoxides and ketones, has been less established, however. Investigations using synthetic GMM, mycolic acids and sulfoglycolipids indicate that chain length is an important structural determinant for antigen presentation by CD1b.[15–19] The degree of *C*-methyl branching and the orientation thereof have been shown to have an influence on the activation of T-cells by sulfoglycolipids,[18,20] while the effect of distal decorations on mycolic acids depends on the T-cell line.[16] While it is not confirmed yet if phenolic glycolipids (PGLs) are presented by CD1b, PGLs are known to bind to TLR2[21–24] and TLR4,[25] both of which are known to have major hydrophobic pockets[26,27] and some PGLs are able to bind to human macrophage-inducible C-type lectin (Mincle).[28,29,30] PGLs contain a distal methyl and methoxide and multiple *C*-methyl branches in their lipid aglycone, but their role in shaping immune responses is not known. To further explore the role of the PGL aglycone in immune receptor interactions this Chapter describes the synthesis of multiple aglycone structural variants, with different degrees of aglycone complexity, of PGLs originating from *M. tuberculosis* and *M. leprae*.

The first aglycone analogues described in this chapter, are based on PGL-tb1 of *M. tuberculosis* and PGL-I of *M. leprae*, as depicted in Figure 1. Three different lipid analogues will be synthesized, changing the complexity on the phthiocerol and/or mycocerosic acids. With respect to the natural PGLs (**A**) analogues lacking either the distal *C*-methyl and methoxide of phthiocerol (**B**), the *C*-methyl branches of the mycocerosic acids (**C**) or both (**D**) will be generated. In addition, even simpler analogues bearing a C_{18} (**E**) or phenolic (**F**) aglycone will also be synthesized.

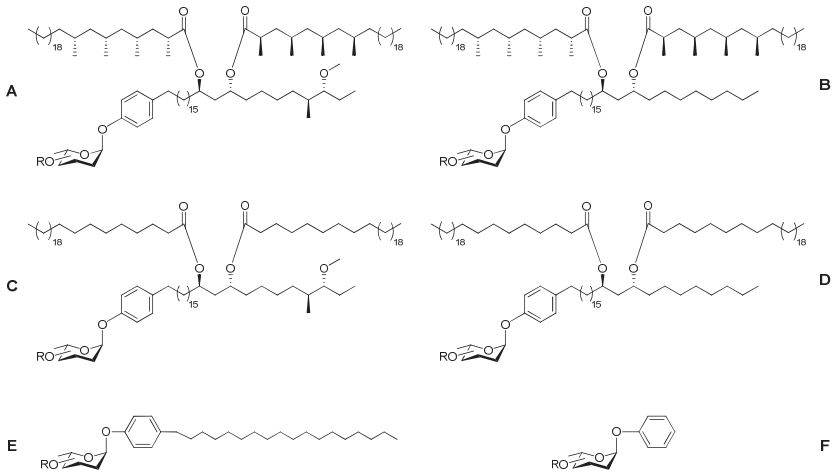


Figure 1. First group of proposed phenolic glycolipids with varying degrees of aglycone complexity.

Analogues **B**-**D** can be synthesized using the same strategy that was applied in the previous Chapters (4-6) of this thesis[31] and the building blocks for analogues **B**-**D** are depicted in Figure 2, alongside a retrosynthetic analysis to access these. Glycans protected with hydrogenation labile groups bearing an iodophenol on the reducing end can be coupled to either phthiocerol alkyne **1** or alkyne **3** using a Sonogashira cross coupling. The resulting diol can then be esterified with either mycocerosic acid (**2**) or commercially available octacosanoic acid (**4**). Thereafter hydrogenation leads to the global deprotection and concurrently reduces the conjugated internal alkyne which was formed in the Sonogashira reaction. The syntheses of phthiocerol alkyne **1** and iodoaryl bearing PGL-tb1 and PGL-I glycans are outlined in chapters 3, 4 and 5, respectively. Alkyne diol **3** is to be synthesized from iodide **5** (Chapter 3) and Weinreb amide **6** can be derived from ethyl 3-oxoundecanoate (**7**). Analogue **E** can be synthesized from the same glycans as **B**-**D** by

coupling the iodoaryl glycans with octadec-1-yne followed by hydrogenation and analogue **F** can be accessed by hydrogenation of the iodoaryl group.

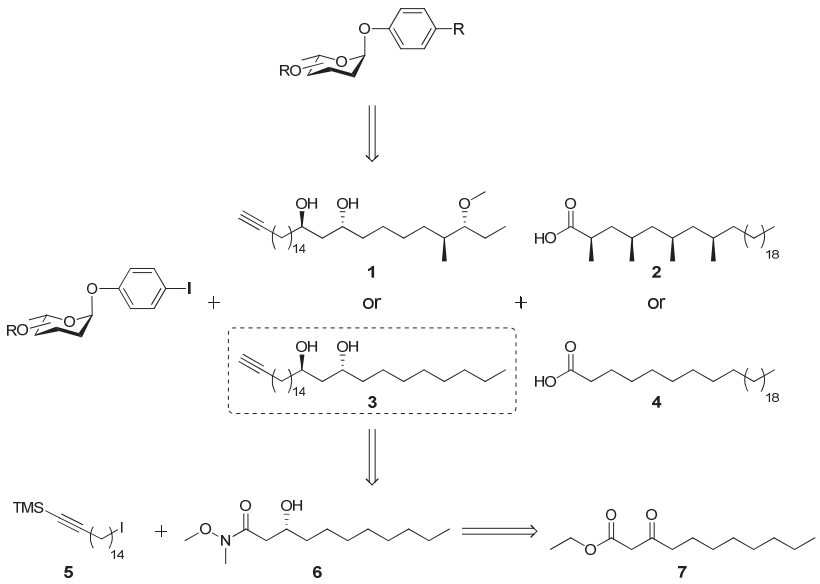


Figure 2. Retrosynthetic analysis of the analogues **B-D** outlined in Figure 1.

The second group of aglycone analogues targeted in this chapter, are based on PGL-III of *M. leprae*, a known Mincle ligand, which lacks the C-3 methyl of the terminal glucose of PGL-I (Figure 3).[32,33] This PGL-III glycan fits the criteria for binding to Mincle as it features a terminal C3,C4-*trans*-diequatorial diol,[34] which may enable bind to the Ca^{2+} ion coordinated by the receptor[30] and the C-6 methyl ether and relatively hydrophobic sugar attached to the C-1 position may bind to the shallow hydrophobic patches.[30,35,36] In order to confirm these hypothetical interactions and gain further understanding of the interaction between Mincle and PGL-III it would be worthwhile to obtain a crystal structure of Mincle bound to a ligand. PGL-III itself is not well suited for this purpose as crystallization studies often require a large excess of ligand and PGL-III is poorly soluble in water. An analogue with a more water soluble aglycone could possibly circumvent this problem, but binding to Mincle requires at least some hydrophobic interactions. Therefore, several PGL-III aglycones, of varying hydrophobicity, will be generated. All structures can be synthesized from iodoaryl glycan **8**, either by conjugation of

commercially available alkynes or phthiocerol alkyne **1** via a Sonogashira coupling followed by hydrogenation.

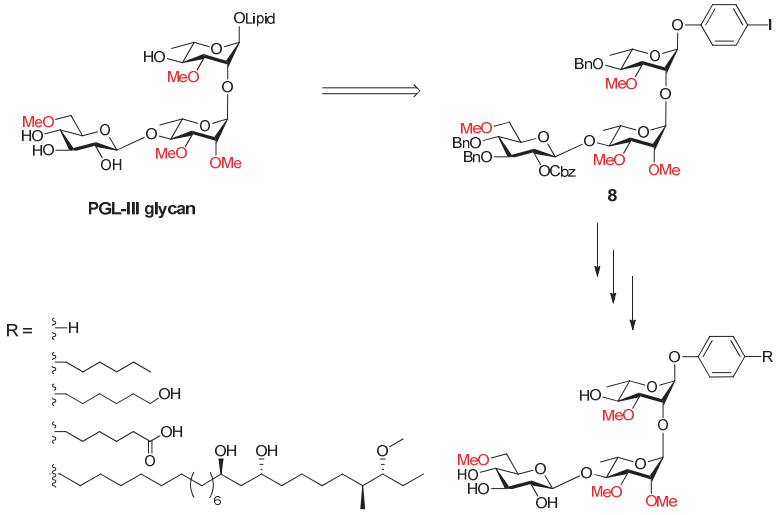
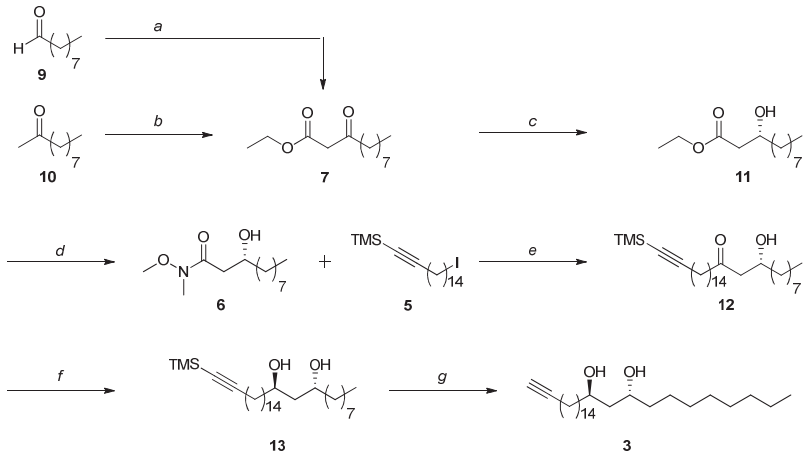


Figure 3. Analogues of PGL-III, carrying a more hydrophilic aglycone.

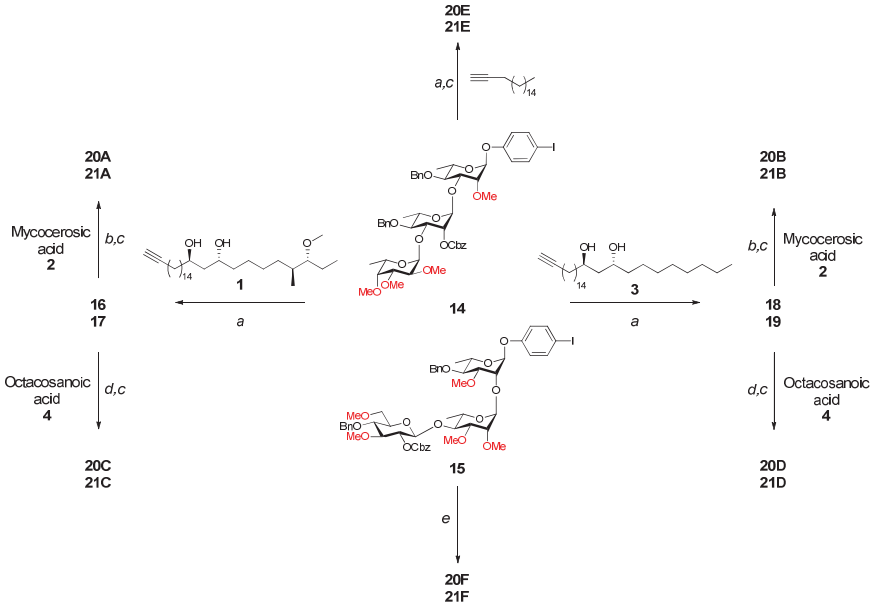
Results and discussion

The synthesis of alkyne diol **3** is depicted in Scheme 1. Ethyl 3-oxoundecanoate (**7**) was synthesized by elongating nonanal (**9**) with ethyl diazoacetate under the agency of $NbCl_5$,[37] a reaction that was also performed for the synthesis of phthiocerol, shown in Chapter 3. Alternatively, it could synthesized via a Claisen condensation of diethyl carbonate with 2-decanone by treatment with NaH in refluxing Et_2O,[38] a method that uses cheaper reagents and that can be more easily scaled up. The resulting keto-ester was then stereoselectively hydrogenated with a chiral Ruthenium catalyst developed by Noyori and co-workers[39,40] to give ß-hydroxyester **11** in 74% yield. The ethyl ester was then transformed into Weinreb amide **6** with *N,O*-dimethylhydroxylamine hydrochloride and $AlMe_3$ in DCM in 84% yield. Coupling of this amide to iodide **5** (chapter 3) under the agency of *t*-BuLi gave ß-hydroxyketone **12** in moderate yield. Finally, selective reduction of **12** to the 1,3-*anti* diol[41] followed by deprotection of the terminal alkyne gave diol **3** in 68% yield over 2 steps.



Scheme 1. Synthesis of diol **3**. Reagents and conditions: (a) Ethyl diazoacetate, $NbCl_5$, DCM, 58%, (b) diethyl carbonate, NaH, Et_2O, reflux, 66%, (c) (*R*)-[(RuCl(tol-BINAP))$_2$(μ-Cl)$_3$][NH_2Me_2], 20 bar H_2, EtOH, 74%, (d) N,O-dimethylhydroxylamine hydrochloride, $AlMe_3$, DCM, 84%, (e) *t*-BuLi, Et_2O, -70 °C, 52%, (f) $NMe_4BH(OAc)_3$, AcOH/MeCN/THF, 0 °C, 96%, (g) K_2CO_3, MeOH, 71%.

The synthesis of analogues **20A-F** and **21A-F** is depicted in Scheme 2 and the yields for the transformations have been summarized in Table 1. Trisaccharides **14** and **15** were coupled to phthiocerol to give diols **16** (Chapter 4) and **17** (Chapter 5) in 90% and 83% yield, respectively. From there on, PGL-tb1 (**20A**) has been synthesized in 77%, and PGL-I (**21A**) in 62% yield over 2 steps, being esterification and hydrogenation. Coupling of **14** and **15** to alkyne **3** gave diols **18** and **19** in 96% and 75% yield, respectively.



Scheme 2. Synthesis of aglycone analogues **20A**-**21F**. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, 40 °C, (b) DIC, DMAP, DCM, 0 °C → RT → 40 °C, (c) Pd/C, H_2, THF/EtOH, (d) DIC, DMAP, DCM, 40 °C, (e) 1. Pd/C, H_2, NH_4OAc, EtOH, 2. Pd/C, H_2, EtOH.

Esterification of these diols with mycocerosic acid followed by hydrogenation produced **20B** and **21B** in 63% and 61% yield over 2 steps, respectively. Diols **16**, **17**, **18** and **19** were also esterified with octacosanoic acid which, in contrast to mycocerosic acid, is not soluble in DCM at room temperature. Fortunately, octacosanoic acid is less prone to form unwanted byproducts than mycocerosic acid and the desired diesters were formed in good yields when the reaction was performed at 40 °C. Finally, hydrogenation gave **20C**, **21C**, **20D**, and **21D** in 63%, 67%, 59% and 54% yield over 2 steps, respectively. The C_{18}

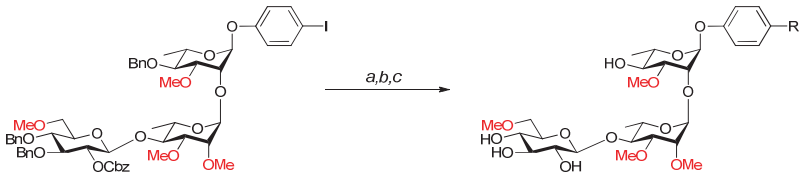
analogues **20E** and **21E** were synthesized from **14** and **15** in 59% and 56% yield over 2 steps, respectively. Attempts to form phenolic aglycone analogues **20F** and **21F** with standard hydrogenation conditions did not proceed well. Therefore, **20F** and **21F** were generated by means of a "double hydrogenation" procedure. At first, the starting material was dissolved in EtOH together with NH_4OAc and hydrogenated to selectively remove the Cbz moiety and reduce the aryl iodide.[42] After a quick work up to remove the catalyst and salts, the remaining benzyls were removed using standard hydrogenation conditions to give **20F** and **21F** in 92% and 94% yield over 2 steps, respectively.

Table 1. Yields of the assembly of aglycone analogues of PGL-tb1 and PGL-I.

Starting material	Sonogashira	Esterification	Hydrogenation	Overall yield	Product
14	90%	94%	82%	69%	**20A**
15	83%	79%	79%	52%	**21a**
14	96%	73%	86%	60%	**20B**
15	75%	77%	79%	46%	**21B**
14	90%	88%	72%	57%	**20C**
15	83%	86%	78%	56%	**21C**
14	96%	100%	59%	57%	**20D**
15	75%	91%	59%	40%	**21D**
14	89%	n.a.	66%	59%	**20E**
15	86%	n.a.	65%	56%	**21E**
14	n.a.	n.a.	92%	92%	**20F**
15	n.a.	n.a.	94%	94%	**21F**

The synthesis and yields of the series of PGL-III analogues is depicted in Table 2. Interestingly, trisaccharide **8** could, in contrast to **14** and **15**, be directly reduced under standard hydrogenation conditions to provide phenolic trisaccharide **22** in 77% yield. Sonogashira coupling of trisaccharide **8** to hex-1-yne, 5-hexyn-1-ol and phthiocerol alkyne **1**, followed by hydrogenation gave products **23**, **24** and **26** in 69%, 73% and 60% yield over 2 steps, respectively. Hexanoic acid derivative **25** was synthesized by coupling **8** to methyl 5-hexynoate, followed by hydrogenation and saponification. This provided **25** in 84% yield over 3 steps.

Table 2. Yields of the assembly of aglycone analogues of PGL-III.



Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, 40 °C, (b) Pd/C, H_2, THF/EtOH, (c) 1 M NaOH, EtOH (1:4).

Sonogashira	Hydrogenation	Saponification	Overall yield	Product	R
n.a.	77%	n.a.	77%	**22**	**H**
91%	76%	n.a.	69%	**23**	**hexyl**
81%	90%	n.a.	73%	**24**	**6-hydrohexyl**
84%	100%	100%	84%	**25**	**6-carboxyhexyl**
81%	74%	n.a.	60%	**26**	**phthiocerol**

Conclusion

In order to gain understanding of the role of structural details in the lipid part of phenolic glycolipids in the detection and/or presentation of the compounds by the host immune system, the synthesis of several aglycone analogues with varying degrees of structural simplification has been achieved. This accomplishment highlights the flexibility of the highly convergent strategy to access PGL molecules, based on a late stage Sonogashira coupling of iodoaryl glycans and alkyne lipids, combined with a protecting group strategy which allows for hydrogenation as a single global deprotection step. The compounds synthesized in this chapter are at present being investigated for their immunomodulatory capabilities and used in crystallisation trials.

EXPERIMENTAL:

General procedures

All reactions were carried out in oven-dried glassware (80 °C). Prior to reactions, traces of water and solvent were removed by co-evaporation with toluene where appropriate. Reactions sensitive to air or moisture were carried out under N_2 atmosphere (balloon). Commercially available reagents and solvents (Aldrich Chemistry, Honeywell, Merck, Fischer Scientific, Biosolve, Fluka, VWR Chemicals, Acros Organics, Fluorochem, Brunschwig, Carbosynth) were used as received unless stated otherwise.

Solvents for reactions were reagent grade and dried by storage over flame dried 4 Å molecular sieves when needed. Et_2O used for column chromatography was distilled before use and stored over iron filings. EtOAc used for column chromatography was distilled before use. NEt_3 used for Sonogashira couplings was distilled from KOH, degassed with N_2, and stored over KOH for a maximum of 24 hours. DMAP used for Steglich esterifications was recrystallized from toluene before use.

Reaction progress was monitored using aluminium-supported silica gel TLC plates (Merck, Kieselgel 60, F254); visualization was carried out by irradiation with UV light (254 nm), and spraying with 20% H_2SO_4 in EtOH (w/v) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% H_2SO_4 or $KMnO_4$ (7.5 g/L) and K_2CO_3 (50 g/L) in H_2O, followed by charring. Additional analysis with TLC-MS was used when needed.

Column chromatography was carried out using silica gel (Fluka, 40-63 μm mesh). The column was prepared using the apolar component mentioned in the corresponding experimental. If the apolar component was pentane the product was brought up in toluene. If the apolar component was DCM the product was brought up in DCM, possibly with a few drops of methanol if needed. Colum chromatography was performed using a gradient ranging from 0% polar component up to the ratio mentioned in the corresponding experimental in 2 to 5 steps depending on the ease of separation.

NMR spectra were recorded at ambient temperature on a Bruker AV-400LIQ or AV-850 spectrometer. Samples were prepared in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) in $CDCl_3$ are reported in ppm relative to Me_4Si (δ: 0.00 ppm) for ^{1}H-NMR and $CDCl_3$ (δ: 77.16 ppm) for ^{13}C-NMR. Chemical shifts in CD_3OD are reported in ppm relative to H_2O (δ: 4.87 ppm) for ^{1}H-NMR and CD_3OD (δ: 49.00 ppm) for ^{13}C-NMR. ^{13}C-APT spectra are ^{1}H decoupled and structural assignment was achieved using HH-COSY and HSQC 2D experiments. Coupling constants (J) are given in Hz. Coupling constants of anomeric carbon atoms ($J_{H1,C1}$) were determined using HMBC-GATED experiments. Optical rotations were measured on an Anton Paar Modular Circular Polarimeter MCP 100/150. High resolution mass spectra were recorded on a Synapt G2-Si or a Q Exactive HF Orbitrap equipped with an electron spray ion source positive mode. Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR.

General procedure A: Sonogashira cross coupling

Iodoaryl glycoside (1.0 eq) was dissolved in freshly distilled NEt_3 (0.05 M) together with alkyne (1.2-5 eq). A mixture of $Pd(PPh_3)_2Cl_2$, PPh_3 and CuI (ratio 1:1:2) was dissolved in freshly distilled NEt_3 and was stirred for 15 minutes at 40 °C. Of this cocktail, enough was added to the sugar/alkyne mixture to amount to 0.05 eq $Pd(PPh_3)_2Cl_2$, 0.05 eq PPh_3 and 0.1 eq CuI. The reaction was allowed to stir at 40 °C until the complete consumption of the starting material as indicated by TLC. The solvent was then removed under a stream of N_2. The crude was then transferred to a silica column in toluene and the column was flushed with toluene. Thereafter the product was purified by means of column chromatography.

General procedure B: Esterification – mycocerosic acid

Starting material (1.0 eq) was dissolved in dry DCM (0.05 M) together with mycocerosic acid (3.0 eq) and DMAP (9 eq). The resulting mixture was cooled to 0 °C after which DIC (6 eq) was added. The reaction was allowed to stir for 16 hours while warming to rT, after which it was warmed to 40 °C and stirred until all intermediates moved to single high running spot on TLC. The reaction mixture was then cooled to rT, diluted with Et_2O and the organic layer was washed 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography. Note: In order to detect the most prevalent byproducts, staining with $KMnO_4$ is required.

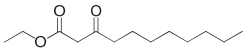
General procedure C: Esterification – octacosanoic acid

Starting material (1.0 eq) was dissolved in dry DCM (0.05 M) together with octacosanoic acid (3.0 eq) and DMAP (9 eq). DIC (6 eq) was added to the mixture and the solution was warmed to 40 °C. The reaction was allowed to stir for 24 hours or until all intermediates moved to single high running spot on TLC. The reaction mixture was then cooled to rT, diluted with Et_2O and the organic layer was washed 1 M HCl, sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography. Note: In order to detect the most prevalent byproducts, staining with $KMnO_4$ is required.

General procedure D: Hydrogenation

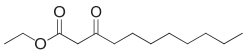
Starting material (1.0 eq) was dissolved in a mixture of THF and EtOH (1:1, 0.007 M) and the solution was purged with N_2. Pd/C (10%, 1.0 eq) was then added to the solution and the resulting mixture was purged with H_2. The reaction was left to stir under H_2 atmosphere until TLC complete conversion of the starting material and reaction intermediates to a single low running spot (DCM-MeOH 19:1). The reaction mixture was then purged with N_2, filtered over celite and concentrated *in vacuo*. Purification by means of column chromatography (DCM-MeOH 19:1).

Ethyl 3-oxoundecanoate (7)



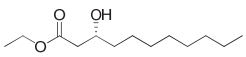
Nonanal (**9**) (1.52 mL, 8.49 mmol, 1.0 eq) was dissolved in DCM (85 mL, 0.1 M) and a catalytic amount [the amount was not weighed due to tendency for hydrolysis] of $NbCl_5$ was added to the solution and it was cooled to 0 °C. EDAA (87%, 1.53 mL, 12.7 mmol, 1.5 eq) was slowly added and the reaction was allowed to stir for 4 hours after which it was diluted with H_2O and extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 9:1) gave the title compound (1.12 g, 4.9 mmol, 58%) as a clear oil. Spectroscopic data were in accordance with those previously reported in the literature.[43]

Ethyl 3-oxoundecanoate (7)



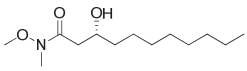
Diethyl carbonate (1.28 mL, 10.6 mmol, 4.0 eq) was dissolved in dry Et_2O (20 mL, 0.52 M) and NaH (60%, 0.211 g, 5.27 mmol, 2.0 eq) was added to the solution. The mixture was warmed to reflux and 2-decanone (0.5 mL, 2.64 mmol, 1.0 eq) was slowly added. The reaction was refluxed for 20 hours after which it was cooled to rt and quenched by addition of EtOH. The resulting sludge was filtered and concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 19:1) gave the title compound (0.397 g, 1.74 mmol, 66%) as a slightly yellow oil. Spectroscopic data were in accordance with those previously reported in the literature.[43]

Ethyl (3*R*)-3-hydroxyundecanoate (11)



Compound **7** (1.12 g, 4.9 mmol, 1.0 eq) was dissolved in EtOH (25 mL, 0.2 M) and (*R*)-[(RuCl(tol-BINAP))$_2$(μ-Cl)$_3$[NH_2Me_2] (87 mg, 49 μmol, 0.01 eq) was added to the solution. The mixture was purged with N_2 after which it was stirred under 22 bar of H_2 atmosphere for 24 hours. The mixture was then diluted with toluene, concentrated *in vacuo* and purification by means of column chromatography (*n*-pentane-Et_2O 7:3) gave **11** (0.84 g, 3.65 mmol, 74%) as a slightly green oil. $[\alpha]_D^{25}$ = -14.3° (c = 4.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 4.18 (q, 2H, *J* = 7.2 Hz, OC*H*$_2$); 4.02-3.97 (m, 1H, C*H*OH); 2.95 (d, 1H, *J* = 4.0 Hz, O*H*); 2.51 (dd, 1H, *J* = 2.8, 16.4 Hz, C*H*H); 2.40 (dd, 1H, *J* = 9.0, 16.4 Hz, CH*H*); 1.54-1.26 (m, 17H, C*H*$_2$, C*H*$_3$); 0.88 (t, 3H, *J* = 7.0 Hz, C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 173.3 (*C*O); 68.2 (*C*H); 60.8, 41.4, 36.7, 32.0, 29.7, 29.4, 25.6, 22.8 (*C*H$_2$); 14.3, 14.3 (*C*H$_3$).

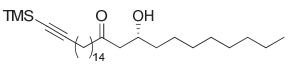
***N*-methoxy-*N*-methyl (3*R*)-hydroxyundecanamide (6)**



N,O-dimethylhydroxylamine hydrochloride (1.77 g, 18.2 mmol, 5.0 eq) was dissolved in dry DCM (25 mL) and the solution was cooled to 0 °C. A solution of $AlMe_3$ in toluene (2 M, 9.1 mL, 18.2 mmol, 5.0 eq) was added. This mixture was allowed to stir for 1 hour after which compound **11** (0.99 g, 3.61 mmol, 1.0 eq) was added and the reaction was allowed to stir for 3 hours while slowly warming to rt. The reaction was then quenched by addition of methanol and the resulting mixture was diluted with Et_2O. The organic layer was washed with 1 M HCl and the resulting aqueous layer was extracted with Et_2O. The organic layers were combined, washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (Et_2O) gave the title compound (751 mg, 3.06 mmol, 84%) as a clear oil. $[\alpha]_D^{25}$ = -36.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 4.06-3.98 (m, 1H, C*H*OH); 3.79 (d, 1H, *J* = 2.8 Hz, O*H*), 3.69 (s, 3H, OC*H*$_3$);

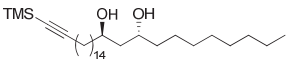
3.20 (s, 3H, NCH_3); 2.67 (d, 1H, J = 16.8 Hz, CHH); 2.44 (dd, 1H, J = 9.6, 16.8 Hz, CHH); 1.62–1.49 (m, 1H); 1.49– 1.23 (m, 14H, CH_2); 0.88 (t, 3H, J = 7.0 Hz, CH_3). ^{13}C-APT NMR (101 MHz) δ: 174.2 (CO); 68.0 (OCH$_3$); 61.4 (COH); 38.3, 36.7, 32.0 (CH$_2$); 32.0 (NCH$_3$); 29.8, 29.7, 29.4, 25.7, 22.8 (CH$_2$); 14.3 (CH$_3$). IR (thin film, cm^{-1}): 1076, 1388, 1465, 1648, 1653, 2855, 2926, 3443. HRMS calculated for $C_{13}H_{27}NO_3Na$ 268.18886 [M+Na]$^+$; found 268.18810.

(9*R*)-9-hydroxy-27-(trimethylsilyl)heptacos-26-yn-11-one (12)



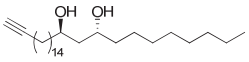
Compound **5** (0.595 g, 1.42 mmol, 2.2 eq) was dissolved in Et$_2$O (16 mL, 0.09 M) and the solution was cooled to -78 °C. A 1.7 M solution of *t*-BuLi in hexane (2.1 mL, 3.57 mmol, 5.4 eq) was added to the solution and the mixture was allowed to stir for 1 hour. After this time a solution of compound **6** (0.161 g, 0.66 mmol, 1.0 eq) in Et$_2$O (1.7 mL, 0.4 M) was slowly added and the reaction was allowed to stir for 1 hour. The reaction was then quenched by the addition of sat. aq. NH_4Cl and allowed to warm to rt. The layers were then separated and the organic layer was washed with H_2O and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et$_2$O 7:3) gave the title compound (162 mg, 0.34 mmol, 52%) as a white waxy solid. $[\alpha]_D^{25}$ = -21.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 4.05-4.01 (m, 1H, CHOH); 3.12 (bs, 1H, OH); 2.60 (dd, 1H, J = 2.8, 17.2 Hz, CHH); 2.50 (dd, 1H, J = 9.2, 17.6 Hz, CHH); 2.42 (t, 2H, J = 7.4 Hz, CH_2); 2.21 (t, 2H, J = 7.2 Hz, CH_2); 1.59-1.20 (m, 40H, CH_2); 0.89 (t, 3H, J = 7.0 Hz, CH_3) 0.15 (s, 9H, C$H_{3,TMS}$). ^{13}C-APT NMR (101 MHz) δ: 212.7 (CO); 107.9, 84.3 ($C_{q,alkyne}$); 67.7 (CHOH); 49.1, 43.8, 36.6, 32.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 28.7, 25.6, 23.7, 22.8, 20.0 (CH$_2$); 14.2 (CH$_3$); 0.3 (CH$_{3,TMS}$). IR (thin film, cm^{-1}): 1006, 1066, 1079, 1249, 1468, 1701, 2850, 2918, 2958, 3410. HRMS calculated for $C_{30}H_{58}O_2SiNa$ 501.41038 [M+Na]$^+$; found 501.41007.

(9*R*,11*R*)-27-(trimethylsilyl)heptacos-26-yne-9,11-diol (13)



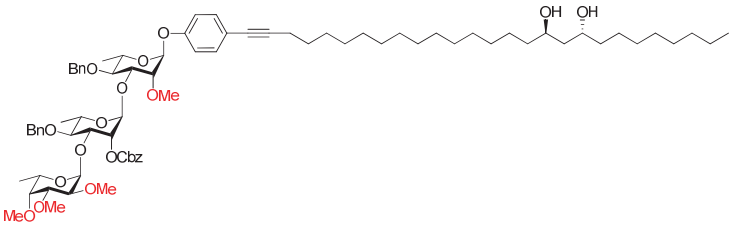
Compound **12** (92 mg, 0.192 mmol, 1.0 eq) was dissolved in a 12:12:1 mixture of MeCN AcOH and THF (50 mL, 0.004 M) and this solution was cooled to 0 °C. $Me_4NBH(OAc)_3$ (132 mg, 0.5 mmol, 6.0 eq) was added in 4 portions over 90 minutes and the reaction was allowed to stir for 1 more hour. The reaction was quenched by the addition of H_2O and the layers were separated. The aqueous layer was extracted with Et$_2$O (3×) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (3×) and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification of the product by means of column chromatography (*n*-pentane-Et$_2$O 1:1) gave the title compound (89 mg, 0.185 mmol, 96%) as a white waxy solid. $[\alpha]_D^{25}$ = -3.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 3.97-3.91 (m, 2H, CHOH); 2.21 (t, 2H, J = 7.2 Hz, CH_2); 1.76 (bs, 2H, OH); 1.62-1.26 (m, 44H, CH_2); 0.88 (t, 3H, J = 6.8 Hz, CH_3); 0.15 (s, 9H, C$H_{3,TMS}$). ^{13}C-APT NMR (101 MHz) δ: 108.0, 84.4 ($C_{q,alkyne}$); 69.7 (CHOH); 42.4, 37.7, 32.0, 29.8, 29.8, 29.7, 29.7, 29.4, 29.2, 29.0, 28.8, 25.9, 22.8, 20.0 (CH$_2$); 14.3 (CH$_3$); 0.3 (CH$_{3,TMS}$). IR (thin film, cm^{-1}): 1470, 2849, 2918, 3278. HRMS calculated for $C_{30}H_{60}O_2SiNa$ 503.42603 [M+Na]$^+$; found 503.42551.

(9*R*,11*R*)-heptacos-26-yne-9,11-diol (3)



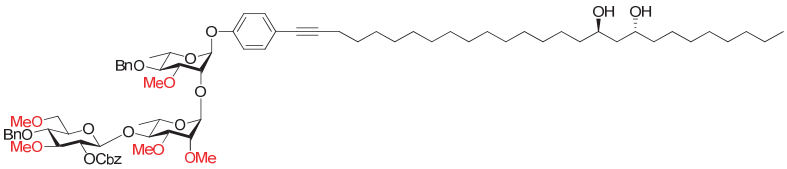
Compound **13** (105 mg, 0.218 mmol, 1.0 eq) was dissolved in MeOH (22 mL, 0.01 M) and K_2CO_3 (0.15 g, 1.09 mmol, 5.0 eq) was added solution and the reaction was allowed to stir overnight. The mixture was then diluted with Et_2O and H_2O, the layers were separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by means of column chromatography (*n*-pentane-Et_2O 1:1) gave the title compound (63 mg, 0.15 mmol, 71%) as a white waxy solid. $[\alpha]_D^{25}$ = -6.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 3.97-3.91 (m, 2H, C*H*OH); 2.18 (dt, 2H, *J* = 2.8, 7.2 Hz, CH_2); 2.12 (bs, 2H, O*H*); 1.94 (t, 1H, *J* = 2.6 Hz, CC*H*); 1.59 (t, 2H, *J* = 9.4 Hz, CH_2); 1.56-1.26 (m, 46H, CH_2); 0.88 (t, 3H, *J* = 6.8 Hz, CH_3). ^{13}C-APT NMR (101 MHz) δ: 85.0, 74.3 (C_{alkyne}); 69.7 (*C*OH); 68.2, 42.4, 37.6, 32.0, 29.9, 29.8, 29.8, 29.7, 29.7, 29.3, 28.9, 28.6, 25.9, 18.5 (*C*H_2); 14.3 (*C*H_3). IR (thin film, cm^{-1}): 1464, 1472, 2849, 2915, 3294, 3510. HRMS calculated for $C_{27}H_{52}O_2Na$ 431.38650 [M+Na]$^+$; found 431.38594.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diol)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (18)



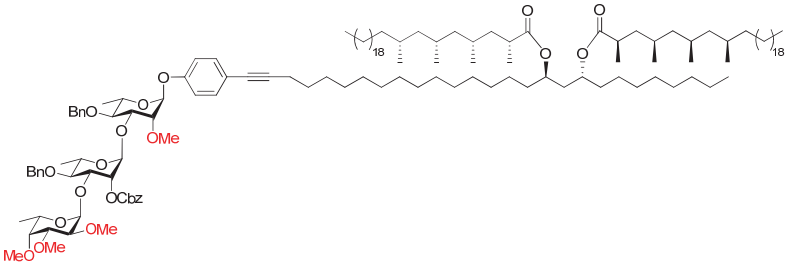
The title compound was synthesized according to general procedure A using glycan **14** (53 mg, 52 µmol, 1.0 eq) and alkyne **3** (25 mg, 62 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:19) yielded the product (65 mg, 50 µmol, 96%) as a yellow oil. $[\alpha]_D^{25}$ = -83.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.42-7.26 (m, 17H, CH_{arom}); 6.94 (d, 2H, *J* = 8.8 Hz, CH_{arom}); 5.52 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.10 (m, 6H, H-1', H-1'', H-2', PhCH_2, PhC*H*H); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.22-4.18 (m, 2H, H-3, H-3'); 4.03-3.99 (m, 1H, H-5'); 3.93-3.90 (m, 2H, CH_{diol}); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.74-3.66 (m, 2H, H-2, H-5); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OCH_3); 3.33 (s, 3H, OCH_3); 3.31 (s, 3H, OCH_3); 3.27 (d, 1H, *J* = 1.6 Hz, H-4''); 2.37 (t, 2H, *J* = 7.2 Hz, C$H_{2,diol}$); 1.70-1.05 (m, 61H, H-6, H-6', C$H_{2,diol}$); 0.97 (d, 3H, *J* = 6.8 Hz, H-6''); 0.88 (t, 3H, *J* = 6.8 Hz, C$H_{3,diol}$). ^{13}C-APT NMR (101 MHz) δ: 155.6 ($C_{q,arom}$); 154.8 (CO_{Cbz}); 139.0, 138.1, 135.2 ($C_{q,arom}$); 133.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 127.8, 127.6, 127.5 (*C*H$_{arom}$); 118.0 ($C_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 ($C_{q,alkyne}$); 80.3 (C-3); 80.1 ($C_{q,alkyne}$); 80.1 (C-2 and C-3''); 79.9, 79.7 (C-4 and C-4'); 79.3 (C-4''); 78.3 (C-3'); 77.7 (C-2''); 76.8 (C-2'); 75.7, 75.1, 70.1 (Ph*C*H$_2$); 69.6 (*C*OH$_{diol}$); 68.9 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2 (O*C*H$_3$); 42.4, 37.6, 32.0, 29.8, 29.7, 29.7, 29.7 29.4, 29.3, 29.1, 29.0, 25.9, 22.8, 19.5 (*C*H$_{2,diol}$); 18.2 (C-6); 18.0 (C-6'); 16.3 (C-6''); 14.3, (*C*H$_{3,diol}$). IR (thin film, cm^{-1}): 1003, 1040, 1142, 1235, 1261, 1457, 1485, 1507, 1747, 2360, 2850, 3387. HRMS calculated for $C_{77}H_{112}O_{17}Na$ 1331.77917 [M+]$^+$; found 1331.77936.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diol)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (19)



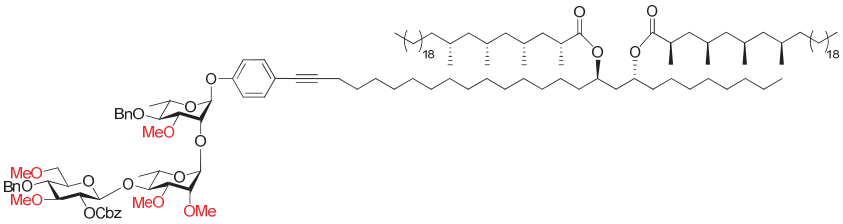
The title compound was synthesized according to general procedure A using glycan **15** (56 mg, 53 µmol, 1.0 eq) and alkyne **3** (26 mg, 63 µmol, 1.2 eq). Column chromatography (*n*-pentane-Et_2O 1:19) yielded the product (53 mg, 40 µmol, 75%) as a yellow oil. $[\alpha]_D^{25}$ = -61.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.26 (m, 17, C*H*$_{arom}$); 6.95 (dd, 2H, *J* = 2.0, 7.2 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.29-5.22 (m, 2H, PhC*H*$_2$); 5.18 (d, 1H, *J* = 1.2 Hz, H-1'); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.79 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (dd, 1H, *J* = 1.8, 3.0 Hz, H-2); 3.96-3.90 (m, 2H, C*H*$_{diol}$); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.76-3.47 (m, 16H, H-2', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 3.45-3.39 (m, 2H, H-4, H-4'); 3.36-3.33 (m, 8H, H-3', H-3'', OC*H*$_3$); 2.38 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,diol}$); 2.05 (bs, 2H, O*H*$_{diol}$); 1.61-1.05 (m, 64H, H-6, H-6', C*H*$_{2,diol}$); 0.88 (t, 3H, *J* = 6.8 Hz, C*H*$_{3,diol}$). ^{13}C-APT NMR (101 MHz) δ: 155.3 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5, 138.2, 135.6 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 84.9 (C-3''); 82.0 (C-3); 80.8 (C-4'); 80.1 (C-4); 80.1 (C$_{q,alkyne}$); 78.1 (C-2''); 77.7, 77.6 (C-4'' and C-5''); 77.0 (C-2'); 75.2, 75.0 (PhC*H*$_2$); 74.8 (C-3'); 73.0 (C-2); 71.0 (C-6''); 69.9 (PhC*H*$_2$); 69.6 (*C*H$_{diol}$); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6 (O*C*H$_3$); 42.4, 37.6, 32.0, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 29.3, 29.1, 29.0, 25.9, 25.5, 22.8, 19.5 (*C*H$_{2,diol}$); 18.2, 18.0 (C-6 and C-6'); 14.3 (*C*H$_{3,diol}$). IR (thin film, cm^{-1}): 1055, 1075, 1120, 1238, 1259, 1457, 1507, 1560, 1751, 2852, 2922, 3380. HRMS calculated for $C_{78}H_{114}O_{18}Na$ 1361.78974 [M+Na]$^+$; found 1361.79001.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (27)



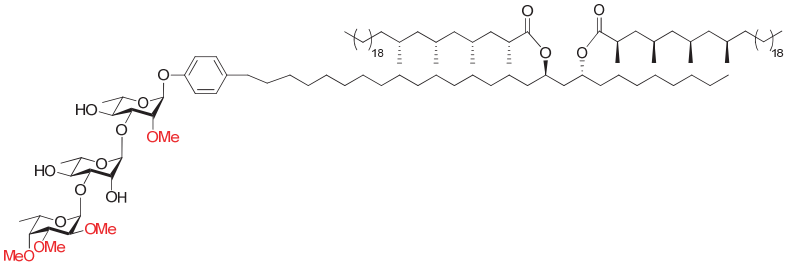
The title compound was synthesized according to general procedure D using diol **18** (24 mg, 18 µmol, 1.0 eq), mycocerosic acid (**2**) (26 mg, 55 µmol, 3.0 eq), DIC (17 µL, 110 µmol, 6.0 eq) and DMAP (20 mg, 165 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (30 mg, 13 µmol, 73%) as a waxy solid. $[\alpha]_D^{25}$ = -68.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.41-7.26 (m, 17H, C*H*$_{arom}$); 6.93 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.10 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.93 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.84 (quint, 2H, *J* = 6.4 Hz, C*H*$_{diol}$); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.22-4.18 (m, 2H, H-3, H-3'); 4.04-3.97 (m, 1H, H-5'); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.74-3.68 (m, 2H, H-2, H-5); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.27 (d, 1H, *J* = 1.6 Hz, H-4''); 2.57-2.47 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,diol}$); 1.77-1.70 (m, 4H, C*H*$_{2,Myc}$); 1.59-1.05 (m, 161H, H-6, H-6', C*H*$_{2,diol}$, C*H*$_{2,Myc}$); 1.02-0.93 (m, 5H, H-6'', C*H*$_{2,Myc}$); 0.91-0.83 (m, 36H, C*H*$_{3,diol}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 155.7 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 138.2, 135.2 (C$_{q,arom}$); 133.0, 128.9, 128.9, 128.8, 128.5, 128.5, 128.4, 127.9, 127.6, 127.5 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.0 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyne}$); 80.4 (C-3); 80.1 (C$_{q,alkyne}$); 80.1 (C-2 and C-3''); 79.9, 79.7 (C-4 and C-4'); 79.3 (C-4''); 78.3 (C-3'); 77.8 (C-2''); 76.8 (C-2'); 75.7, 75.1, 70.4 (Ph*C*H$_2$); 68.9 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2 (O*C*H$_3$); 45.7, 45.4 (*C*H$_{2,Myc}$); 41.1 (*C*H$_{2,diol}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.8 (*C*H$_{2,diol}$); 32.1 (*C*H$_{2,Myc}$); 32.0, 30.2 (*C*H$_{2,diol}$) 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0, (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.3 (*C*H$_{2,diol}$); 22.8, 22.8 (*C*H$_{2,Myc}$); 20.9, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,diol}$); 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6); 18.1 (C-6'); 16.4 (C-6''); 14.3 (*C*H$_{3,Myc}$). IR (thin film, cm^{-1}): 1030, 1102, 1120, 1179, 1261, 1379, 1438, 1457, 1454, 1507, 1734, 2853, 2923. HRMS calculated for $C_{141}H_{237}O_{19}$ 2235.76077 $[M+H]^+$; found 2235.76608.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (28)



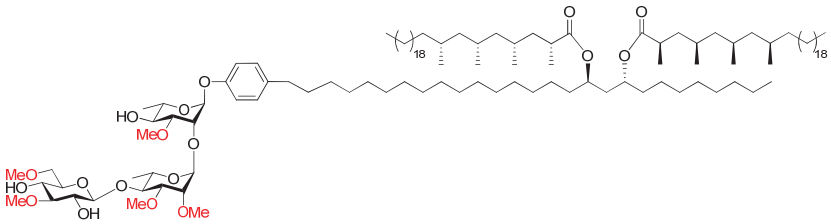
The title compound was synthesized according to general procedure D using diol **19** (23 mg, 17 µmol, 1.0 eq), mycocerosic acid (**2**) (25 mg, 52 µmol, 3.0 eq), DIC (16 µL, 103 µmol, 6.0 eq) and DMAP (19 mg, 155 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 2:3) yielded the product (30 mg, 13 µmol, 77%) as a waxy solid. $[\alpha]_D^{25}$ = -36.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.42-7.26 (m, 17, C*H*$_{arom}$); 6.97-6.93 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 2.0 Hz, H-1); 5.29-5.22 (m, 2H, PhC*H*$_2$); 5.19 (d, 1H, *J* = 1.2 Hz, H-1'); 4.91-4.78 (m, 4H, PhC*H*H, C*H*$_{diol}$); 4.79 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.74-3.47 (m, 16H, H-2', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 3.45-3.39 (m, 2H, H-4, H-4'); 3.36-3.33 (m, 8H, H-3', H-3'', OC*H*$_3$); 2.57-2.47 (m, 2H, C*H*$_{Myc}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,diol}$); 1.77-1.05 (m, 167H, H-6, H-6', C*H*$_{2,diol}$, C*H*$_{2,Myc}$,); 1.02-0.93 (m, 4H, C*H*$_{2,Myc}$); 0.91-0.83 (m, 36H, C*H*$_{3,diol}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.1 (*C*O$_{Myc}$); 155.3 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5, 138.3, 135.6 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 85.0 (C-3''); 82.0 (C-3); 80.8 (C-4'); 80.1 (C-4); 80.1 (C$_{q,alkyne}$); 78.1 (C-2''); 77.7, 77.6 (C-4'' and C-5''); 77.0 (C-2'); 75.3, 75.1 (Ph*C*H$_2$); 74.8 (C-3'); 73.0 (C-2); 71.1 (C-6''); 70.4 (*C*H$_{diol}$); 69.9 (Ph*C*H$_2$); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6 (O*C*H$_3$); 45.7, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,diol}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.8 (*C*H$_{2,diol}$); 32.1 (*C*H$_{2,Myc}$); 32.0, 30.2 (*C*H$_{2,diol}$) 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.5, 29.4, 29.2, 29.1, (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.3 (*C*H$_{2,diol}$); 22.8, 22.8 (*C*H$_{2,Myc}$); 20.9, 20.6, 20.5 (*C*H$_{3,Myc}$); 19.6 (*C*H$_{2,diol}$); 18.6 (*C*H$_{3,Myc}$); 18.2 (C-6'); 18.0 (C-6); 14.3 (*C*H$_{3,Myc}$). IR (thin film, cm^{-1}): 1055, 1073, 1095, 1120, 1259, 1378, 1457, 1464, 1507, 1734, 2853, 2923. HRMS calculated for $C_{142}H_{239}O_{20}$ 2265.77825 $[M+H]^+$; found 2265.77134.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (20B)



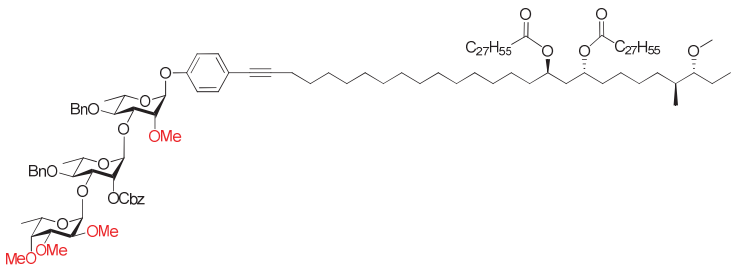
Compound **27** (27 mg, 12 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (20 mg, 10 µmol, 86%) as a pale oil. $[\alpha]_D^{25}$ = -44.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.99 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.15-5.14 (m, 2H, H-1', H-1''); 4.84 (quint, 2H, *J* = 6.3 Hz, C*H*$_{diol}$); 4.11 (s, 1H, H-2'); 4.08-4.03 (m, 2H, H-3, H-5''); 3.97-3.90 (m, 1H, H-5'); 3.82-3.74 (m, 3H, H-2, H-3', H-5); 3.70-3.58 (m, 11H, H-2'', H-3'', H-4, H-4', O*H*, OC*H*$_3$); 3.52 (s, 3H, OC*H*$_3$); 3.49 (s, 3H, OC*H*$_3$); 3.48 (d, 1H, *J* = 1.2 Hz, H-4''); 2.57-2.50 (m, 4H, C*H*$_{2,Diol}$, C*H*$_{Myc}$); 2.28 (bs, 1H, O*H*); 2.16 (bs, 1H, O*H*); 1.77-0.81 (m, 270H, H-6, H-6', H-6'', C*H*$_{2,Diol}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2 (*C*O$_{Myc}$); 154.7, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 102.3 (C-1''); 101.0 (C-1'); 95.0 (C-1); 83.3 (C-3'); 81.1 (C-3''); 80.2 (C-2); 80.1 (C-3); 79.1 (C-4''); 78.9 (C-2''); 71.9 (C-4'); 71.8 (C-4); 71.3 (C-2'); 70.5 (*C*H$_{diol}$); 69.2 (C-5); 68.8 (C-5'); 67.7 (C-5''); 62.1, 60.4, 58.7, 57.9 (O*C*H$_3$); 45.7, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,diol}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 34.8 (*C*H$_{2,diol}$); 32.1 (*C*H$_{2,Myc}$); 32.0 31.9, 30.2 (*C*H$_{2,diol}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.7, 25.3 (*C*H$_{2,diol}$); 22.8, 22.8 (*C*H$_{2,Myc}$); 20.9, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 18.0, 17.9 (C-6 and C-6'); 16.8 (C-6''); 14.3 (*C*H$_{3,Myc}$). IR (thin film, cm^{-1}): 1043, 1100, 1129, 1173, 1229, 1378, 1460, 1484, 1508, 1734, 2853, 2923, 3436. HRMS calculated for $C_{119}H_{223}O_{17}$ 1925.66471 $[M+H]^+$; found 1925.66457.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bismycocerosate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (21B)



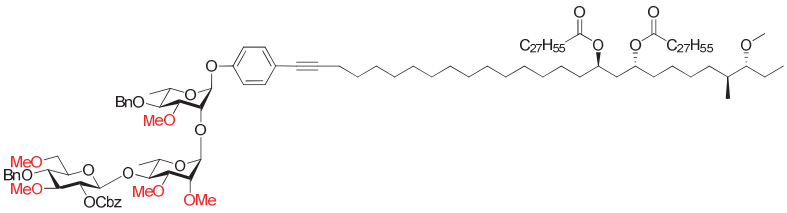
Compound **28** (22 mg, 9.7 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (15 mg, 7.7 µmol, 79%) as a pale oil. $[\alpha]_D^{25}$ = -23.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.94 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 2.0 Hz, H-1); 5.10 (d, 1H, *J* = 1.2 Hz, H-1'); 4.91 (quint, 2H, *J* = 6.4 Hz, C*H*$_{diol}$); 4.41 (d, 1H, *J* = 7.6 Hz, H-1''); 4.23 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2); 3.89 (d, 1H, *J* = 0.8 Hz, 2''-O*H*); 3.79-3.71 (m, 3H, H-2', H-5, H-5'); 3.68-3.60 (m, 8H, H-3, H-3', H-4', H-6'', OC*H*$_3$); 3.58-3.47 (m, 11H, H-4, H-4'', OC*H*$_3$); 3.45-3.38 (m, 5H, H-2'', H-5'', OC*H*$_3$); 3.17 (t, 1H, *J* = 9.0 Hz, H-3''); 2.81 (bs, 1H, O*H*); 2.56-2.48 (m, 4H, C*H*$_{2,diol}$, C*H*$_{Myc}$); 2.29 (bs, 1H, O*H*); 2.16 (bs, 1H, O*H*); 1.77-0.81 (m, 249H, H-6, H-6', C*H*$_{2,Diol}$, C*H*$_{Myc,}$ C*H*$_{2,Myc}$, C*H*$_{3,Myc}$). ^{13}C-APT NMR (101 MHz) δ: 176.2 (*C*O$_{Myc}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.8 (C-1''); 98.5 (C-1'); 97.5 (C-1); 85.6 (C-3''); 81.8 (C-4'); 81.5 (C-3); 80.3 (C-3'); 75.9 (C-2'); 75.1 (C-2''); 74.1 (C-5''); 73.0 (C-6''); 72.2 (C-2); 72.0 (C-4); 71.4 (C-4''); 70.5 (*C*H$_{diol}$); 69.1 (C-5); 68.4 (C-5'); 60.7, 59.7, 59.2, 57.8, 57.5, 56.7 (O*C*H$_3$); 38.6, 35.3 (*C*H$_2$); 34.9 (*C*H$_{Phth}$); 45.7, 45.4 (*C*H$_{2,Myc}$); 41.1, 38.6 (*C*H$_{2,diol}$); 37.9 (*C*H$_{Myc}$); 36.7 (*C*H$_{2,Myc}$); 35.3, 34.8 (*C*H$_{2,diol}$); 32.1 (*C*H$_{2,Myc}$); 32.0 31.9, 30.2 (*C*H$_{2,diol}$); 30.1 (*C*H$_{Myc}$); 29.9, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4 (*C*H$_2$); 28.2 (*C*H$_{Myc}$); 27.3 (*C*H$_{Myc}$); 27.1 (*C*H$_{2,Myc}$); 25.3 (*C*H$_{2,diol}$); 22.9, 22.8 (*C*H$_{2,Myc}$); 20.9, 20.6, 20.5, 18.6 (*C*H$_{3,Myc}$); 17.9 (C-6) 17.7 (C-6'); 14.3 (*C*H$_{3,Myc}$). IR (thin film, cm^{-1}): 1010, 1016, 1072, 1085, 1089, 1132, 1175, 1233, 1378, 1457, 1509, 1734, 2853, 2923, 3457. HRMS calculated for $C_{120}H_{225}O_{18}$ 1955.67196 $[M+H]^+$; found 1955.67024.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bisoctacosanoate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (29)



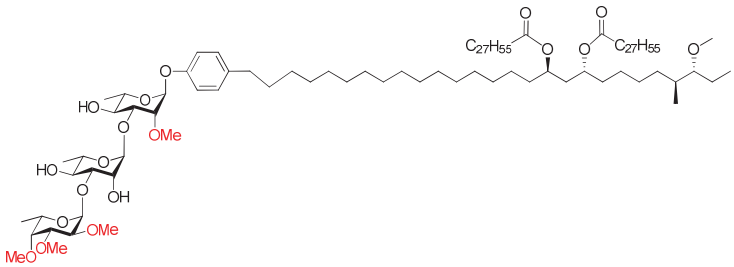
The title compound was synthesized according to general procedure D using diol **16** (22 mg, 16 µmol, 1.0 eq) and octacosanoic acid (**4**) (21 mg, 49 µmol, 3.0 eq), DIC (15 µL, 98 µmol, 6.0 eq) and DMAP (18 mg, 146 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (31 mg, 14 µmol, 88%) as a waxy solid. $[\alpha]_D^{25}$ = -51.2 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.42-7.26 (m, 17H, C*H*$_{arom}$); 6.94 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.13 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.94-4.88 (m, 3H, PhC*H*H, C*H*$_{Phth}$); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.22-4.18 (m, 2H, H-3, H-3'); 4.04-3.97 (m, 1H, H-5'); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.74-3.66 (m, 2H, H-2, H-5); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.27 (d, 1H, *J* = 1.6 Hz, H-4''); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_{2,Phth}$); 2.26 (t, 4H, *J* = 7.4 Hz, C*H*$_{2,oct}$); 1.75-1.05 (m, 188H, H-6, H-6', C*H*$_{2,Phth}$, C*H*$_{2,oct}$); 0.97 (d, 3H, *J* = 6.4 Hz, H-6''); 0.93-0.80 (m, 12H, C*H*$_{3,Phth}$, C*H*$_{3,oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{Oct}$); 155.7 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 138.2, 135.2 (C$_{q,arom}$); 133.0, 128.9, 128.9, 128.8, 128.5, 128.5, 128.4, 127.9, 127.6, 127.6 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.0 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 80.4 (C-3); 80.1 (C$_{q,alkyne}$); 80.1 (C-2 and C-3''); 79.9, 79.7 (C-4 and C-4'); 79.3 (C-4''); 78.3 (C-3'); 77.8 (C-2''); 76.8 (C-2'); 75.7, 75.1 (Ph*C*H$_2$); 70.2 (*C*H$_{Phth}$); 70.1 (Ph*C*H$_2$); 68.9 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2, 57.5 (O*C*H$_3$); 38.6 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 34.9, 32.7, 32.1, 29.9, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0, 27.6, 25.7, 25.3, 25.1, 22.8, 22.5, 19.5 (*C*H$_2$); 18.2 (C-6); 18.1 (C-6'); 16.4 (C-6''); 14.9 (*C*H$_{3,Phth}$). 14.3 (*C*H$_{3,Oct}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1043, 1100, 1262, 1457, 1462, 1472, 1507, 1734, 2849, 2916. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bisoctacosanoate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (30)



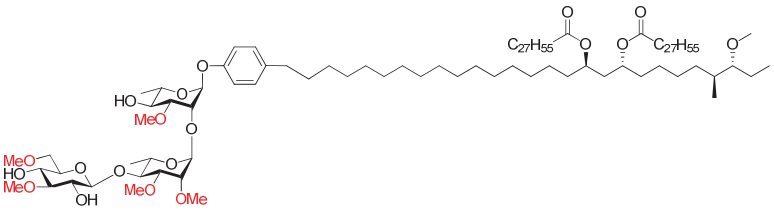
The title compound was synthesized according to general procedure D using diol **17** (25 mg, 18 µmol, 1.0 eq) and octacosanoic acid (**4**) (23 mg, 54 µmol, 3.0 eq), DIC (20 µL, 126 µmol, 7.0 eq) and DMAP (20 mg, 163 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (34 mg, 15 µmol, 86%) as a waxy solid. $[\alpha]_D^{25}$ = -35.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.26 (m, 17, C*H*$_{arom}$); 6.95 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.47 (s, 1H, H-1); 5.29-5.22 (m, 2H, PhC*H*$_2$); 5.19 (s, 1H, H-1'); 4.94-4.88 (m, 3H,PhC*H*H, C*H*$_{Phth}$); 4.79 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (s, 1H, H-2); 3.79 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.76-3.47 (m, 16H, H-2', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 3.45-3.39 (m, 2H, H-4, H-4'); 3.36-3.33 (m, 8H, H-3', H-3'', OC*H*$_3$); 2.90-2.84 (m, 1H, C*H*$_{Phth}$); 2.38 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 2.26 (t, 4H, *J* = 7.4 Hz, C*H*$_{2,oct}$); 1.73 (t, 2H, *J* = 6.6 Hz, C*H*$_{2,oct}$); 1.68-1.03 (m, 168H, H-6, H-6', C*H*$_{2,Phth}$, C*H*$_{2,oct}$); 0.93-0.81 (m, 12H, C*H*$_{3,Phth,}$ C*H*$_{3,oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{oct}$); 155.3 (C$_{q,arom}$); 154.9 (*C*O$_{Cbz}$); 138.5, 138.3, 135.6 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 86.8 (*C*H$_{Phth}$); 85.0 (C-3''); 82.0 (C-3); 80.8 (C-4'); 80.1 (C-4); 80.1 (C$_{q,alkyne}$); 78.1 (C-2''); 77.7, 77.6 (C-4'' and C-5''); 77.0 (C-2'); 75.3, 75.1 (Ph*C*H$_2$); 74.8 (C-3'); 73.0 (C-2); 71.1 (C-6''); 70.2 (*C*H$_{Phth}$), 69.9 (Ph*C*H$_2$); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6, 57.5 (O*C*H$_3$); 34.9, 34.9, 34.7, 32.7, 32.1, 29.9, 29.7, 29.5, 29.4, 29.2, 29.0, 27.6, 25.7, 25.3, 25.1, 22.8, 22.5, 19.6 (*C*H$_2$); 18.2, 18.0 (C-6 and C-6'); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Oct}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1073, 1079, 1120, 1176, 1198, 1261, 1454, 1464, 1472, 1508, 1736, 2849, 2916. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bisoctacosanoate)phenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (20C)



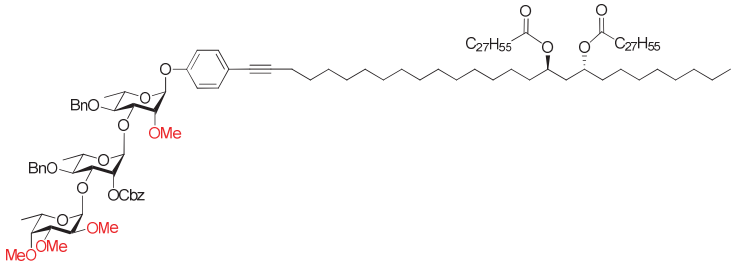
Compound **29** (31 mg, 14 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (19 mg, 10 µmol, 72%) as a pale oil. $[\alpha]_D^{25}$ = -40.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.99 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.15-5.14 (m, 2H, H-1', H-1"); 4.91 (quint, 2H, *J* = 6.4 Hz, C*H*$_{Phth}$); 4.11 (s, 1H, H-2'); 4.08-4.03 (m, 2H, H-3, H-5"); 3.98-3.91 (m, 1H, H-5'); 3.84-3.74 (m, 3H, H-2, H-3', H-5); 3.70-3.58 (m, 11H, H-2", H-3", H-4, H-4', O*H*, OC*H*$_3$); 3.52 (s, 3H, OC*H*$_3$); 3.49 (s, 3H, OC*H*$_3$); 3.48 (d, 1H, *J* = 1.2 Hz, H-4"); 3.33 (s, 3H, OC*H*$_3$); 2.88-2.83 (m, 1H, C*H*$_{Phth}$); 2.55 (t, 2H, *J* = 7.8 Hz, C*H*$_{2,Phth}$); 2.29-2.20 (m, 5H, C*H*$_{2,Oct}$, O*H*); 2.15 (bs, 1H, O*H*); 1.77-0.98 (m, 168H, H-6, H-6', H-6", C*H*$_{2,Phth}$, C*H*$_{2,oct}$); 0.93-0.81 (m, 12H, C*H*$_{3,Phth}$, C*H*$_{3,Oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{Oct}$); 154.7, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 102.3 (C-1"); 101.0 (C-1'); 95.0 (C-1); 86.8 (*C*H$_{Phth}$); 83.3 (C-3'); 81.1 (C-3"); 80.2 (C-2); 80.1 (C-3); 79.1 (C-4"); 78.9 (C-2"); 71.9 (C-4'); 71.8 (C-4); 71.3 (C-2'); 70.2 (*C*H$_{Phth}$); 69.2 (C-5); 68.7 (C-5'); 67.7 (C-5"); 62.1, 60.4, 58.7, 57.9, 57.5 (OCH$_3$); 38.6, 35.3 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 34.9, 34.7, 32.7 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,Oct}$); 31.9 (*C*H$_{2,Phth}$); 29.9, 29.9, 29.8, 29.7, 29.5, 29.4 (*C*H$_2$); 27.6 (*C*H$_{2,Phth}$); 25.7, 25.3, 25.2 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,Oct}$); 22.5 (*C*H$_{2,Phth}$); 18.0, 17.9 (C-6 and C-6'); 16.8 (C-6"); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,Oct}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1060, 1118, 1464, 1472, 1734, 2849, 2916, 3394. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diyl bisoctacosanoate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (21C)



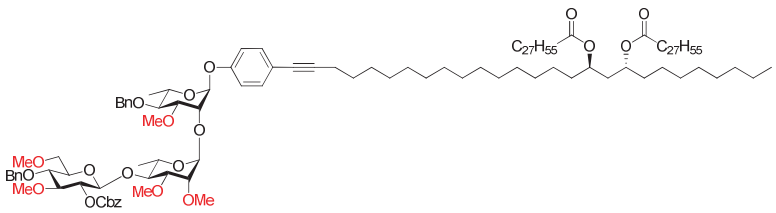
Compound **30** (33 mg, 15 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (22 mg, 12 µmol, 78%) as a pale oil. $[\alpha]_D^{25}$ = -27.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.94 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 1.6 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.91 (quint, 2H, *J* = 6.3 Hz, C*H*$_{Phth}$); 4.41 (d, 1H, *J* = 8.0 Hz, H-1''); 4.23 (dd, 1H, *J* = 1.6, 2.8 Hz, H-2); 3.89 (bs, 1H, 2''-O*H*); 3.79-3.71 (m, 3H, H-2', H-5, H-5'); 3.68-3.60 (m, 8H, H-3, H-3', H-4', H-6'', OC*H*$_3$); 3.58-3.49 (m, 11H, H-4, H-4'', OC*H*$_3$); 3.46-3.39 (m, 5H, H-2'', H-5'', OC*H*$_3$); 3.17 (t, 1H, *J* = 9.0 Hz, H-3''); 2.88-2.82 (m, 1H, C*H*$_{Phth}$); 2.55 (t, 2H, *J* = 8.0 Hz, C*H*$_{2,Phth}$); 2.30-2.20 (m, 4H, C*H*$_{2,oct}$); 1.77-1.03 (m, 176H, H-6, H-6', C*H*$_{2,Phth}$, C*H*$_{2,oct}$); 0.93-0.86 (m, 12H, C*H*$_{3,Phth}$, C*H*$_{3,Oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{oct}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.7 (C-1''); 98.5 (C-1'); 97.5 (C-1); 86.8 (*C*H$_{Phth}$); 85.6 (C-3''); 81.7 (C-4'); 81.5 (C-3); 80.3 (C-3'); 75.9 (C-2'); 75.1 (C-2''); 74.2 (C-5''); 73.0 (C-6''); 72.2 (C-2); 72.0 (C-4); 71.4 (C-4''); 70.2 (*C*H$_{Phth}$); 69.1 (C-5); 68.4 (C-5'); 60.7, 59.7, 59.2, 57.8, 57.5, 56.7 (O*C*H$_3$); 38.6, 35.3 (*C*H$_{2,Phth}$); 34.9 (*C*H$_{Phth}$); 34.9, 34.7, 32.7 (*C*H$_{2,Phth}$); 32.1 (*C*H$_{2,oct}$); 31.9 (*C*H$_{2,Phth}$); 29.9, 29.8, 29.7, 29.5, 29.4 (*C*H$_2$); 27.6 (*C*H$_{2,Phth}$); 25.7, 25.3, 25.2 (*C*H$_{2,Phth}$); 22.9 (*C*H$_{2,oct}$); 22.5 (*C*H$_{2,Phth}$); 17.9 (C-6); 17.7 (C-6'); 14.9 (*C*H$_{3,Phth}$); 14.3 (*C*H$_{3,oct}$); 10.2 (*C*H$_{3,Phth}$). IR (thin film, cm^{-1}): 1070, 1119, 1464, 1472, 1511, 1736, 2849, 2916, 3444. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bis octacosanoate)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (31)



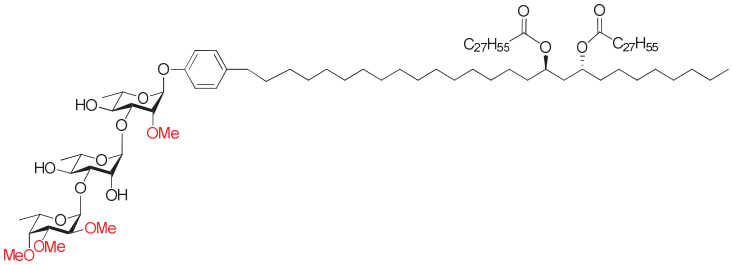
The title compound was synthesized according to general procedure D using diol **18** (33 mg, 25 µmol, 1.0 eq) and octacosanoic acid (**4**) (33 mg, 77 µmol, 3.0 eq), DIC (27 µL, 176 µmol, 7.0 eq) and DMAP (28 mg, 227 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (53 mg, 25 µmol, 100%) as a waxy solid. $[\alpha]_D^{25}$ = -51.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.41-7.26 (m, 17H, C*H*$_{arom}$); 6.94 (d, 2H, *J* = 9.2 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.13 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.98-4.88 (m, 3H, PhC*H*H, C*H*$_{diol}$); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.22-4.18 (m, 2H, H-3, H-3'); 4.04-3.97 (m, 1H, H-5'); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.74-3.66 (m, 2H, H-2, H-5); 3.57-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.33 (s, 3H, OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.27 (d, 1H, *J* = 1.6 Hz, H-4''); 2.37 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,Phth}$); 2.28 (t, 4H, *J* = 8.2 Hz, C*H*$_{2,oct}$); 1.77-1.04 (m, 172H, H-6, H-6'C*H*$_{2,diol}$, C*H*$_{2,Oct}$); 0.97 (d, 3H, *J* = 6.8 Hz, H-6''); 0.90-0.86 (m, 9H, C*H*$_{3,diol}$, C*H*$_{3,oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{Oct}$); 155.7 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 138.2, 135.2 (C$_{q,arom}$); 133.0, 128.9, 128.9, 128.8, 128.5, 128.5, 128.4, 127.8, 127.6, 127.5 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 99.9 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyne}$); 80.3 (C-3); 80.1 (C$_{q,alkyne}$); 80.1 (C-2 and C-3''); 79.9, 79.7 (C-4 and C-4'); 79.3 (C-4''); 78.3 (C-3'); 77.7 (C-2''); 76.8 (C-2'); 75.7, 75.1, 70.2 (Ph*C*H$_2$); 68.9 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2 (O*C*H$_3$); 38.6, 34.9, 34.7, 32.1, 32.0, 29.9, 29.8, 29.7, 29.7, 29.5, 29.4, 29.1, 29.0, 25.3, 25.1, 22.8, 19.5 (*C*H$_2$); 18.2 (C-6); 18.0 (C-6'); 16.4 (C-6''); 14.3 (*C*H$_{3,oct}$ and *C*H$_{3,diol}$). IR (thin film, cm^{-1}): 1235, 1258, 1457, 1464, 1472, 1507, 1736, 2849, 2916. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bis octacosanoate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (32)



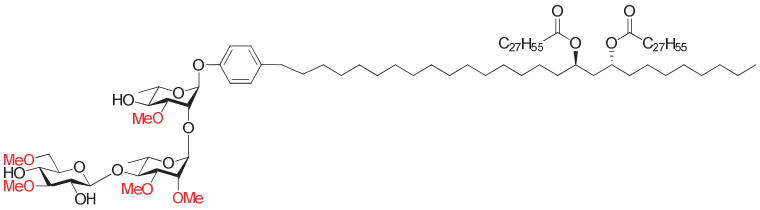
The title compound was synthesized according to general procedure D using diol **19** (30 mg, 22 µmol, 1.0 eq) and octacosanoic acid (**4**) (29 mg, 67 µmol, 3.0 eq), DIC (24 µL, 157 µmol, 7.0 eq) and DMAP (25 mg, 202 µmol, 9.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (44 mg, 20 µmol, 91%) as a waxy solid. $[\alpha]_D^{25}$ = -35.5 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.40-7.26 (m, 17, C*H*$_{arom}$); 6.95 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.29-5.22 (m, 2H, PhC*H*$_2$); 5.19 (d, 1H, *J* = 1.2 Hz, H-1'); 4.94-4.88 (m, 3H, PhC*H*H, C*H*$_{diol}$); 4.79 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 3.79 (dd, 1H, *J* = 3.2, 9.2 Hz, H-3); 3.76-3.47 (m, 16H, H-2', H-4'', H-5, H-5', H-5'', H-6'', OC*H*$_3$); 3.45-3.39 (m, 2H, H-4, H-4'); 3.36-3.33 (m, 8H, H-3', H-3'', OC*H*$_3$); 2.38 (t, 2H, *J* = 7.2 Hz, C*H*$_{2,diol}$); 2.26 (t, 4H, *J* = 9.0 Hz, C*H*$_{2,oct}$); 1.73 (t, 2H, *J* = 6.6 Hz, C*H*$_{2,oct}$); 1.68-1.05 (m, 206H, H-6, H-6', C*H*$_{2,diol}$, C*H*$_{2,oct}$); 0.90-0.83 (m, 9H, C*H*$_{3,diol}$, C*H*$_{3,oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{oct}$); 155.3 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 138.5, 138.3, 135.6 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 (C$_{q,alkyne}$); 85.0 (C-3''); 82.0 (C-3); 80.8 (C-4'); 80.1 (C-4); 80.1 (C$_{q,alkyne}$); 78.1 (C-2''); 77.7, 77.6 (C-4'' and C-5''); 77.0 (C-2'); 75.3, 75.0 (PhCH_2); 74.8 (C-3'); 73.0 (C-2); 71.1 (C-6''); 70.2 (*C*H$_{diol}$); 69.9 (PhCH_2); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6 (O*C*H$_3$); 34.9, 34.7, 32.1, 32.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.2, 29.0, 25.3, 25.1, 22.8, 19.6 (*C*H$_{2,diol}$); 18.2, 18.0 (C-6 and C-6'); 14.3 (*C*H$_{3,oct}$ and *C*H$_{3,diol}$). IR (thin film, cm^{-1}): 1036, 1063, 1076, 1096, 1123, 1259, 1462, 1472, 1507, 1736, 2849, 2916. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bis octacosanoate)phenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (20D)



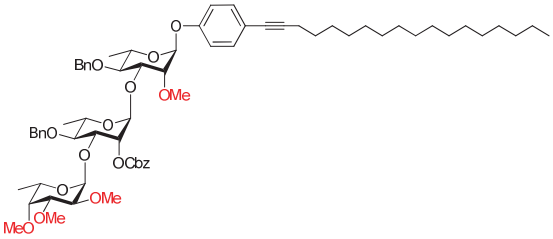
Compound **31** (56 mg, 25 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (27 mg, 15 µmol, 59%) as a pale oil. $[\alpha]_D^{25}$ = -48.0 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.99 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.15-5.14 (m, 2H, H-1', H-1''); 4.91 (quint, 2H, *J* = 6.4 Hz, C*H*$_{diol}$); 4.11 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2'); 4.09-4.03 (m, 2H, H-3, H-5''); 3.99-3.90 (m, 1H, H-5'); 3.83-3.74 (m, 3H, H-2, H-3', H-5); 3.70-3.57 (m, 11H, H-2'', H-3'', H-4, H-4', O*H*, OC*H*$_3$); 3.52 (s, 3H, OC*H*$_3$); 3.49 (s, 3H, OC*H*$_3$); 3.48 (d, 1H, *J* = 1.2 Hz, H-4''); 2.55 (t, 2H, *J* = 7.6 Hz, C*H*$_{2,diol}$); 2.32-2.18 (m, 5H, C*H*$_{2,oct}$, O*H*); 1.77-1.03 (m, 168H, H-6, H-6', H-6'', C*H*$_{diol}$, C*H*$_{2,oct}$); 0.92-0.86 (m, 12H, C*H*$_{3,diol}$, C*H*$_{3,oct}$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{Oct}$); 154.7, 137.0 (C$_{q,arom}$); 129.5, 116.3 (*C*H$_{arom}$); 102.3 (C-1''); 100.9 (C-1'); 95.0 (C-1); 83.3 (C-3'); 81.1 (C-3''); 80.2 (C-2); 80.2 (C-3); 79.1 (C-4''); 78.9 (C-2''); 71.9 (C-4'); 71.8 (C-4); 71.3 (C-2'); 70.2 (*C*H$_{diol}$); 69.2 (C-5); 68.8 (C-5'); 67.6 (C-5''); 62.1, 60.4, 58.7, 57.9 (O*C*H$_3$); 38.6, 35.3 (*C*H$_{2,Diol}$); 34.9, 34.7 (*C*H$_{2,Diol}$); 32.1 (*C*H$_{2,Oct}$); 32.0 (*C*H$_{2,Diol}$); 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4 (*C*H$_2$); 25.3, 25.2 (*C*H$_{2,Diol}$); 22.8 (*C*H$_{2,Oct}$); 22.8 (*C*H$_{2,Diol}$); 18.0, 17.9 (C-6 and C-6'); 16.8 (C-6''); 14.3 (*C*H$_{3,oct}$ and *C*H$_{3,diol}$). IR (thin film, cm^{-1}): 1041, 1132, 1262, 1464, 1472, 1736, 2849, 2916, 3420. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-((9*R*,11*R*)-heptacos-26-yne-9,11-diyl bis octacosanoate)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (21D)



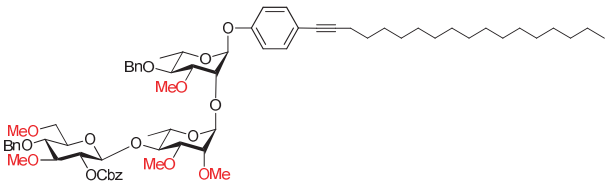
Compound **32** (44 mg, 20 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (22 mg, 12 µmol, 59%) as a pale oil. $[\alpha]_D^{25}$ = -47.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.94 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 2.0 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.91 (quint, 2H, *J* = 6.4 Hz, C*H*$_{diol}$); 4.41 (d, 1H, *J* = 7.6 Hz, H-1"); 4.23 (dd, 1H, *J* = 2.0, 2.4 Hz, H-2); 3.89 (d, 1H, *J* = 0.8 Hz, 2"-O*H*); 3.79-3.72 (m, 3H, H-2', H-5, H-5'); 3.68-3.60 (m, 8H, H-3, H-3', H-4', H-6", OC*H*$_3$); 3.58-3.49 (m, 11H, H-4, H-4", OC*H*$_3$); 3.45-3.35 (m, 5H, H-2", H-5", OC*H*$_3$); 3.17 (t, 1H, *J* = 9.0 Hz, H-3"); 2.81 (s, 1H, O*H*); 2.55 (t, 2H, *J* = 7.8 Hz, C*H*$_{2,diol}$); 2.29-2.22 (m, 5H, C*H*$_{2,oct}$, O*H*); 1.73 (t, 2H, 6.6 Hz, C*H*$_2$); 1.63-1.38 (m, 17H, C*H*$_2$); 1.34-1.03 (m, 168H, C*H*$_2$, H-6, H-6'); 0.90-0.86 (m, 9H, C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 173.5 (*C*O$_{oct}$); 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.8 (C-1"); 98.5 (C-1'); 97.5 (C-1); 85.6 (C-3"); 81.8 (C-4'); 81.5 (C-3); 80.3 (C-3'); 75.9 (C-2'); 75.1 (C-2"); 74.1 (C-5"); 73.0 (C-6"); 72.2 (C-2); 72.0 (C-4); 71.4 (C-4"); 70.2 (*C*H$_{diol}$); 69.1 (C-5); 68.4 (C-5'); 60.7, 59.8, 59.2, 57.8, 56.7 (O*C*H$_3$); 38.6, 35.3 (*C*H$_{2,diol}$); 34.9, 34.7 (*C*H$_{2,diol}$); 32.1 (*C*H$_{2,oct}$); 32.0, 31.9 (*C*H$_{2,diol}$); 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4 (*C*H$_2$); 25.3, 25.2 (*C*H$_{2,diol}$); 22.8 (*C*H$_{2,oct}$); 22.8 (*C*H$_{2,diol}$); 17.9 (C-6); 17.7 (C-6'); 14.3 (*C*H$_{3,oct}$ and *C*H$_{3,diol}$). IR (thin film, cm^{-1}): 1012, 1129, 1198, 1235, 1458, 1464, 1472, 1508, 1736, 2849, 2916, 3444. Despite multiple attempts, HRMS data for this molecule could not be obtained.

4-(octadec-1-ynyl)phenyl 2-*O*-methyl-3-*O*-(2-*O*-benzyloxycarbonyl-3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (33)



The title compound was synthesized according to general procedure A using **14** (30 mg, 29 µmol, 1.0 eq) and 1-octadecyn (37 mg, 146 µmol, 5.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (30 mg, 26 µmol, 89%) as a yellow oil. $[\alpha]_D^{25}$ = -100.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.44-7.24 (m, 17H, C*H*$_{arom}$); 6.95-6.91 (m, 2H, C*H*$_{arom}$); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.22-5.10 (m, 6H, H-1', H-1'', H-2', PhC*H*$_2$, PhC*H*H); 4.93 (d, 1H, *J* = 10.4 Hz, PhC*H*H); 4.60-4.53 (m, 2H, PhCH*H*, PhCH*H*); 4.22-4.18 (m, 2H, H-3, H-3'); 4.03-3.97 (m, 1H, H-5'); 3.81 (q, 1H, *J* = 6.4 Hz, H-5''); 3.76-3.68 (m, 2H, H-2, H-5); 3.59-3.48 (m, 13H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.31 (s, 3H, OC*H*$_3$); 3.27 (d, 1H, *J* = 2.0 Hz, H-4''); 2.37 (t, 2H, *J* = 7.0 Hz, C*H*$_2$); 1.58 (quint, 2H, *J* = 6.8 Hz, C*H*$_2$); 1.44-1.17 (m, 34H, H-6, H-6', C*H*$_2$) 0.97 (d, 3H, *J* = 6.4 Hz, H-6''); 0.88 (t, 3H, *J* = 6.8 Hz, C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 155.7 (C$_{q,arom}$); 154.8 (*C*O$_{Cbz}$); 139.0, 138.2, 135.2 (C$_{q,arom}$); 133.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 127.8, 127.6, 127.5 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 100.0 (C-1''); 99.5 (C-1'); 94.4 (C-1); 89.5 (C$_{q,alkyn}$); 80.4 (C-4'); 80.1 (C-4); 79.9 (C-2); 79.7 (C-3''); 79.6 (C-3'); 79.3 (C-4''); 78.3 (C-3); 77.8 (C-2''); 76.8 (C-2'); 75.7, 75.1, 70.1 (Ph*C*H$_2$); 68.9 (C-5'); 68.7 (C-5); 67.1 (C-5''); 61.9, 59.1, 58.8, 58.2 (O*C*H$_3$); 32.1, 29.8, 29.8, 29.7, 29.5, 29.3, 29.1, 29.0, 22.8, 19.5 (*C*H$_2$); 18.2 (C-6); 18.1 (C-6'); 16.4 (C-6''); 14.3 (*C*H$_3$). IR (thin film, cm^{-1}): 1009, 1045, 1098, 1176, 1235, 1357, 1382, 1457, 1484, 1507, 1747, 2853, 2926. HRMS calculated for $C_{68}H_{94}O_{15}Na$ 1173.64849 [M+Na]$^+$; found 1173.64598.

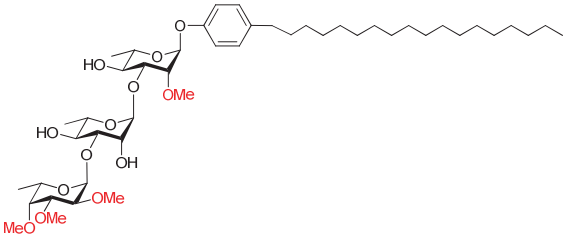
4-(octadec-1-ynyl)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,6-di-*O*-methyl-4-*O*-benzyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (34)



The title compound was synthesized according to general procedure A using **15** (26 mg, 25 µmol, 1.0 eq) and 1-octadecyne (31 mg, 123 µmol, 5.0 eq). Column chromatography (*n*-pentane-Et_2O 1:1) yielded the product (25 mg, 21 µmol, 86%) as a yellow oil. $[\alpha]_D^{25}$ = -50.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.42-7.26 (m, 17, C*H*$_{arom}$); 6.97-6.92 (m, 2H, C*H*$_{arom}$); 5.47 (d, 1H, *J* = 1.6 Hz, H-1); 5.29-5.22 (m, 2H, Ph*C*H$_2$); 5.19

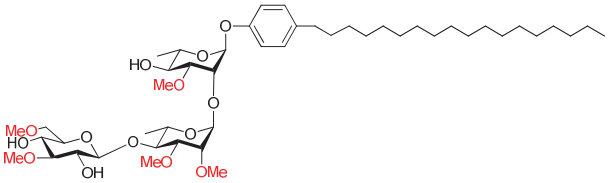
(d, 1H, *J* = 1.2 Hz, H-1'); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.79 (d, 1H, *J* = 10.8 Hz, PhCHH); 4.74 (d, 1H, *J* = 8.0 Hz, H-1''); 4.67-4.62 (m, 3H, H-2'', PhCH*H*, PhCH*H*); 4.24 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 3.81-3.31 (m, 27H, H-2', H-3, H-3', H-3'', H-4, H-4', H-4'', H-5, H-5', H-5'', H-6'', OCH_3); 2.38 (t, 2H, *J* = 7.0 Hz, CH_2); 1.62-1.55 (m, 2H, CH_2); 1.45-1.37 (m, 2H, CH_2); 1.36-1.24 (m, 34H, H-6, H-6', CH_2); 0.88 (t, 3H, *J* = 6.8 Hz, CH_3).^{13}C-APT NMR (101 MHz) δ: 155.3 ($C_{q,arom}$); 154.8 (CO_{Cbz}); 138.5, 138.3, 135.6 ($C_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9 (CH_{arom}); 118.0 ($C_{q,arom}$); 116.2 (CH_{arom}); 100.9 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.5 ($C_{q,alkyne}$); 85.0 (C-4''); 82.0 (C-2); 80.8 (C-4'); 80.1 (C-4); 80.1 ($C_{q,alkyne}$); 78.1 (C-2''); 77.7, 77.6 (C-3 and C-5''); 77.0 (C-2'); 75.3, 75.0 (PhCH_2); 74.8 (C-3'); 73.0 (C-2); 71.1 (C-6''); 69.9 (PhCH_2); 68.7 (C-5); 67.9 (C-5'); 61.0, 59.8, 59.1, 58.3, 57.6, (OCH_3); 32.1, 29.8, 29.8, 29.7, 29.5, 29.3, 29.1, 29.0, 22.8, 19.5 (CH_2); 18.2, 18.0 (C-6 and C-6'); 14.9 (CH_3). IR (thin film, cm^{-1}): 1017, 1056, 1075, 1093, 1120, 1139, 1206, 1259, 1384, 1454, 1484, 1507, 1606, 1756, 2853, 2923. HRMS calculated for $C_{69}H_{96}O_{16}Na$ 1203.65906 [M+Na]$^+$; found 1203.65660.

4-octadecylphenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (20E)



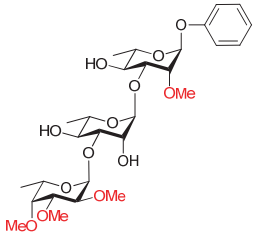
Compound **33** (25 mg, 22 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (12 mg, 14 µmol, 66%) as a pale oil. $[\alpha]_D^{25}$ = -91.8 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, CH_{arom}); 6.99 (dd, 2H, *J* = 2.2, 6.6 Hz, CH_{arom}); 5.51 (d, 1H, *J* = 1.6 Hz, H-1); 5.15-5.14 (m, 2H, H-1', H-1''); 4.11 (s, 1H, H-2'); 4.09-4.03 (m, 2H, H-3, H-5''); 3.97-3.90 (m, 1H, H-5'); 3.81-3.74 (m, 3H, H-2, H-3', H-5); 3.70-3.57 (m, 10H, H-2'', H-3'', H-4, H-4', OCH_3); 3.52 (s, 3H, OCH_3); 3.49 (s, 3H, OCH_3); 3.48 (d, 1H, *J* = 1.6 Hz, H-4''); 2.55 (t, 2H, *J* = 7.6 Hz, CH_2); 2.35 (bs, 1H, O*H*); 2.21 (bs, 1H, O*H*); 1.55 (quint, 2H, *J* = 7.6 Hz, CH_2); 1.36 (d, 3H, *J* = 6.4 Hz, H-6'); 1.34-1.25 (m, 38H, H-6, H-6'', CH_2); 0.88 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C-APT NMR (101 MHz) δ: 154.7, 137.0 ($C_{q,arom}$); 129.5, 116.3 (CH_{arom}); 102.3 (C-1''); 100.9 (C-1'); 95.0 (C-1); 83.3 (C-3'); 81.1 (C-3''); 80.2 (C-2); 80.0 (C-3); 79.1 (C-4''); 78.9 (C-2''); 71.9 (C-4'); 71.7 (C-4); 71.3 (C-2'); 69.2 (C-5); 68.8 (C-5'); 67.6 (C-5''); 62.1, 60.4, 58.7, 57.9 (OCH_3); 35.3, 32.1, 29.8, 29.8, 29.7, 29.5, 29.5, 22.8 (CH_2); 18.0, 17.9 (C-6 and C-6'); 16.8 (C-6''); 14.3 (CH_3). IR (thin film, cm^{-1}): 1043, 1089, 1129, 1195, 1229, 1510, 2852, 2923, 3433. HRMS calculated for $C_{46}H_{84}O_{13}N$ 858.59372 [M+NH_4]$^+$; found 858.59328.

4-octadecylphenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (21E)



Compound **34** (21 mg, 18 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (10 mg, 11 µmol, 65%) as a pale oil. $[\alpha]_D^{25}$ = -19.1 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.96-6.93 (m, 2H, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 2.0 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.41 (d, 1H, *J* = 7.6 Hz, H-1''); 4.23 (dd, 1H, *J* = 2.4, 4.8 Hz, H-2); 3.89 (d, 1H, *J* = 1.2 Hz, 2''-O*H*); 3.78-3.72 (m, 3H, H-2', H-5, H-5'); 3.68-3.49 (m, 19H, H-3, H-3', H-4, H-4', H-4'', H-6'', OC*H*$_3$); 3.45-3.39 (m, 5H, H-2'', H-5'', OC*H*$_3$); 3.17 (t, 1H, *J* = 9.2 Hz, H-3''); 2.81 (d, 1H, *J* = 1.6 Hz, O*H*); 2.55 (t, 2H, *J* = 7.8 Hz, C*H*$_2$); 2.30 (d, 1H, *J* = 1.6 Hz, O*H*); 2.29-2.22 (m, 4H, CH_2); 1.73 (t, 2H, *J* = 6.6 Hz, C*H*$_2$); 1.61-1.56 (m, 2H, C*H*$_2$); 1.34-1.25 (m, 38H, H-6, H-6', C*H*$_2$); 0.88 (t, 3H, *J* = 6.8 Hz, C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.8 (C-1''); 98.5 (C-1'); 97.5 (C-1); 85.6 (C-3''); 81.8 (C-4'); 81.5 (C-3); 80.3 (C-3'); 75.9 (C-2'); 75.1 (C-2''); 74.1 (C-5''); 73.0 (C-6''); 72.2 (C-2); 72.0 (C-4); 71.4 (C-4''); 69.1 (C-5); 68.4 (C-5'); 60.7, 59.8, 59.2, 57.8, 56.7 (O*C*H$_3$); 35.3, 32.1, 29.8, 29.8, 29.7, 29.5, 29.5, 22.8 (*C*H$_2$); 17.9 (C-6); 17.7 (C-6'); 14.3 (*C*H$_3$). IR (thin film, cm^{-1}): 1016, 1067, 1120, 1198, 1229, 1510, 2853, 2923, 3443. HRMS calculated for $C_{47}H_{82}O_{14}Na$ 893.55968 $[M+Na]^+$; found 893.55943.

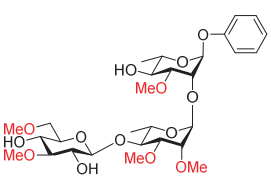
Phenyl 2-*O*-methyl-3-*O*-(3-*O*-(2,3,4-tri-*O*-methyl-α-L-fucopyranosyl-α-L-rhamnopyranosyl)-4-*O*-benzyl-α-L-rhamnopyranoside (20F)



Compound **14** (40 mg, 39 µmol, 1.0 eq) was dissolved in EtOH (5 mL, 0.01 M) together with NH_4OAc (10 mg, 130 µmol, 3.3 eq)) and the solution was purged with N_2. A catalytic amount of Pd/C (10%) was then added and the resulting mixture was purged with H_2. The reaction was left to stir under H_2 atmosphere until all intermediates converged to a single spot on TLC (m/z = 791 ($M+Na^+$)) after which the solution was filtered over celite, diluted with H_2O and extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was then subjected to general hydrogenation procedure C to give the title compound (21 mg, 36 µmol, 92%) as a pale oil. $[\alpha]_D^{25}$ = -123.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.29 (t, 2H, *J* = 7.6 Hz, C*H*$_{arom}$); 7.08 (dd, 2H, *J* = 0.5, 8.6 Hz, C*H*$_{arom}$); 7.03 (t, 2H, *J* = 7.8 Hz, C*H*$_{arom}$); 5.56 (d, 1H, *J* = 1.2 Hz, H-1); 5.15-5.14 (m, 2H, H-1', H-1''); 4.11 (s, 1H, H-2'); 4.09-4.03 (m, 3H, H-3, H-5'', O*H*); 3.96-3.90 (m, 1H, H-5'); 3.82-3.71 (m, 3H, H-2, H-3', H-5); 3.69-3.58 (m, 10H, H-2'', H-3'', H-4, H-4', OC*H*$_3$); 3.55-3.45 (m, 7H, H-4'', OC*H*$_3$); 2.45 (d, 1H, *J* = 3.2 Hz, O*H*); 2.29 (d, 1H, *J* = 3.2 Hz, O*H*); 1.37 (d, 3H, *J* = 6.0 Hz, H-6'); 1.30-1.25 (m, 6H, H-6, H-6''). ^{13}C-APT NMR (101 MHz) δ: 156.6, (C$_{q,arom}$); 129.7, 122.4 116.4 (*C*H$_{arom}$); 102.3 (C-1''); 100.9 (C-1'); 94.8 (C-1); 83.2 (C-3'); 81.1 (C-3''); 80.1 (C-2); 79.9 (C-3); 79.1 (C-4''); 78.9 (C-2''); 71.9 (C-4'); 71.7 (C-4); 71.3 (C-2'); 69.3 (C-5);

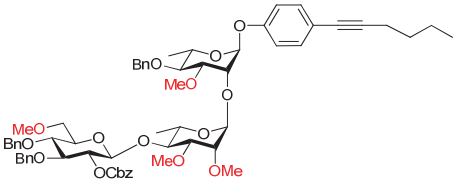
68.8 (C-5'); 67.6 (C-5''); 62.1, 60.4, 58.8, 57.9 (O*C*H$_3$); 18.0 (C-6') 17.9 (C-6); 16.8 (C-6''). IR (thin film, cm^{-1}): 1042, 1089, 1128, 1365, 1495, 2853, 2925, 3419. HRMS calculated for $C_{28}H_{44}O_{13}Na$ 611.26741 [M+Na]$^+$; found 611.26758.

Phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (21F)



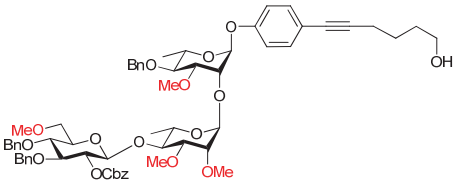
Compound **15** (51 mg, 48 µmol, 1.0 eq) was dissolved in EtOH (5 mL, 0.01 M) together with NH_4OAc (12 mg, 156 µmol, 3.2 eq)) and the solution was purged with N_2. A catalytic amount of Pd/C (10%) was then added and the resulting mixture was purged with H_2. The reaction was left to stir under H_2 atmosphere until all intermediates converged to a single spot on TLC (m/z = 821 (M+Na$^+$)) after which the solution was filtered over celite, diluted with H_2O and extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was then subjected to general hydrogenation procedure C to give the title compound (28 mg, 45 µmol, 94%) as a pale oil. $[\alpha]_D^{25}$ = -64.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.29-7.27 (m, 2H, C*H*$_{arom}$); 7.06-7.01 (m, 3H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 2.0 Hz, H-1); 5.11 (d, 1H, *J* = 1.6 Hz, H-1'); 4.41 (d, 1H, *J* = 8.0 Hz, H-1''); 4.24 (dd, 1H, *J* = 2.4, 4.8 Hz, H-2); 3.89 (d, 1H, *J* = 1.2 Hz, 2''-O*H*); 3.78-3.71 (m, 3H, H-2', H-5, H-5'); 3.69-3.49 (m, 19H, H-3, H-3', H-4, H-4', H-4'', H-6'', OC*H*$_3$); 3.45-3.38 (m, 5H, H-2'', H-5'', OC*H*$_3$); 3.17 (t, 1H, *J* = 9.0 Hz, H-3''); 2.94 (d, *J* = 1.6 Hz, 1H, O*H*); 2.45 (d, *J* = 1.6 Hz, 1H, O*H*); 1.34 (d, 3H, *J* = 6.0 Hz, H-6'); 1.27 (d, 3H, *J* = 6.0 Hz, H-6'). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 129.7, 122.4, 116.3 (*C*H$_{arom}$); 105.7 (C-1''); 98.6 (C-1'); 97.2 (C-1); 85.6 (C-3''); 81.7 (C-4'); 81.5 (C-3); 80.3 (C-3'); 75.8 (C-2'); 75.1 (C-2''); 74.2 (C-5''); 72.9 (C-6''); 72.2 (C-2); 71.9 (C-4); 71.2 (C-4''); 69.1 (C-5); 68.4 (C-5'); 60.7, 59.7, 59.2, 57.8, 56.7 (O*C*H$_3$); 17.9 (C-6); 17.7 (C-6'). IR (thin film, cm^{-1}): 1009, 1069, 1120, 1228, 1387, 1494, 2854, 2928, 3429. HRMS calculated for $C_{29}H_{46}O_{14}Na$ 641.27798 [M+H]$^+$; found 641.27776.

4-(hex-1-ynyl)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (35)



The title compound was synthesized according to general procedure A using glycan **8** (46 mg, 41 µmol, 1.0 eq) and 1-hexyne (14 µL, 122 µmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 4:6) yielded the product (40 mg, 37 µmol, 91%) as a yellow oil. $[\alpha]_D^{25}$ = -60.9 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.21 (m, 22H, C*H*$_{arom}$); 6.96-6.94 (m, 2H, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.24-5.15 (m, 3H, H-1', PhC*H*$_{2,Cbz}$); 4.89 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.80-4.76 (m, 4H, PhC*H*H, PhC*H*H, H-1'', H-2''); 4.70-4.62 (m, 3H, PhCH*H*, PhCH*H*, PhCH*H*); 4.25 (dd, 1H, *J* = 2.4, 2.8 Hz, H-2); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.76-3.61 (m, 7H, H-2', H-3'', H-4'', H-5, H-5', H-5'', H-6''); 3.57-3.43 (m, 9H, H-4, H-4', H-6'', OC*H*$_3$); 3.39-3.32 (m, 7H, H-3', OC*H*$_3$); 2.39 (t, 1H, *J* = 7.0 Hz, C*H*$_2$); 1.63-1.52 (m, 2H, C*H*$_2$); 1.51-1.42 (m, 2H, C*H*$_2$); 1.32-1.25 (m, 6H, H-6, H-6'); 0.94 (t, 3H, *J* = 7.4 Hz, C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 155.3 (C$_{q,arom}$); 154.7 (*C*O$_{Cbz}$); 138.5, 138.4, 138.2, 135.5 (C$_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (*C*H$_{arom}$); 118.0 (C$_{q,arom}$); 116.2 (*C*H$_{arom}$); 101.1 (C-1''); 98.5 (C-1'); 96.9 (C-1); 89.4 (C$_{q,alkyne}$); 83.3 (C-4''); 82.0 (C-3); 80.8, 80.1 (C-4 and C-4'); 80.1 (C$_{q,alkyne}$); 78.2 (C-2''); 77.9, 77.7 (C-3'', C-5''); 77.0 (C-2'); 75.4, 75.2, 75.1 (Ph*C*H$_2$); 75.0 (C-3') 73.0 (C-2); 71.1 (C-6''); 69.9 (Ph*C*H$_2$); 68.7 (C-5); 68.0 (C-5'); 59.9, 59.1, 58.3, 57.6, (O*C*H$_3$); 31.0, 22.1, 19.2 (*C*H$_2$); 18.2, 18.1 (C-6 and C-6'); 13.8 (*C*H$_3$). IR (thin film, cm^{-1}): 1030, 1055, 1072, 1093, 1120, 1140, 1258, 1387, 1454, 1507, 1757, 2929. HRMS calculated for $C_{63}H_{76}O_{16}Na$ 1111.50256 $[M+Na]^+$; found 1111.50185.

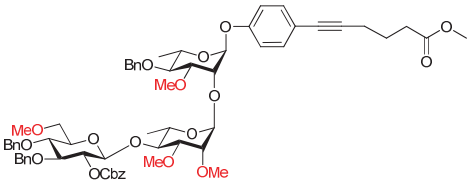
4-(1-hydroxyhex-6-ynyl)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (36)



The title compound was synthesized according to general procedure A using glycan **8** (53 mg, 47 µmol, 1.0 eq) and 5-hexyn-1-ol (15 µL, 140 µmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 1:4) yielded the product (42 mg, 38 µmol, 81%) as a yellow oil. $[\alpha]_D^{25}$ = -105.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.36-7.21 (m, 22H, C*H*$_{arom}$); 6.96 (dd, 2H, *J* = 2.2, 7.0 Hz, C*H*$_{arom}$); 5.48 (d, 1H, *J* = 2.0 Hz, H-1); 5.24-5.15 (m, 3H, H-

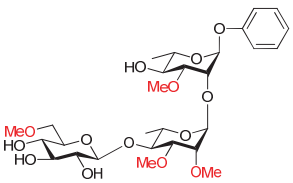
1', PhCH_2); 4.89 (d, 1H, *J* = 10.8 Hz, PhC*H*H); 4.80-4.76 (m, 4H, PhC*H*H, PhC*H*H, H-1'', H-2''); 4.69-4.62 (m, 3H, PhCH*H*, PhCH*H*, PhCH*H*); 4.25 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.76-3.61 (m, 9H, H-2', H-3'', H-4'', H-5, H-5', H-5'', H-6", CH_2OH); 3.56-3.42 (m, 9H, H-4, H-4', H-6'', OCH_3); 3.39-3.34 (m, 7H, H-3', OCH_3); 2.44 (t, 1H, *J* = 7.0 Hz, C$H_{2,Phth}$); 1.77-1.59 (m, 4H, CH_2); 1.29 (d, 3H, *J* = 6.4 Hz, H-6'); 1.26 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 155.3 ($C_{q,arom}$); 154.7 (CO_{Cbz}); 138.5, 138.4, 138.2, 135.5 ($C_{q,arom}$); 133.0, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{arom}); 117.8 ($C_{q,arom}$); 116.2 (CH_{arom}); 101.1 (C-1''); 98.5 (C-1'); 96.9 (C-1); 88.9 ($C_{q,alkyne}$); 83.3 (C-4''); 82.0 (C-3); 80.8, 80.6 (C-4 and C-4'); 80.1 ($C_{q,alkyne}$); 78.2 (C-2''); 77.9, 77.7 (C-3" and C-5"); 77.0 (C-2'); 75.4, 75.2, 75.1 (PhCH_2); 75.0 (C-3') 73.0 (C-2); 71.1 (C-6''); 69.9 (PhCH_2); 68.7 (C-5); 68.0 (C-5'); 62.6 (CH_2OH); 59.8, 59.1, 58.3, 57.6, (OCH_3); 32.0, 25.2, 19.3 (CH_2); 18.2, 18.0 (C-6 and C-6'). IR (thin film, cm^{-1}): 1055, 1072, 1092, 1120, 1140, 1258, 1455, 1507, 1747, 2932. HRMS calculated for $C_{63}H_{80}O_{17}N$ 1122.54208 $[M+NH_4]^+$; found 1122.54262.

Methyl 6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranosyl))phenylhex-5-ynoate (37)



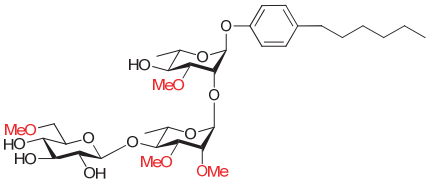
The title compound was synthesized according to general procedure A using glycan **8** (55 mg, 48 µmol, 1.0 eq) and methyl 5-hexynoate (19 µL, 145 µmol, 3.0 eq). Column chromatography (*n*-pentane-Et_2O 4:6) yielded the product (65 mg, 50 µmol, 96%) as a yellow oil. $[\alpha]_D^{25}$ = -64.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.37-7.21 (m, 22H, CH_{arom}); 6.97-6.95 (m, 2H, CH_{arom}); 5.48 (d, 1H, *J* = 1.6 Hz, H-1); 5.24-5.15 (m, 3H, H-1', PhCH_2); 4.89 (d, 1H, *J* = 11.2 Hz, PhC*H*H); 4.80-4.76 (m, 4H, PhC*H*H, PhC*H*H, H-1'', H-2''); 4.70-4.62 (m, 3H, PhCH*H*, PhCH*H*, PhCH*H*); 4.25 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 3.79 (dd, 1H, *J* = 3.0, 9.4 Hz, H-3); 3.76-3.61 (m, 10H, H-2', H-3'', H-4'', H-5, H-5', H-5'', H-6", COOCH_3); 3.57-3.42 (m, 9H, H-4, H-4', H-6'', OCH_3); 3.39-3.32 (m, 7H, H-3', OCH_3); 2.53-2.45 (m, 4H, CH_2); 1.92 (quint, 2H, *J* = 7.2 Hz, CH_2); 1.29 (d, 3H, *J* = 6.0 Hz, H-6'); 1.26 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 173.8 (*C*OOCH$_3$); 155.5 ($C_{q,arom}$); 154.7 (CO_{Cbz}); 138.5, 138.4, 138.2, 135.5 ($C_{q,arom}$); 133.1, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{arom}); 117.6 ($C_{q,arom}$); 116.2 (CH_{arom}); 101.1 (C-1''); 98.5 (C-1'); 96.9 (C-1); 87.8 ($C_{q,alkyne}$); 83.3 (C-4''); 82.0 (C-3); 81.1 ($C_{q,alkyne}$); 80.8, 80.1 (C-4 and C-4'); 78.2 (C-2''); 77.9, 77.7 (C-3" and C-5"); 77.0 (C-2'); 75.4, 75.2, 75.1 (PhCH_2); 75.0 (C-3') 72.9 (C-2); 71.1 (C-6''); 69.9 (PhCH_2); 68.8 (C-5); 68.0 (C-5'); 59.8, 59.1, 58.3, 57.6, (OCH_3); 51.7 (COO*C*H$_3$); 33.0, 24.1, 19.0 (CH_2); 18.2, 18.0 (C-6 and C-6'). IR (thin film, cm^{-1}): 1029, 1055, 1072, 1092, 1120, 1140, 1205, 1256, 1314, 1384, 1454, 1507, 1740, 1754, 2932. HRMS calculated for $C_{64}H_{76}O_{18}Na$ 1155.49239 $[M+Na]^+$; found 1155.49253.

Phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (22)



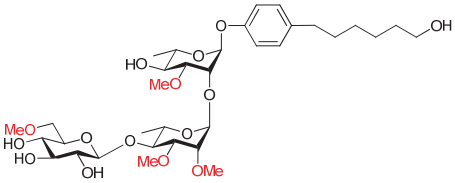
Compound **8** (34 mg, 30 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (14 mg, 23 µmol, 77%) as a pale oil. $[\alpha]_D^{25}$ = -53.7 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.33-7.28 (m, 2H, C*H*$_{arom}$); 7.05-7.02 (m, 3H, C*H*$_{arom}$); 5.49 (d, 1H, *J* = 1.6 Hz, H-1); 5.11 (d, 1H, *J* = 1.2 Hz, H-1'); 4.45 (d, 1H, *J* = 7.6 Hz, H-1''); 4.24 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 4.12 (bs, 1H, O*H*); 3.79-3.59 (m, 8H, H-2', H-3, H-3', H-4', H-5, H-5', H-6''); 3.57-3.35 (m, 18H, H-2'', H-3'', H-4, H-4'', H-5'', OC*H*$_3$); 2.52 (bs, 1H, O*H*); 1.34 (d, 3H, *J* = 6.4 Hz, H-6'); 1.27 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 156.2 (C$_{q,arom}$); 129.7, 122.4, 116.3 (*C*H$_{arom}$); 105.2 (C-1''); 98.5 (C-1'); 97.2 (C-1); 81.5, (C-3); 81.3 (C-4'); 80.3 (C-3'); 76.6 (C-3''); 75.9 (C-2'); 74.8 (C-2''); 74.3 (C-4''); 72.9 (C-6''); 72.3 (C-2); 71.9 (C-4); 71.5 (C-5''); 69.2 (C-5); 68.3 (C-5'); 59.8, 59.1, 57.8, 56.7 (O*C*H$_3$); 17.9 (C-6); 17.7 (C-6'). IR (thin film, cm^{-1}): 1009, 1067, 1118, 1202, 1229, 1457, 2931, 3400. HRMS calculated for $C_{28}H_{44}O_{14}Na$ 627.26233 [M+Na]$^+$; found 627.26222.

4-hexylphenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (23)



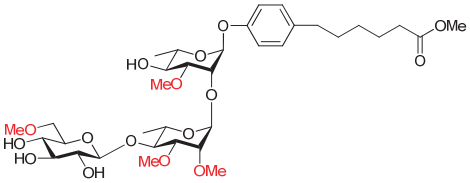
Compound **35** (32 mg, 29 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (15 mg, 22 µmol, 74%) as a pale oil. $[\alpha]_D^{25}$ = -50.3 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.4 Hz, C*H*$_{arom}$); 6.95 (dd, 2H, *J* = 2.0, 6.8 Hz, C*H*$_{arom}$); 5.44 (d, 1H, *J* = 2.0 Hz, H-1); 5.10 (d, 1H, *J* = 1.6 Hz, H-1'); 4.45 (d, 1H, *J* = 7.6 Hz, H-1''); 4.24 (dd, 1H, *J* = 2.0, 2.8 Hz, H-2); 4.09 (bs, 1H, O*H*); 3.78-3.59 (m, 8H, H-2', H-3, H-3', H-4', H-5, H-5', H-6''); 3.57-3.35 (m, 18H, H-2'', H-3'', H-4, H-4'', H-5'', OC*H*$_3$); 3.21 (bs, 2H, O*H*); 2.55 (t, 2H, *J* = 7.6 Hz, C*H*$_2$); 2.45 (bs, 1H, O*H*); 1.58 (quint, 2H, *J* = 7.2 Hz, C*H*$_2$); 1.33-1.25 (m, 12H, C*H*$_2$, H-6, H-6'); 0.88 (t, 3H, *J* = 6.8 Hz, C*H*$_3$). ^{13}C-APT NMR (101 MHz) δ: 154.3, 137.0 (C$_{q,arom}$); 129.5, 116.1 (*C*H$_{arom}$); 105.2 (C-1''); 98.4 (C-1'); 97.4 (C-1); 81.5, (C-3); 81.4 (C-4'); 80.3 (C-3'); 76.6 (C-3''); 75.9 (C-2'); 74.8 (C-2''); 74.2 (C-4''); 73.0 (C-6''); 72.3 (C-2); 71.9 (C-4); 71.6 (C-5''); 69.1 (C-5); 68.3 (C-5'); 59.8, 59.1, 57.8, 56.7 (O*C*H$_3$); 35.3, 31.9, 31.8, 29.1, 22.8 (*C*H$_2$); 17.9 (C-6); 17.7 (C-6'); 14.2 (*C*H$_3$). IR (thin film, cm^{-1}): 1013, 1066, 1116, 1457, 1510, 2856, 2929, 3427. HRMS calculated for $C_{34}H_{56}O_{14}Na$ 711.35623 [M+Na]$^+$; found 711.35585.

4-(6-hydroxyhexyl)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (24)



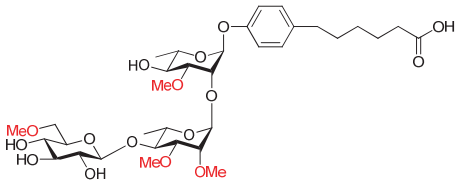
Compound **36** (28 mg, 25 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (16 mg, 23 µmol, 90%) as a pale oil. $[\alpha]_D^{25}$ = -39.6 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, C*H*$_{arom}$); 6.95 (dd, 2H, *J* = 2.0, 6.4 Hz, C*H*$_{arom}$); 5.43 (d, 1H, *J* = 2.0 Hz, H-1); 5.11 (d, 1H, *J* = 1.6 Hz, H-1'); 4.45 (d, 1H, *J* = 7.6 Hz, H-1''); 4.24 (dd, 1H, *J* = 1.6, 3.2 Hz, H-2); 4.03 (bs, 1H, O*H*); 3.78-3.72 (m, 3H, H-2', H-5, H-5'); 3.70-3.58 (m, 7H, H-3, H-3', H-4', H-6'', C*H*$_2$OH); 3.57-3.35 (m, 17H, H-2'', H-3'', H-4, H-4'', H-5'', OC*H*$_3$); 3.08 (bs, 1H, O*H*); 2.98 (bs, 1H, O*H*); 2.56 (t, 2H, *J* = 7.6 Hz, C*H*$_2$); 2.45 (bs, 1H, O*H*); 1.59 (quint, 4H, *J* = 7.2 Hz, C*H*$_2$); 1.40-1.33 (m, 4H, C*H*$_2$); 1.33 (d, 3H, *J* = 6.4 Hz, H-6'); 1.28 (d, 3H, *J* = 6.4 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 154.3, 136.8 (C$_{q,arom}$); 129.5, 116.2 (*C*H$_{arom}$); 105.3 (C-1''); 98.4 (C-1'); 97.5 (C-1); 81.5, (C-3); 81.4 (C-4'); 80.3 (C-3'); 76.6 (C-3''); 75.9 (C-2'); 74.8 (C-2''); 74.1 (C-4''); 73.0 (C-6''); 72.2 (C-2); 72.0 (C-4); 71.8 (C-5''); 69.1 (C-5); 68.3 (C-5'); 63.1 (*C*H$_2$OH); 59.8, 59.1, 57.8, 56.7 (O*C*H$_3$); 35.2, 32.8, 31.7, 29.2, 25.7 (*C*H$_2$); 17.9 (C-6); 17.7 (C-6'). IR (thin film, cm^{-1}): 1007, 1066, 1118, 1199, 1229, 1508, 2929, 3398. HRMS calculated for $C_{34}H_{60}O_{15}N$ 722.39575 $[M+NH_4]^+$; found 722.39540.

Methyl 6-(4-(2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranosyl))phenyl hexanoate (38)



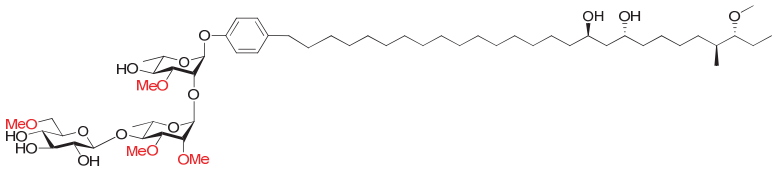
Compound **37** (31 mg, 27 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (11 mg, 15 µmol, 55%) as a pale oil. Spectroscopic data were accordance with those previously reported in the literature.[44]

4-(6-carboxyhexyl)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (25)



Compound **38** (11 mg, 15 µmol, 1.0 eq) was dissolved in EtOH/1N NaOH (3:1, 4 mL, 0.004 M) and the resulting mixture was allowed to stir for 16 hours. The mixture was then neutralized with amberlite H^+, filtered and concentrated *in vacuo*. Column chromatography (DCM-MeOH 4:1) gave the title compound (11 mg, 15 µmol, 100%) as a pale oil. $[\alpha]_D^{25}$ = -253.3 ° (c = 0.2, MeOH). ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.13 (dd, 2H, *J* = 2.3, 6.8 Hz, CH_{arom}); 6.96 (dd, 2H, *J* = 2.0, 6.5 Hz, CH_{arom}); 5.52 (d, 1H, *J* = 1.5 Hz, H-1); 5.12 (d, 1H, *J* = 2.0 Hz, H-1'); 4.57 (d, 1H, *J* = 8.0 Hz, H-1''); 4.25 (dd, 1H, *J* = 2.0, 3.0 Hz, H-2); 3.79-3.76 (m, 2H, H-2', H-5'); 3.72-3.58 (m, 8H, H-3, H-3', H-4', H-5, H-6'', CH_2OH); 3.53-3.46 (m, 7H, H-4, OCH_3); 3.40-3.28 (m, 6H, H-3'', H-4, H-5'', OCH_3); 3.17 (t, 1H, *J* = 8.5 Hz, H-2''); 2.59 (t, 2H, *J* = 7.5 Hz, CH_2); 2.29 (t, 2H, *J* = 7.2 Hz, CH_2); 1.59 (quint, 4H, *J* = 7.5 Hz, CH_2); 1.40-1.33 (m, 2H, CH_2); 1.27 (d, 3H, *J* = 6.0 Hz, H-6'); 1.24 (d, 3H, *J* = 6.0 Hz, H-6). ^{13}C-APT NMR (101 MHz) δ: 177.9 (*C*OOH); 155.9, 137.9 ($C_{q,arom}$); 130.5, 117.4 (*C*H$_{arom}$); 104.9 (C-1''); 100.4 (C-1'); 98.9 (C-1); 82.2 (C-3); 82.0 (C-4'); 79.1 (C-3'); 77.9 (C-3''); 77.8 (C-2'); 76.9 (C-4); 76.0 (C-2); 75.6 (C-2''); 73.3 (C-4''); 73.1 (C-6''); 71.7 (C-5''); 69.2 (C-5); 68.3 (C-5'); 59.8, 59.1, 58.5, 57.5 (O*C*H$_3$); 35.9, 35.1, 32.5, 29.8, 26.0 (*C*H$_2$); 18.3 (C-6); 18.2 (C-6'). IR (thin film, cm^{-1}): 1067, 1119, 1199, 1229, 1510, 1717, 2923, 3409. HRMS calculated for $C_{34}H_{54}O_{16}Na$ 741.33041 $[M+Na]^+$; found 741.33005.

4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-α-L-rhamnopyranoside (26)



4-((3*R*,4*S*,9*R*,11*R*)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)phenyl 2-*O*-(2,3-di-*O*-methyl-4-*O*-(2-*O*-benzyloxycarbonyl-3,4-di-*O*-benzyl-6-*O*-methyl-ß-D-glucopyranosyl)-α-L-rhamnopyranosyl)-3-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (Chapter 5, 26 mg, 18 µmol, 1.0 eq) was hydrogenated using general procedure C to give the title compound (14 mg, 13 µmol, 74%) as a pale oil. $[\alpha]_D^{25}$ = -38.4 ° (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz) δ: 7.10 (d, 2H, *J* = 8.8 Hz, CH_{arom}); 6.95 (d, 2H, *J* = 8.4 Hz, CH_{arom}); 5.43 (d, 1H, *J* = 1.2 Hz, H-1); 5.10 (d, 1H, *J* = 1.2 Hz, H-1'); 4.45 (d, 1H, *J* = 7.6 Hz, H-1''); 4.23 (d, 1H, *J* = 2.4 Hz, H-2); 4.09 (bs, 1H, O*H*); 3.98-3.90 (m, 2H, CH_{Phth}); 3.78-3.71 (m, 3H, H-2', H-5, H-5'); 3.69-3.60 (m, 5H, H-3, H-3', H-4', H-6''); 3.58-3.47 (m, 12H, H-3'', H-4, H-5'', OCH_3); 3.46-3.34 (m, 8H, H-2'', H-4'', OCH_3); 2.88-2.79 (m, 1H, CH_{Phth}); 2.55 (t, 2H, *J* = 7.6 Hz, C$H_{2,Phth}$); 2.49 (bs, 2H, O*H*); 1.72-1.64 (m, 1H, CH_{Phth}); 1.62-1.25 (m, 51H, H-6, H-6',

C$H_{2,Phth}$); 1.15-1.05 (m, 1H, CH_{Phth}); 0.91 (t, 3H, J = 7.4 Hz, C$H_{3,Phth}$); 0.83 (d, 3H, J = 6.8 Hz, C$H_{3,Phth}$). ^{13}C-APT NMR (101 MHz) δ: 154.3, 137.0 ($C_{q,arom}$); 129.5, 116.2 (CH_{arom}); 105.2 (C-1''); 98.4 (C-1'); 97.5 (C-1); 86.8 (CH_{Phth}); 81.5, (C-3); 81.3 (C-4'); 80.3 (C-3'); 76.6 (C-3''); 75.9 (C-2'); 74.8 (C-2''); 74.3 (C-4''); 72.9 (C-6''); 72.2 (C-2); 71.9 (C-4); 71.5 (C-5''); 69.6, 69.5 (CH_{Phth}); 69.1 (C-5); 68.3 (C-5'); 59.8, 59.1, 57.8, 57.5, 56.7 (OCH_3); 42.4, 37.6, 35.2 ($CH_{2,Phth}$); 34.9 (CH_{Phth}); 32.8, 31.8, 29.8, 29.7, 29.6, 29.4, 27.7, 26.3, 25.9, 22.5 ($CH_{2,Phth}$); 17.9, 17.7 (C-6 and C-6'); 15.0, 10.2 ($CH_{3,Phth}$). IR (thin film, cm^{-1}): 1012, 1070, 1116, 1228, 1511, 2855, 2925, 3363. HRMS calculated for $C_{57}H_{102}O_{17}Na$ 1081.70092 $[M+Na]^+$; found 1081.70035.

References

1. Akira, S., Uematsu, S. & Takeuchi, O. Pathogen Recognition and Innate Immunity. *Cell* **124**, 783–801 (2006).
2. Moody, D. B. & Cotton, R. N. Four pathways of CD1 antigen presentation to T cells. *Curr. Opin. Immunol.* **46**, 127–133 (2017).
3. Gras, S. *et al.* T cell receptor recognition of CD1b presenting a mycobacterial glycolipid. *Nat. Commun.* **7**, 13257 (2016).
4. Le Nours, J., Shahine, A. & Gras, S. Molecular features of lipid-based antigen presentation by group 1 CD1 molecules. *Semin. Cell Dev. Biol.* **84**, 48–57 (2018).
5. Cambier, C. J. *et al.* Mycobacteria manipulate macrophage recruitment through coordinated use of membrane lipids. *Nature* **505**, 218–222 (2014).
6. Queiroz, A. & Riley, L. W. Bacterial immunostat: Mycobacterium tuberculosis lipids and their role in the host immune response. *Rev. Soc. Bras. Med. Trop.* **50**, 9–18 (2017).
7. Karakousis, P. C., Bishal, W. R. & Dorman, S. E. Mycobacterium tuberculosis cell envelope lipids and the host immune response. *Cell. Microbiol.* **6**, 105–116 (2004).
8. Angala, S. K., Belardinelli, J. M., Huc-Claustre, E., Wheat, W. H. & Jackson, M. *The cell envelope glycoconjugates of Mycobacterium tuberculosis. Critical Reviews in Biochemistry and Molecular Biology* vol. 49 (2014).
9. Parrish, N. M., Dick, J. D. & Bishai, W. R. Mechanisms of latency in Mycobacterium tuberculosis. *Trends Microbiol.* **6**, 107–112 (1998).
10. Chan, E. D., Heifets, L. & Iseman, M. D. Immunologic diagnosis of tuberculosis: A review. *Tuber. Lung Dis.* **80**, 131–140 (2000).
11. Houben, E. N. G., Nguyen, L. & Pieters, J. Interaction of pathogenic mycobacteria with the host immune system. *Curr. Opin. Microbiol.* **9**, 76–85 (2006).
12. Scollard, D. M. *et al.* The continuing challenges of leprosy. *Clin. Microbiol. Rev.* **19**, 338–381 (2006).
13. Holzheimer, M., Buter, J. & Minnaard, A. J. Chemical Synthesis of Cell Wall Constituents of Mycobacterium tuberculosis. *Chem. Rev.* **121**, 9554–9643 (2021).
14. Moody, D. B. *et al.* Structural requirements for glycolipid antigen recognition by CD1b- restricted T cells. *Science (80-.).* **278**, 283–286 (1997).
15. Moody, D. B. *et al.* CD1b-mediated T cell recognition of a glycolipid antigen generated from mycobacterial lipid and host carbohydrate during infection. *J. Exp. Med.* **192**, 965–976 (2000).
16. Van Rhijn, I. *et al.* CD1b-mycolic acid tetramers demonstrate T-cell fine specificity for mycobacterial lipid tails. *Eur. J. Immunol.* **47**, 1525–1534 (2017).
17. Ernst, W. A. *et al.* Molecular interaction of CD1b with lipoglycan antigens. *Immunity* **8**, 331–340 (1998).
18. Guiard, J. *et al.* Fatty Acyl Structures of Mycobacterium tuberculosis Sulfoglycolipid Govern T Cell Response. *J. Immunol.* **182**, 7030–7037 (2009).
19. de Jong, A. *et al.* CD1c Presentation of Synthetic Glycolipid Antigens with Foreign Alkyl Branching Motifs. *Chem. Biol.* **14**, 1232–1242 (2007).
20. James, C. A. *et al.* CD1b Tetramers Identify T Cells that Recognize Natural and Synthetic Diacylated Sulfoglycolipids from Mycobacterium tuberculosis. *Cell Chem. Biol.* **25**, 392-402.e14 (2018).
21. Elsaidi, H. R. H., Barreda, D. R., Cairo, C. W. & Lowary, T. L. Mycobacterial phenolic glycolipids with a simplified lipid aglycone modulate cytokine levels through toll-like receptor 2. *ChemBioChem* **14**, 2153–2159 (2013).

22. Elsaidi, H. R. H. & Lowary, T. L. Inhibition of cytokine release by mycobacterium tuberculosis phenolic glycolipid analogues. *ChemBioChem* **15**, 1176–1182 (2014).

23. Elsaidi, H. R. H. & Lowary, T. L. Effect of phenolic glycolipids from Mycobacterium kansasii on proinflammatory cytokine release. A structure - activity relationship study. *Chem. Sci.* **6**, 3161–3172 (2015).

24. Sato, K. *et al.* Synthesis and Biological Evaluation of O-Methylated Glycolipids Related to PGLs via Direct Stereoselective Glycosidation and Sequential Suzuki–Miyaura Coupling using Boracyclane. *Chem. – A Eur. J.* **23**, 16374–16379 (2017).

25. Oldenburg, R. *et al.* Mycobacterial phenolic glycolipids selectively disable TRIF-dependent TLR4 signaling in macrophages. *Front. Immunol.* **9**, 1–12 (2018).

26. Jin, M. S. *et al.* Crystal Structure of the TLR1-TLR2 Heterodimer Induced by Binding of a Tri-Acylated Lipopeptide. *Cell* **130**, 1071–1082 (2007).

27. Park, B. S. *et al.* The structural basis of lipopolysaccharide recognition by the TLR4–MD-2 complex. *Nature* **458**, 1191–1195 (2009).

28. Zheng, R. B. *et al.* Insights into Interactions of Mycobacteria with the Host Innate Immune System from a Novel Array of Synthetic Mycobacterial Glycans. *ACS Chem. Biol.* **12**, 2990–3002 (2017).

29. Ishikawa, T. *et al.* Identification of Distinct Ligands for the C-type Lectin Receptors Mincle and Dectin-2 in the Pathogenic Fungus Malassezia. *Cell Host Microbe* **13**, 477–488 (2013).

30. Furukawa, A. *et al.* Structural analysis for glycolipid recognition by the C-type lectins Mincle and MCL. *Proc. Natl. Acad. Sci. U. S. A.* **110**, 17438–17443 (2013).

31. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie Int. Ed.* **51**, 11774–11777 (2012).

32. Zheng, R. B. *et al.* Insights into Interactions of Mycobacteria with the Host Innate Immune System from a Novel Array of Synthetic Mycobacterial Glycans. *ACS Chem. Biol.* **12**, 2990–3002 (2017).

33. Unpublished results of Sho Yamasaki and Shige Ishizuka of Osaka University.

34. Smith, D. G. M., Hosono, Y., Nagata, M., Yamasaki, S. & Williams, S. J. Design of potent Mincle signalling agonists based on an alkyl β-glucoside template. *Chem. Commun.* **56**, 4292–4295 (2020).

35. Jegouzo, S. A. F. *et al.* Defining the conformation of human mincle that interacts with mycobacterial trehalose dimycolate. *Glycobiology* **24**, 1291–1300 (2014).

36. Feinberg, H. *et al.* Mechanism for recognition of an unusual mycobacterial glycolipid by the macrophage receptor mincle. *J. Biol. Chem.* **288**, 28457–28465 (2013).

37. Yadav, J. S., Subba Reddy, B. V., Eeshwaraiah, B. & Reddy, P. N. Niobium(V) chloride-catalyzed C–H insertion reactions of α-diazoesters: synthesis of β-keto esters. *Tetrahedron* **61**, 875–878 (2005).

38. Liang, J. C. & Cross, J. O. Synthesis and Liquid Crystalline Phases of Pyridazine Derivatives I. *Mol. Cryst. Liq. Cryst.* **132**, 123–130 (1986).

39. Noyori, R. *et al.* Stereoselective hydrogenation via dynamic kinetic resolution. *J. Am. Chem. Soc.* **111**, 9134–9135 (1989).

40. Mashima, K. *et al.* Cationic BINAP-Ru(II) Halide Complexes: Highly Efficient Catalysts for Stereoselective Asymmetric Hydrogenation of .alpha.- and .beta.-Functionalized Ketones. *J. Org. Chem.* **59**, 3064–3076 (1994).

41. Evans, D. A., Chapman, K. T. & Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **110**, 3560–3578 (1988).

42. Kim, K. S., Kim, J. H., Lee, Y. J., Lee, Y. J. & Park, J. 2-(Hydroxycarbonyl)benzyl Glycosides: A Novel Type of Glycosyl Donors for Highly Efficient β-Mannopyranosylation and Oligosaccharide Synthesis by Latent-Active Glycosylation. *J. Am. Chem. Soc.* **123**, 8477–8481 (2001).

43. Presley, C. C. *et al.* Isolation, structure elucidation, and synthesis of antiplasmodial quinolones from Crinum firmifolium. *Bioorganic Med. Chem.* **25**, 4203–4211 (2017).

44. van Dijk, J. H. M. *et al.* Synthetic Phenolic Glycolipids for Application in Diagnostic Tests for Leprosy. *ChemBioChem* **22**, 1487–1493 (2021).

Chapter 8

Summary and Future Prospects

Mycobacteria, such as *Mycobacterium tuberculosis* and *M. leprae*, have a thick, highly lipophilic outer membrane called the mycomembrane. This protective barrier contains many (glyco)lipids which are thought to aid the bacterium in the evasion and manipulation of the host immune response. One group of glycolipids present in many pathogenic mycobacteria are the phenolic glycolipids (PGLs). These are mostly rhamnose containing, partially *O*-methylated oligosaccharides which are connected to phenolphthiocerol on the 'reducing end', which also carries two mycocerosic acid moieties. Chemical synthesis of complete PGLs may help to gain understanding of the exact interaction of these molecules with the host immune system and thereby also their role in the pathogenicity of the corresponding mycobacteria. Therefore this thesis has described the synthesis of PGLs originating from the *M. tuberculosis* complex (MTBC), *M. leprae*, *M. haemophilum*, *M. kansasii* and *M. gastri*, so that these can be used in immunological studies to unravel their exact mode of action, with the ultimate goal of finding a therapeutic target or vaccine candidate.

Chapter 1 has provided a concise overview of the current knowledge of the interactions of PGLs at the molecular level. It has described the previously reported syntheses of truncated PGLs, and the application of these molecules. Only one synthesis

of a complete PGL has been reported to date, and the global synthetic strategy used throughout this dissertation has been based on this synthesis. The reported total synthesis of PGL-tb1, shown in Figure 1, was based on the use of an iodophenol bearing trisaccharide that can be attached to a phthiocerol alkyne derivative by means of a Sonogashira cross coupling. The resulting diol was then esterified with two equivalents of mycocerosic acid. Thereafter hydrogenation led to the global deprotection and concurrent reduction of the conjugated internal alkyne which was formed in the Sonogashira reaction.

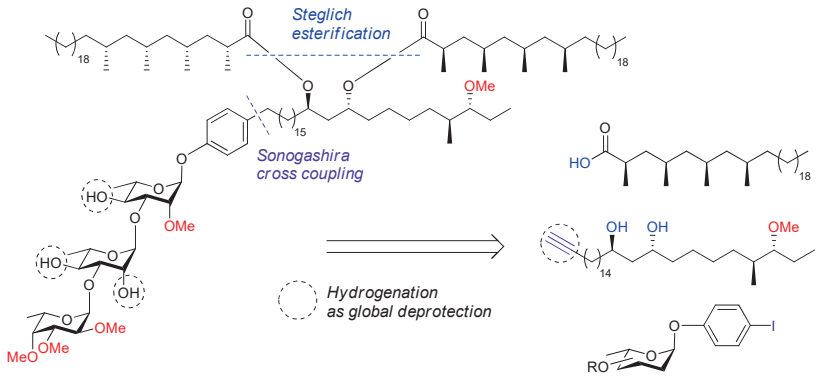


Figure 1. General synthetic strategy of this thesis which is based on the synthesis of PGL-tb1 as reported by Barroso et al.[1]

Chapter 2 has described the synthesis of protein-glycoconjugates carrying *M. leprae* glycans, that can be used for the detection of anti-PGL-I antibodies in sera to diagnose leprosy infections (See Figure 2). In addition to the standard disaccharide conjugate (so-called ND-O-BSA) which is normally used for diagnosis, this chapter has describes the synthesis of BSA-conjugates of three different *M. leprae* PGL trisaccharides. While these conjugates did not appear to be an improvement over the currently used diagnostic standard in terms of diagnostic potential, a trisaccharide was identified that can be used for this purpose and the devised synthetic route could be scaled up to provide the product on gram-scale. Furthermore, the trisaccharide conjugates reaffirmed that the C-3 methyl of the terminal glucose of PGL-I is a highly important determinant for antibody binding.

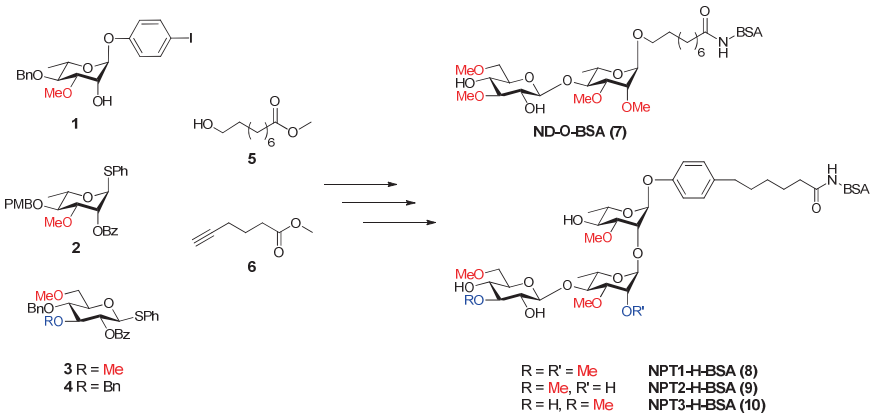


Figure 2. Synthesis of glycoconjugates of *M. leprae* PGL glycans as described in Chapter 2.

Chapter 3 has described the synthesis of a phthiocerol alkyne derivative which is required for the synthesis of the complete PGLs. Although a synthesis of the alkyne had been described before, the starting compound, 7-hexadecyn-1-ol, was no longer available. Therefore, a new route had to be devised for iodide **11**, which made use of a Corey-Fuchs homologation of an aldehyde derived from pentadecanolide (See Figure 3). This way, the synthesis could be easily scaled up which was required for the large amounts of phenolic glycolipids to be synthesized in the ensuing chapters.

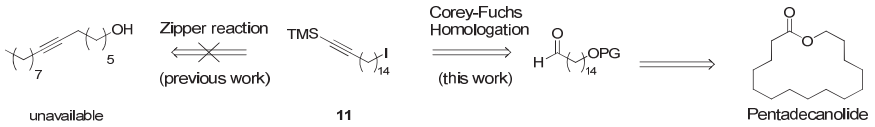


Figure 3. Retrosynthetic analysis of the iodide building block which was synthesized in Chapter 3.

Chapter 4 has described the synthesis of all known complete PGLs of the MTBC. It was found that making use of a carboxybenzyl (Cbz) carbonate as a participating protecting group which can be removed by hydrogenation increased the overall efficiency of the synthetic route compared to a strategy based on the use of benzoyl ester protection (See Figure 4). The use of an additive based glycosylation method increased the selectivity and overall efficiency of the 1,2-*cis* fucosylations and it further reduced the number of required steps.

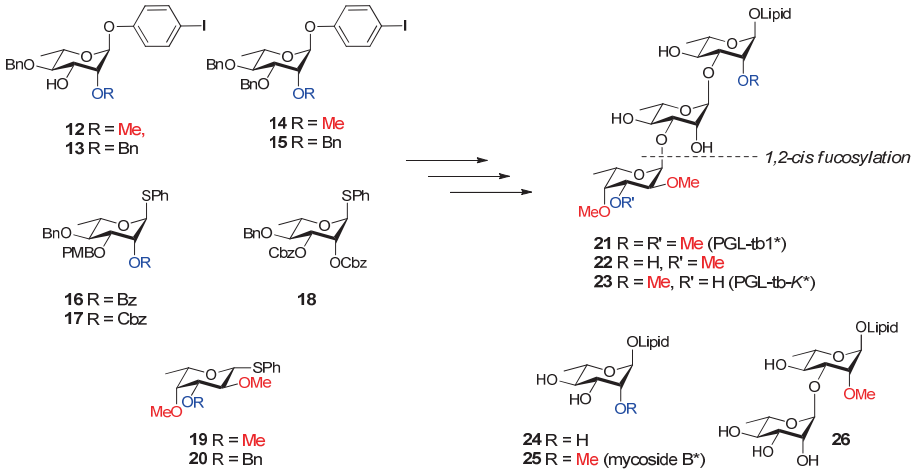


Figure 4. Synthesis of PGLs of the MTBC as described in Chapter 4.

One interesting result of this chapter has been the apparent influence of a distal methyl or benzyl ether on the stereoselectivity of glycosylation reactions of the used disaccharide acceptors. Although it is generally assumed that methyl and benzyl ethers behave similarly in a glycosylation reaction, this result indicates that significant differences can be encountered. It will be of interest to investigate the effect of (distal) protecting groups on the reactivity and selectivity of the (disaccharide) acceptors. Generating a set of disaccharide acceptors with different combinations of methyl and benzyl ethers and coupling these to the same donor (Figure 5A) can provide insight into the influence of these groups on the conformation and reactivity of the disaccharide in the glycosylation reaction. Along this line, it was also found that replacing the C-3 methyl ether of a fucose donor for a benzyl ether had a large influence on selectivity of the donor. It will therefore be of interest to generate a set of donors with different combinations of methyl and benzyl ethers and to couple these to the same acceptor (See Figure 5B). Both sets of experimental results can be complemented with calculated conformational landscapes of reactive intermediates, such as oxocarbenium ions, to computationally probe the effect of the methyl *vs* benzyl ethers.[2]

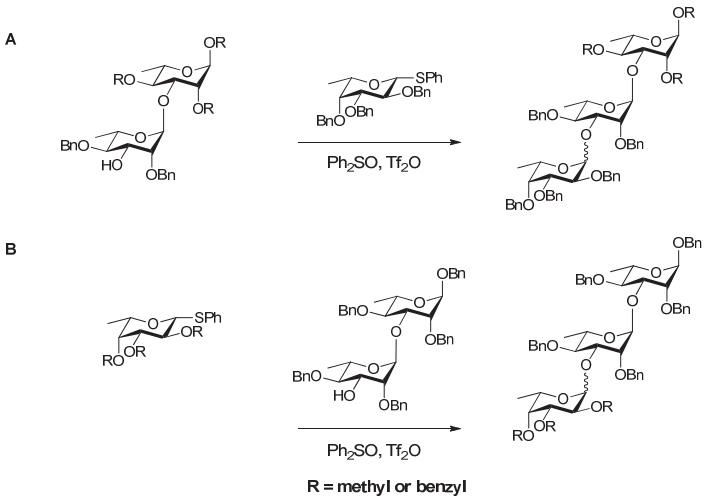


Figure 5. Proposed model reactions for investigating the effect of (distal) methyls and benzyls on the selectivity of donors and disaccharide acceptors.

Chapter 5 has described the synthesis of all known PGLs originating from *M. leprae* and a PGL of *M. haemophilum* as well as a hypothesized biosynthetic intermediate thereof (Figure 6). The Cbz was used again as a hydrogenation-labile, participating protecting group and this increased the efficiency of the synthesis of *M. leprae* trisaccharides compared to the syntheses described in Chapter 2 by circumventing the debenzoylation and benzylation steps required in the trisaccharide stage. However, it was also found that the use of a Cbz carbonate led to a lower yield and selectivity of glycosylation reactions when sterically hindered acceptors were used. For example, when the *M. haemophilum* disaccharide acceptor **36** was used in combination with donor **35** carrying a C-2 Cbz, the 1,2-*cis* linked trisaccharide was produced as the major anomer. While this problem was circumvented by coupling the disaccharide acceptor to a peralkylated donor under the agency of IDCP, the results do warrant further investigation (*vide infra*).

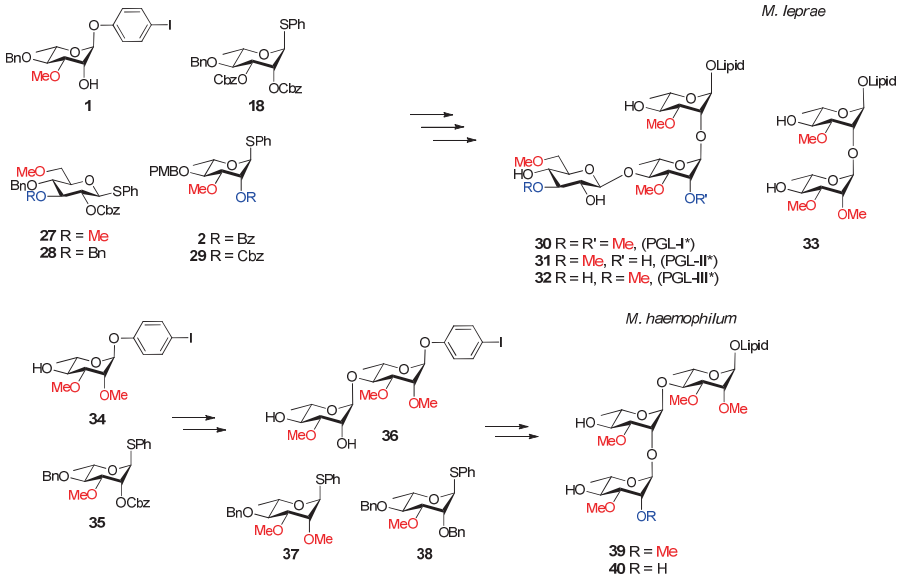


Figure 6. Synthesis of the PGLs originating from *M. leprae* and *M. haemophilum* as described in Chapter 5.

Chapter 6 has described the synthesis of all known PGLs originating from *M. kansasii* and *M. gastri* (Figure 7). Again, the Cbz-carbonate was applied as a participating protecting group, this time from a remote position on the glycosyl donor's ring, as a common occurrence in the desired glycans is the presence of a methyl ether on the C-2 position of 1,2-*trans* linked saccharides. The C-3 Cbz carbonate proved to be effective to steer the selective formation of the desired α-linkages. In the case of C-2 deoxy donor **44** it was found that the use of a C-3 Cbz-protected donor led to excellent stereoselectivity when coupled to an electron rich acceptor but to a lower stereoselectivity when an acceptor with a proximal electron-withdrawing substituent was used.

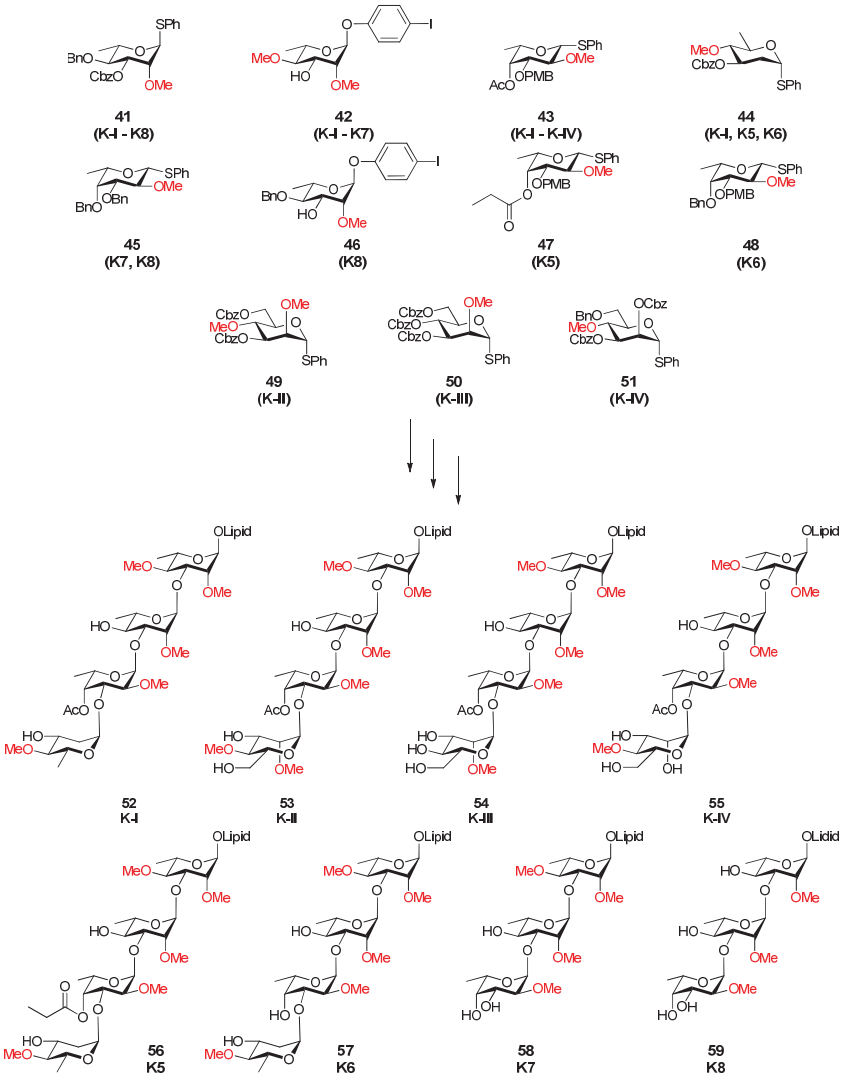
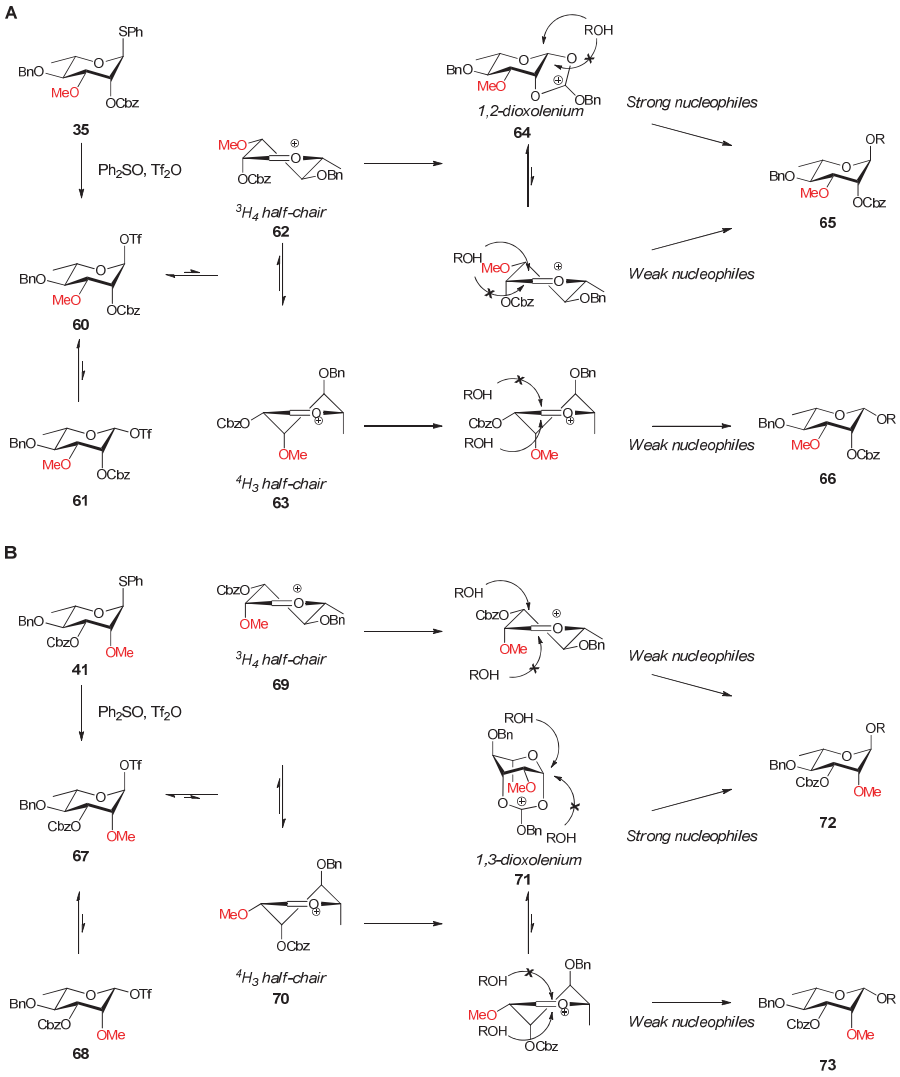


Figure 7. Synthesis of PGLs originating from *M. kansasii* and *M. gastri* as described in Chapter 6.

A proposed mechanistic rationale for the results described in Chapters 5 and 6 is described in Scheme 1. When a donor is activated, an array of reactive intermediates can form, with covalently bound anomeric triflates, participating in S_N2-type substitution

reactions, and more reactive oxocarbenium ions, which likely adopt a half-chair conformation, taking part in S_N1-type substitution reactions. [3] While these oxocarbenium ions can be approached from two sides, it has been proposed that the half-chair intermediates are approached preferably from the side that leads to a chair like transition state, as attack on the other diastereotopic face would lead to a twist-boat conformation, which is energetically less favorable.[4] When a participating protecting group is present it is able to intramolecularly "trap" the oxocarbenium ion and form a more stable dioxolenium ion.[5] A donor with a C-2 participating group can lead to the formation of a 1,2-dioxolenium ion (**64**, Scheme **1A**). Opening of this dioxolenium ion produces the 1,2-*trans* α product **65**. If the acceptor is not reactive enough to substitute the 1,2-dioxolenium ion, either due to steric factors or due to decreased electron density, it will prefer to react with either of the half-chair oxocarbenium ion like intermediates (**62** & **63**), as these are both more reactive and sterically more accessible. The rhamnosyl oxocarbenium ion shown in Scheme 1A, will preferentially adopt a $^4H_3$ half-chair conformation **63**[2] and attack on the $^4H_3$ half-chair leads to the β-product **66**. The glycosylation of the C-2-*O*-Cbz rhamnosyl donor and the sterically hindered axial acceptor **36** predominantly gave the β product, which may be accounted for by attack on the $^4H_3$ half-chair oxocarbenium ion. The C-3-*O*-Cbz group in donor **41** can trap the $^4H_3$-half chair **70** to form a 1,3-dioxolenium ion (**71**, Scheme **1B**).[3,6] This intermediate will be less stable and more reactive than a *cis*-fused 1,2-dioxolenium ion. Substitution of this species will lead to the desired α product.



Scheme 1. Proposed mechanistic rationale of the results of Chapters 5 and 6.

It would be of interest to couple the *M. haemophilum* disaccharide acceptor **36** with the C-3-*O*-Cbz donor **41** used for the synthesis of *M. kansasii* glycans, to further explore this hypothesis. The decreased α-selectivity in glycosylations of C-2 deoxy donor **44**, used

in Chapter 6, with electron-poor acceptors may be explained with the $^{3}H_{4}$ half-chair oxocarbenium ion as product forming intermediate. Deoxy donors more readily form oxocarbenium ions, as they carry less electron withdrawing substituents. It would be of interest to do perform a series of glycosylations to determine how effective the C-3-*O*-Cbz is in providing long range anchimeric assistance with a systematic series of acceptors, of which the nucleophilicity is well understood. The knowledge obtained could be of value for the synthesis of complex oligosaccharides.

Chapter 7 has described the synthesis of structurally simplified aglycone analogues of different PGLs to gain an understanding how structural details of the lipid part of the phenolic glycolipids impact the detection and/or presentation of the compounds by the host immune system. Three different lipid analogues have been assembled, changing the complexity on the phthiocerol and/or mycocerosic acids and these have been attached to the PGL-tb1 and PGL-I glycans (Figure **8A**). The glycans were also attached to a C_{18} aglycone and directly hydrogenated to deliver a phenolic aglycone. In a similar fashion, multiple aglycon analogues have been synthesized of PGL-III, which has been revealed to be a Mincle ligand using the synthetic PGL,[7] to generate an analogue that is better soluble in aqueous solutions. These analogous may be useful for crystallization studies to unravel the atomic details of PGL-Mincle binding. It would be of interest to take the same set of simplified aglycones displayed in Figure **8A** and combine these with the PGL-III glycan to investigate the role of hydrophobic interactions in Mincle binding.

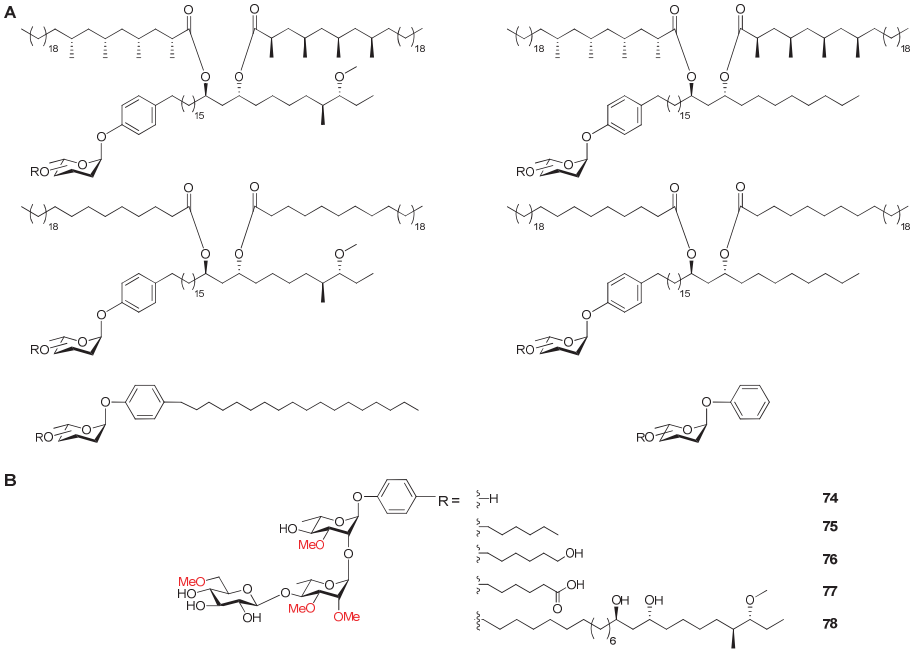
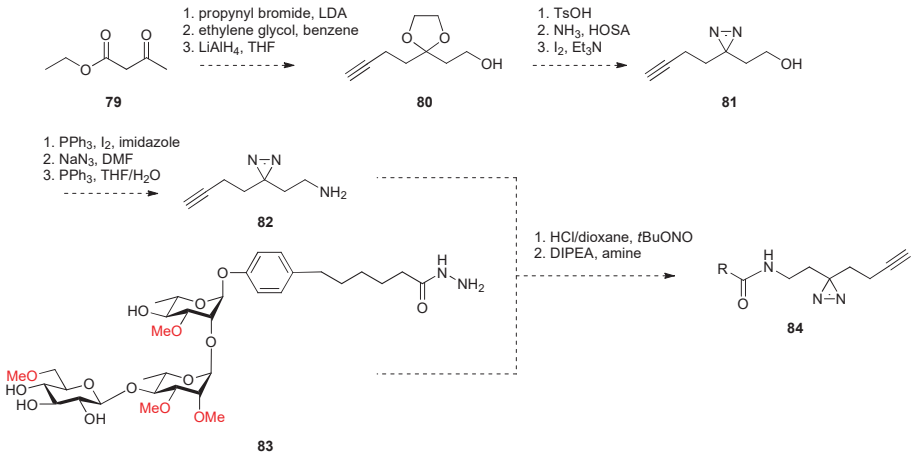


Figure 8. Aglycone analogues synthesized in chapter 7. **A**: Aglycone analogues of PGL-tb1 and PGL-I. **B**: Aglycone analogues of PGL-III.

Future prospects

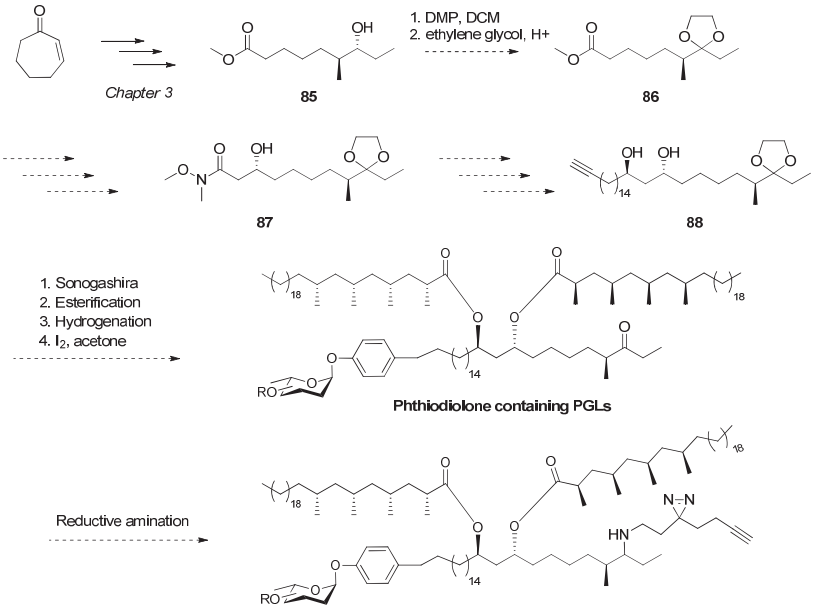
The synthetic PGLs and variations thereof described in this thesis are currently being investigated for their immunomodulatory capabilities, with the ultimate goal of finding a therapeutic target or vaccine candidate.

In the future it could be interesting to make photoaffinity labeling probes of PGLs as it is unknown with which receptors the PGLs interact. The hydrazide intermediate that was synthesized in Chapter 2 to generate the protein conjugates, can be used to attach a linker containing a photoreactive diazirine group as well as an alkyne that can be used to attach a reporter tag or a biotin moiety to capture the PGL binding partners.[8,9]



Scheme 2. Proposed synthesis of the PGL-III glycan with a bifunctional linker which contains a photolabile diazirine group for labelling and an alkyne to attach a reporter.

Alternatively the route of the phthiocerol can be altered in such a way that it gives access to phthiodiolone containing PGLs (Scheme 3). By oxidizing the secondary alcohol of **85** and then masking the resulting ketone as a ketal with ethylene glycol under acidic conditions, the same route could be followed as was described for phthiocerol to obtain protected phthiodiolone alkyne **88**, as no acidic conditions are used in the rest of the route. After the Sonogashira, esterification and hydrogenation steps the ketone can be deprotected in the presence of esters using molecular iodine in acetone.[10] Not only can these phthiodiolone containing PGLs then be investigated for their immunomodulatory capabilities, the ketone could also function as a conjugation handle to attach the bifunctional linker **84** by means of reductive amination.



Scheme 3. Proposed synthesis of phthiodiolone containing PGLs.

The methods that were used in this thesis can also be applied in the synthesis of other complex mycobacterial molecules such as glycopeptidolipids (GPL*s*). These tetrapeptide glycolipids are thought to play a significant role in the biofilm formation, environmental spread and immunomodulation of mycobacteria belonging to the *Mycobacterium avium-intracellulare-scrofulaceum* (MAIS) complex.[11–15] GPL*s* have a relatively well conserved core to which haptenic oligosaccharides are attached. The β-hydroxy lipid tails attached to the N-terminus of the tetrapeptide can be accessed from the corresponding β-keto ester by means of an asymmetric hydrogenation with Noyori's ruthenium catalyst, as was applied in Chapters 3 and 7. This keto-ester can in turn be synthesized either by means of coupling ethyl diazoacetate to an aldehyde or by condensation of the corresponding ketone with diethyl carbonate, as was performed in Chapter 7. The GPL oligosaccharides mostly feature 1,2-*trans* linkages and the formation of these can be achieved with a C-2-*O*-Cbz as a participating protecting group. This way, hydrogenation could be used a single global deprotection step to complete the synthesis.

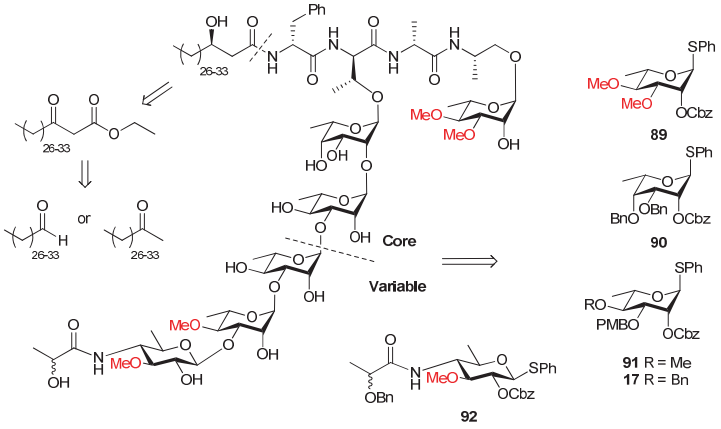


Figure 9. Retrosynthetic analysis of a glycopeptidolipid (GPL) originating from *Mycobacterium avium*.

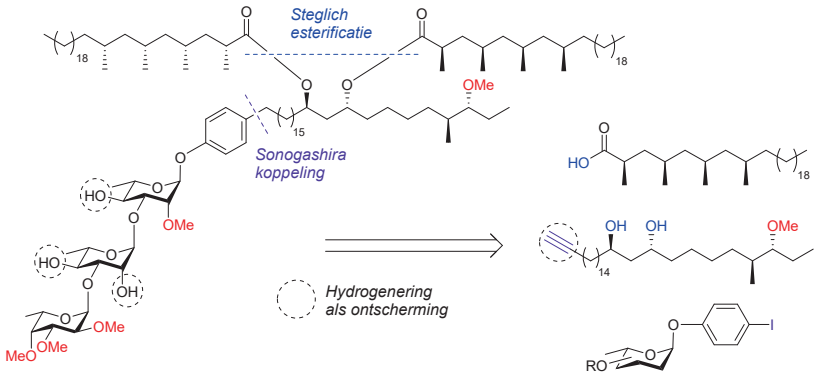
References

1. Barroso, S. *et al.* Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from Mycobacterium tuberculosis. *Angew. Chemie* **124**, 11944–11947 (2012).
2. Hansen, T. *et al.* Defining the SN1 Side of Glycosylation Reactions: Stereoselectivity of Glycopyranosyl Cations. *ACS Cent. Sci.* **5**, 781–788 (2019).
3. Hansen, T. *et al.* Characterization of glycosyl dioxolenium ions and their role in glycosylation reactions. *Nat. Commun.* **11**, 1–9 (2020).
4. Stevens, R. V. Nucleophilic additions to tetrahydropyridinium salts. Applications to alkaloid syntheses. *Acc. Chem. Res.* **17**, 289–296 (1984).
5. Pittman, C. U., McManus, S. P. & Larsen, J. W. 1,3-Dioxolan-2-ylium and related heterocyclic cations. *Chem. Rev.* **72**, 357–438 (1972).
6. Kleijne, F. F. J., Elferink, H., Moons, S. J., White, P. B. & Boltje, T. J. Characterization of Mannosyl Dioxanium Ions in Solution Using Chemical Exchange Saturation Transfer NMR Spectroscopy. *Angew. Chemie Int. Ed.* **61**, (2022).
7. Unpublished results of Sho Yamasaki and Shige Ishizuka of Osaka University.
8. Li, Z. *et al.* Design and Synthesis of Minimalist Terminal Alkyne-Containing Diazirine Photo-Crosslinkers and Their Incorporation into Kinase Inhibitors for Cell- and Tissue-Based Proteome Profiling. *Angew. Chemie* **125**, 8713–8718 (2013).
9. Hill, J. R. & Robertson, A. A. B. Fishing for Drug Targets: A Focus on Diazirine Photoaffinity Probe Synthesis. *J. Med. Chem.* **61**, 6945–6963 (2018).
10. Sun, J. *et al.* Highly Efficient Chemoselective Deprotection of O,O -Acetals and O,O -Ketals Catalyzed by Molecular Iodine in Acetone. *J. Org. Chem.* **69**, 8932–8934 (2004).
11. Schorey, J. S. & Sweet, L. The mycobacterial glycopeptidolipids: Structure, function, and their role in pathogenesis. *Glycobiology* **18**, 832–841 (2008).
12. Fujiwara, N. *et al.* Structural analysis and biosynthesis gene cluster of an antigenic glycopeptidolipid from mycobacterium intracellulare. *J. Bacteriol.* **190**, 3613–3621 (2008).
13. Whang, J. *et al.* Mycobacterium abscessus glycopeptidolipids inhibit macrophage apoptosis and bacterial spreading by targeting mitochondrial cyclophilin D. *Cell Death Dis.* **8**, e3012 (2017).
14. Fujiwara, N. *et al.* Glycopeptidolipid of Mycobacterium smegmatis J15cs affects morphology and survival in host cells. *PLoS One* **10**, 1–11 (2015).
15. Chatterjee, D. & Khoo, K. Cellular and Molecular Life Sciences The surface glycopeptidolipids of mycobacteria : *Cell. Mol. Life Sci.* **58**, 2018–2042 (2001).

Nederlandse Samenvatting

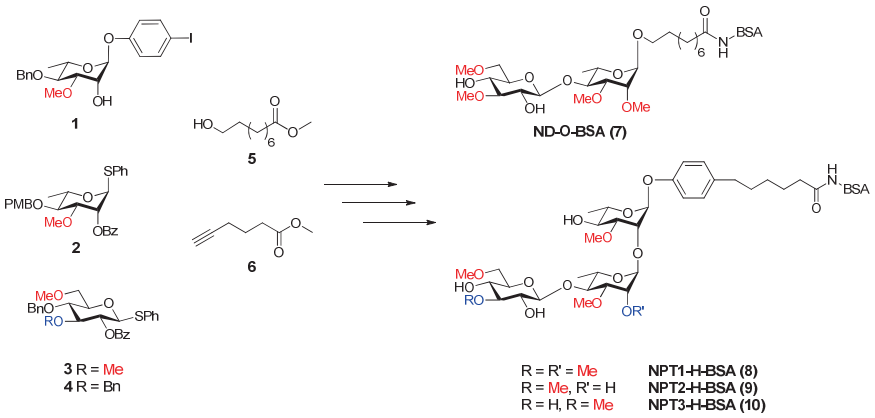
Mycobacteriën, zoals *Mycobacterium tuberculosis* en *M. leprae,* hebben een zeer lipofiel, dik buitenmembraan, het mycomembraan genoemd. Deze beschermde barrière bevat vele (glyco)lipiden waarvan wordt verondersteld dat die de bacterie ondersteunen bij het ontwijken en manipuleren van het menselijk immuunsysteem. Eén groep van glycolipiden, die voorkomt bij vele mycobacteriën is de fenolische glycolipiden (PGL). Dit zijn gedeeltelijk *O*-gemethyleerde oligosachariden, die veelal rhamnose bevatten en die aan het reducerend einde gebonden zijn aan phenolphthiocerol, waarvan de hydroxylen veresterd zijn met mycocerose zuren. De chemische synthese van volledige PGLs zou kunnen bijdragen aan het verschaffen van inzicht in de exacte interactie van deze moleculen met het menselijk immuunsysteem, alsmede hun rol in de pathogeniciteit van de bijbehorende mycobacteriën. Derhalve beschrijft dit proefschrift de synthese van de PGLs die afkomstig zijn van het *M. tuberculosis* complex (MTBC), *M. leprae, M. haemophilum, M. kansasii* en *M. gastri.* De verkregen moleculen zijn geschikt voor immunologisch onderzoek wat vervolgens kan resulteren in de ontdekking van een therapeutisch doelwit dan wel vaccin.

Hoofdstuk 1 geeft een overzicht van de huidige kennis over de interacties van PGLs op moleculair niveau. Er wordt een samenvatting gegeven van gepubliceerde syntheses van PGL fragmenten en hun toepassingen. Tot dusver is in de literatuur slechts één synthese van een volledige PGL beschreven waarvan de globale strategie het uitgangspunt vormt voor de in dit proefschrift besproken syntheses. De totale synthese van PGL-tb1, afgebeeld in Figuur 1, werd bereikt door een jodofenol bevattend trisacharide te koppelen aan een phthiocerol-alkyn derivaat door middel van een Sonogashira reactie. Daarna kon het verkregen diol onder Steglich condities worden veresterd met twee mycocerose zuren. Hydrogenering verwijderde tenslotte alle beschermgroepen en reduceerde tegelijkertijd het interne alkyn dat gevormd was tijdens de Sonogashira koppeling.



Figuur 1. Algemene strategie van de in dit proefschrift beschreven syntheses.

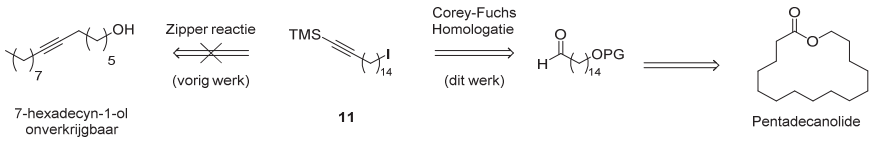
Hoofdstuk 2 is gewijd aan de synthese van glycoconjugaten bestaande uit oligosachariden afkomstig van *M. leprae*, die gebruikt kunnen worden om anti-PGL-I antilichamen te detecteren in serum om daarmee lepra infecties te diagnosticeren (zie Figuur 2). Als aanvulling op het standaard disacharide conjugaat (het zogenoemde ND-O-BSA) zijn er tevens drie trisacharide conjugaten gesynthetiseerd.



Figuur 2. Synthese van glycoconjugaten van *M. leprae* PGL-suikers zoals beschreven in Hoofdstuk 2.

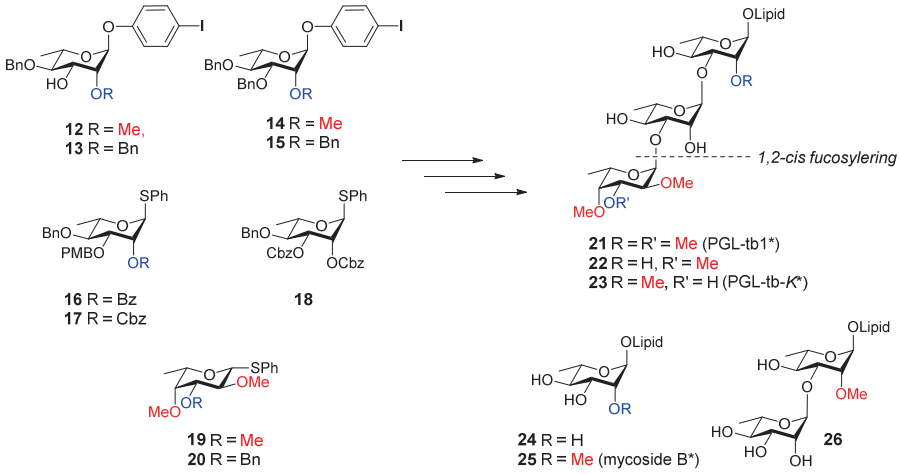
Hoewel deze trisacharide conjugaten op een schaal van meer dan een gram konden worden verkregen en geschikt bleken om de diagnose van lepra infecties vast te stellen, was een verbetering in vergelijking met het disacharide conjugaat niet aantoonbaar. Desalniettemin hebben de verkregen immunologische resultaten met de trisacharide conjugaten herbevestigd dat de C-3 methyl van de terminale glucose van PGL-I in grote mate de binding met antilichamen bepaalt.

Hoofdstuk 3 heeft de synthese van het phthiocerol-alkyn derivaat, dat nodig is voor de synthese van volledige PGLs, als onderwerp. De synthese van dit molecuul is eerder gepubliceerd, maar één van de startmaterialen, 7-hexadecyn-1-ol (zie Figuur 3) was niet langer commercieel verkrijgbaar. Dit hoofdstuk beschrijft een nieuwe route naar jodide **11**, waarbij gebruik gemaakt werd van een Corey-Fuchs homologatie van een aldehyde dat uit pentadecanolide te verkrijgen was. Met deze vondst kon de synthese van het phthiocerol-alkyn derivaat op gemakkelijke wijze opgeschaald worden en was het mogelijk om alle PGLs van de komende hoofdstukken toegankelijk te maken.



Figuur 3. Retro-synthetische analyse van de jodide bouwsteen **11** uit Hoofdstuk 3.

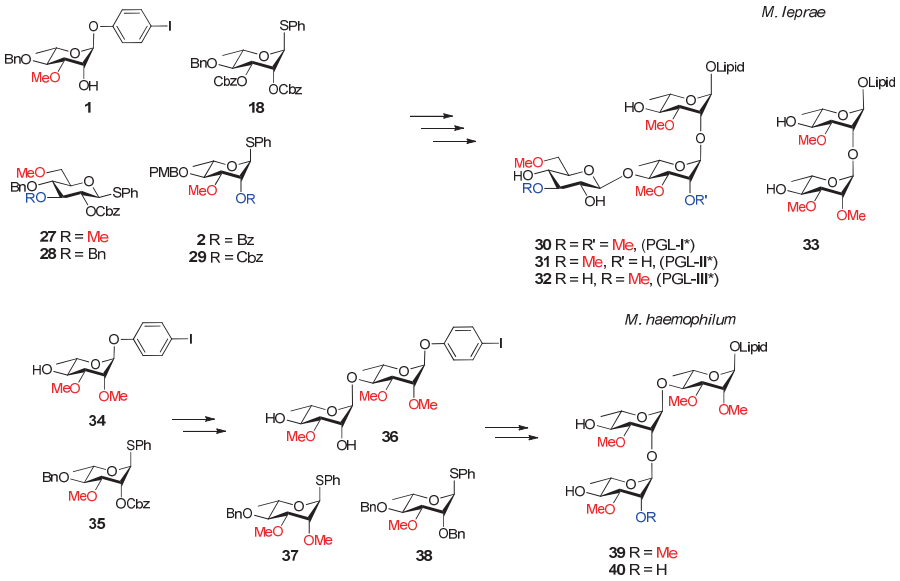
Hoofdstuk 4 behandelt de synthese van alle bekende, volledige PGLs afkomstig van het MTBC (zie Figuur 4). Door het toepassen van de carboxybenzyl (Cbz) als een participerende beschermgroep, die verwijderd kan worden met hydrogenering werd de efficiëntie van de syntheseroute verhoogd, in vergelijking met een procedure met de benzoyl ester in plaats van de Cbz. Het gebruik van een op additieven gebaseerde methode van glycosylering verbeterde de selectiviteit van de 1,2-*cis* fucosylering en verminderde ook het aantal benodigde reactiestappen.



Figuur 4. Synthese van PGLs afkomstig van het MTBC zoals beschreven in Hoofdstuk 4.

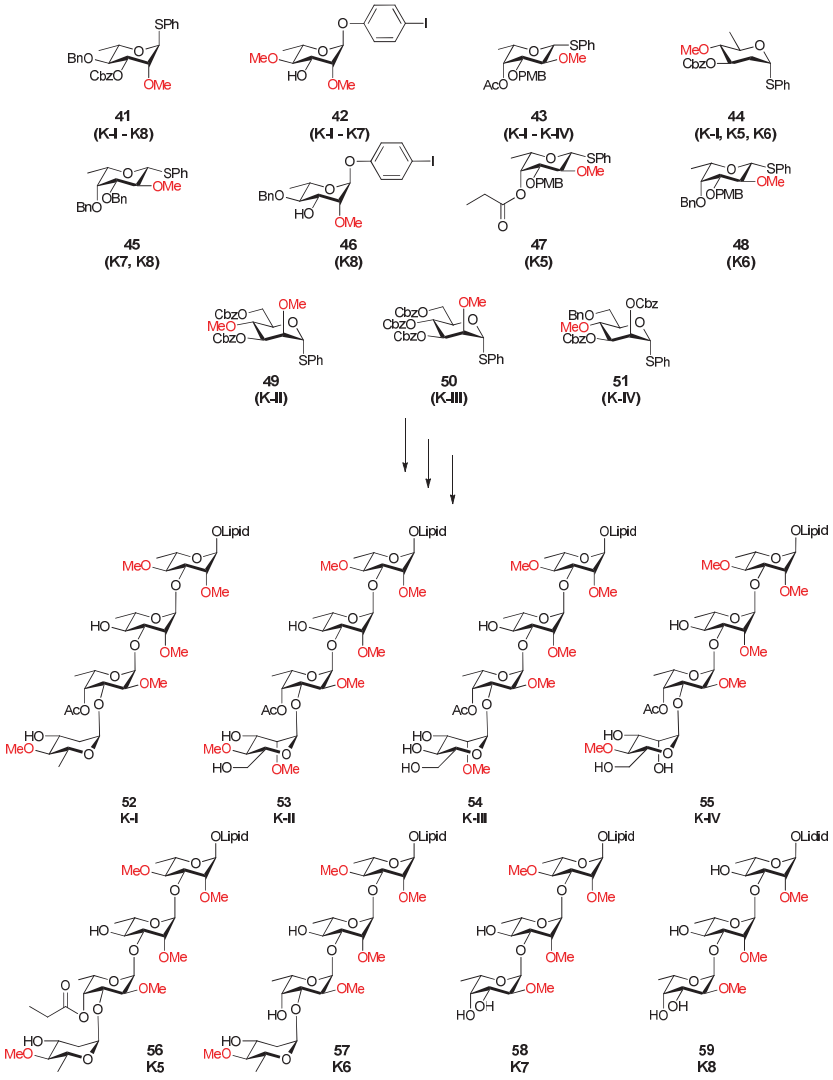
Een opmerkelijk vinding uit dit hoofdstuk is de verschillende invloed van een distale methyl of benzyl ether op de selectiviteit van koppelingen met disacharide acceptoren, terwijl deze groepen normaliter worden geacht een vergelijkbaar resultaat te geven. Op eenzelfde wijze bleek het vervangen van een methyl door een benzyl ether op de C-3 positie van een fucose donor een grote invloed te hebben op de selectiviteit van de glycosylering.

Hoofdstuk 5 bespreekt de synthese van alle bekende volledige PGLs afkomstig van *M. leprae,* een PGL van *M. haemophilum*, en een mogelijk bio-synthetisch intermediair. Zoals eerder beschreven in hoofdstuk 4 verbeterde het gebruik van de Cbz groep als een hydrogeneerbare participerende beschermgroep wederom de efficiëntie van de syntheseroute doordat de debenzoylering en de benzylering reacties in het trisacharide stadium konden worden vermeden. Evenwel bleek het gebruik van een Cbz bevattende donor in combinatie met sterisch gehinderde acceptoren een verminderde opbrengst en selectiviteit op te leveren. Toen bijvoorbeeld *M. haemophilum* disacharide acceptor **36** gekoppeld werd aan donor **35** met een C-2-*O*-Cbz werd voornamelijk het ongewenste 1,2-*cis* product gevormd (zie Figuur 5). Dit probleem werd omzeild door de glycosylering uit te voeren met peralkyeerde donoren en IDCP als activerend agens.



Figuur 5. Synthese van PGLs afkomstig van *M. leprae* en *M. haemophilum* zoals beschreven in Hoofdstuk 5.

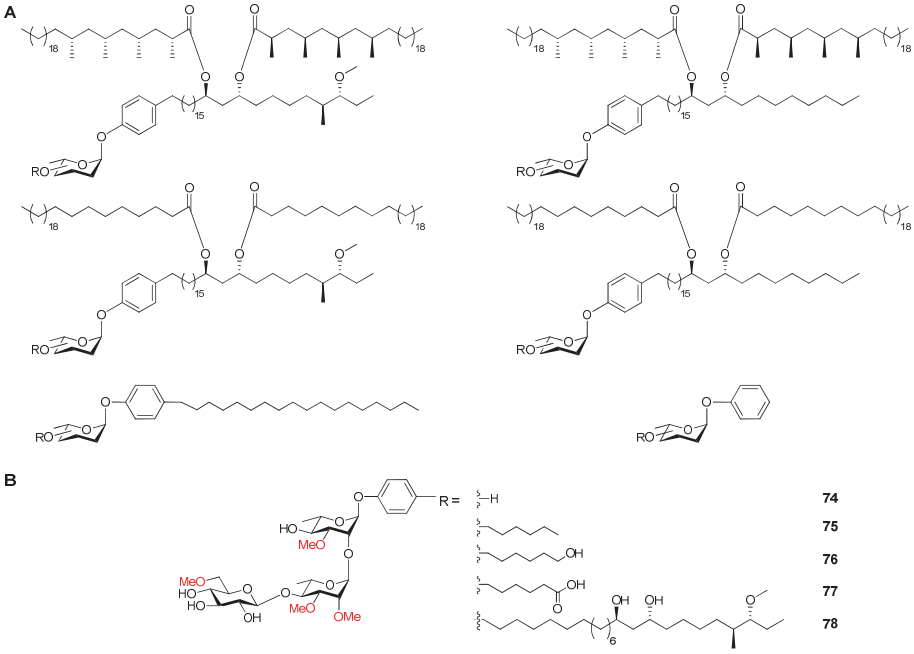
Hoofdstuk 6 beschrijft de synthese van alle bekende volledige PGLs afkomstig van *M. kansasii en M. gastri* (Figuur 6). Ook bij deze syntheses werd de Cbz groep toegepast maar nu niet zozeer voor de bescherming van de C-2 als wel voor de C-3 positie, aangezien



Figuur 6. Synthese van PGLs afkomstig van *M. kansasii* en *M. gastri* zoals beschreven in Hoofdstuk 6.

de gewenste oligosachariden op vrijwel elke C-2 positie een methyl ether bezitten. Er werd gevonden dat de verder gelegen C-3-*O*-Cbz een effectieve participerende beschermgroep is die de glycosylering kan te sturen naar de selectieve vorming van het 1,3-*trans* product (zie Figuur 6). In het geval van 2-deoxy donor **44** was de C-3-*O*-Cbz ook in staat de selectiviteit van de koppeling te sturen, maar de effectiviteit was sterk afhankelijk van de reactiviteit van de acceptor. De glycosylering van deze donor vertoonde een uitstekende selectiviteit bij gebruik van een elektronrijke acceptor, die verminderde bij het gebruik van acceptoren voorzien van een dichtbijgelegen elektronen zuigende groep.

Hoofdstuk 7 behandelt de synthese van analoga van het aglycon van verschillende PGLs die gebruikt kunnen worden voor structuur-activiteit studies van het lipide gedeelte van PGLs in de interactie met het menselijk immuunsysteem. De meest voorkomende trisachariden van het MTBC en *M. leprae* (PGL-tb1 en PGL-I, resp.) zijn gekoppeld met vereenvoudigde versies van phthiocerol dan wel mycocerose zuur dan wel beide (Figuur **7A**). Aanvullend daarop zijn de suikers gekoppeld aan een alifatische C_{18}-staart of zijn ze direct gereduceerd om een fenolisch aglycon te vervaardigen. Op een soortgelijke wijze zijn er meerdere analoga van het PGL-III aglycon gesynthetiseerd, ditmaal voor het verkrijgen van een beter wateroplosbare versie van het betreffende glycolipide, dat gebruikt kan worden voor kristallisatiestudies met Mincle, een immuunreceptor die verschillende glycolipiden kan herkennen. (Figuur **7B**).



Figuur 7. Diverse PGL aglycon analoga uit Hoofdstuk 7. **A**: Analoga van het aglycon van PGL-tb1 en PGL-I. **B**: Analoga van het aglycon van PGL-III.

List of Publications

Developments in the Synthesis of Mycobacterial Phenolic Glycolipids
J. Hessel M. van Dijk, Gijs A. van der Marel, Jeroen D. C. Codée
The Chemical Record, 21(11), **2021**, 3295-3312

Regioselective Palladium Catalyzed Oxidation at C-3 of Methyl Glucoside
Nittert Marinus, J. Hessel M. van Dijk, Marthe T. C.Walvoort, Martin D. Witte, Adriaan J. Minnaard
Carbohydrate Chemistry: Proven Synthetic Methods Vol 5 edited by Paul Kosma et al.
2021 pp. 129.-134

Synthetic Phenolic Glycolipids for Application in Diagnostic Tests for Leprosy
J. Hessel M. van Dijk, Anouk van Hooij, L. Melanie Groot, Jolijn Geboers, Rosita Moretti, Els Verhard-Seymonsbergen, Danielle de Jong, Gijs A. van der Marel, Paul L. A. M. Corstjens, Jeroen D. C. Codée, Annemieke Geluk
ChemBioChem, 22(8), **2021,** 1487-1493

Synthesis of the *Staphylococcus aureus* Strain M Capsular Polysaccharide Repeating Unit
Bas Hagen, J. Hessel M. van Dijk, Qingju Zhang, Herman S. Overkleeft, Gijsbert A. van der Marel, Jeroen D. C. Codée
Organic Letters, 19(10), **2017**, 2514-5217

Curriculum Vitae

The author of this thesis was born in 1992 in The Hague. After finishing his secondary education at Christelijk Gymnasium Sorghvliet he started the bachelor Molecular Science & Technology at Leiden University and Technological University Delft and got his BSc degree in 2014. Thereafter the master Chemistry was commenced with a specialty in Chemical Biology. During the master a research internship was carried out at the Bio-Organic Synthesis (Biosyn) group which involved the synthesis of capsular polysaccharides of *Staphylococcus Aureus* under the supervision of Prof. Dr. Jeroen Codée and Prof. Dr. Gijsbert van der Marel. The degree was obtained in 2017 and in the same year his PhD commenced under the same supervisors. Parts of the work described in this thesis were presented as poster presentations at the CHemistry As INnovating Science (CHAINS) congress in Veldhoven (2017, 2018, 2019), the Molecular Machines Nobel Prize conference in Groningen (2017) and the Reedijk Symposium in Leiden (2019). An oral presentation was given at CHAINS in 2020.

De auteur van dit proefschrift is geboren in 1992 te 's-Gravenhage. Na het behalen van het VWO-diploma aan het Christelijk Gymnasium Sorghvliet begon hij met de bacheloropleiding Molecular Science & Technology aan de Universiteit Leiden en Technische Universiteit Delft en het BSc-diploma werd behaald in 2014. Daaropvolgend werd de masteropleiding Chemistry gevolgd met een specialisatie in chemische biologie. Gedurende de master werd een onderzoeksstage verricht in de Bio-Organische Synthese (Biosyn) vakgroep met als onderwerp de synthese van capsulaire polysachariden afkomstig van *Staphylococcus Aureus* onder begeleiding van Prof. Dr. Jeroen Codée en Prof. Dr. Gijsbert van der Marel. Het masterdiploma werd behaald in 2017 en in datzelfde jaar werd het promotieonderzoek gestart met dezelfde begeleiders. Delen van dit onderzoek zijn gepresenteerd als posterpresentatie op het CHemistry As INnovativing Science (CHAINS) congres te Veldhoven (2017, 2018, 2019), de Molecular Machines Nobelprijs conferentie te Groningen (2017) en het Reedijk Symposium te Leiden (2019). Een mondelinge presentatie is gegeven op CHAINS in 2020.

Dankwoord

Als eerste wil ik Gijs, Jeroen en Hermen bedanken dat ze me de mogelijkheid hebben gegeven om dit promotieonderzoek uit te voeren. Gijs en Jeroen bedankt voor het vertrouwen dat jullie in me hadden en de nuttige werkbesprekingen en nodige aanmoedigingen. Hermen in het bijzonder nog bedankt voor de moeite die je gedaan hebt om ervoor te zorgen dat we zo snel mogelijk weer het lab in mochten in 2020.

Alexander “drs. B” Bakker, bedankt voor al je gezelschap tijdens de bachelor en master. Uiteindelijk hebben we samen de hele rit uitgezeten. Ik wil Bas “Kom op, man!” Hagen bedanken voor zijn begeleiding tijdens mijn masterstage. Hij gaf me precies de schop onder de kont die ik nodig had. Samen met de andere “boys behind the hood” Mickey en Anne Geert had ik een gezellige leerzame omgeving in HB122.

Jim, bedankt dat je voor mij een zuurkast wist te regelen waardoor ik als een verstekeling in het “Dimalab” kwam te staan, waar ik warm onthaald werd door jou, Thomas, Elmer, Alexi en Michel. Ik wil iedereen die in de afgelopen 5 jaar in het DM3.17 lab heeft gestaan bedanken dat ik ze door de jaren heen zo veel kon lastigvallen met GTA radio. Ik wil Ward, mijn eeuwige kantoorbuddy, bedanken voor de vele leuke (vaak niet chemie gerelateerde) gesprekken die dikwijls tot nieuwe inzichten hebben geleid. Merijn bedankt voor het delen van al je smart waardoor ik mijn eigen ellende in perspectief kon plaatsen. Moge Henk Wijngaard nog lang het weekend aankondigen! Pascal bedankt voor de gezellige peukpauzes die later transformeerden naar buitenommetjes, ABG! Hugo bedankt voor je eeuwige vrolijkheid en alle nieuwe muziek die ik door jou heb leren kennen. “Groetjes, groetjes” aan goede buur Sven. Qiang thank you for your calming presence in the office. Jacob bedankt voor de gezellige praatjes en discussies over gekke plannen/bouwsteenroutes. Dennis bedankt voor het doorsturen van vaak relevante artikelen en je tips, o.a. van IDCP. Berend bedankt dat je mij als verdwaalde chemicus op de tweede verdieping hebt geholpen en goed getimed advies hebt gegeven.

Het onderzoek kon natuurlijk niet plaatsvinden zonder onze ondersteunende stafleden. Hans bedankt dat je de afdeling draaiende hebt gehouden. We maken we het vaak niet makkelijk voor je. Ook bedankt voor het meten van vele HRMSen, waarvan sommige “bakvetmoleculen” helaas niet te vinden waren. Nico bedankt voor het zuiveren van een

aantal glycoconjugaten. Bobby bedankt voor je pogingen deze te analyseren en je hulp bij het versturen van vele moleculen de wereld over. Can bedankt voor het meten van de MALDI's voor hoofdstuk 2. Er waren een paar pogingen voor nodig maar ze zijn mooi uit de verf gekomen. Rian bedankt voor je hulp bij de hoge druk hydrogeneringen en alle moeite die je gedaan hebt om ervoor te zorgen dat het lab niet op laste van de veiligheidsinspectie dan wel brandweer gesloten moest worden. Ik wil Fons en Karthick bedanken voor hun vriendelijkheid en behulpzaamheid bij het meten van vele honderden NMRs. We boffen ontzettend erg met zo'n goede NMR afdeling! Onderwijs is natuurlijk ook een belangrijk onderdeel van het promotietraject en daarom wil ik Dima bedanken voor de vermakelijke OC1 en OCS sessies door de jaren heen en Richard voor de goed vormgegeven LO1 en MDD practica.

Ik heb met veel mensen mogen samenwerken die ik ook wil bedanken. Guillaume Le Calvez thank you for synthesizing mycocerosic acid! Without this no PGL could have been made. Anouk en Annemieke, bedankt voor al jullie werk voor het UCP-LFA project wat een mooi artikel en hoofdstuk 2 opgeleverd heeft. Diana thank you for your experiments with my compounds. I would like to thank Sho Yamasaki and Shige Ishizuka for their experiments with the PGL library. Hopefully we will be able to finish our exciting story soon.

Ook mijn studenten wil ik uiteraard bedanken voor hun bijdrage. Koen, jouw BEP was een mooie springplank voor hoofdstuk 6, dank daarvoor. Ik had binnen een week of twee al door dat je snel een collega van me zou worden. Ik kijk uit naar je proefschrift met een mooie roze omslag. Rutger bedankt voor je vele vele migratieloze methyleerpogingen. De uiteindelijke methode noem ik nog steeds de Rutger-methylering. Stavroula thank you for your contribution to chapter 6. Bas(je) bedankt voor al het vermaak dat je me hebt gegeven tijdens je BEP. Daarnaast heb je nog knotsgekke chemie gedaan die (uiteindelijk) bleek te werken ook. Ik zal nooit meer hetzelfde kunnen kijken naar Adidas of Klok bier.

Als laatste en meest belangrijke wil ik Melanie bedanken. Tijdens je stage heb je niet alleen vele trisachs gebakken met nog niet overtroffen opbrengsten, je hebt ook goed gegraven in de achtergrond van het onderzoek waardoor je er achter kwam dat we bijna de verkeerde structuur gemaakt hadden. Met de hoeveelheid bouwstenen die je hebt achtergelaten heb ik nog jaren aan lepra projecten kunnen werken waardoor je een grote bijdrage aan hoofdstuk 2 en 5 hebt geleverd. Na je stage konden we erg moeilijk afscheid

nemen van elkaar en toen hebben we elkaar op een hele andere manier leren kennen. Sindsdien heb je me gesteund op elke manier die je maar kon bedenken en daarvoor heb je mijn eeuwige dank.