Carbohydrates as chiral starting compounds in synthetic organic chemistry

Lastdrager, Bas

Carbohydrates as Chiral Starting Compounds in Synthetic Organic Chemistry

PROEFSCHRIFT

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In memoriam Prof. dr. J. H. van Boom

Table of Contents

List of Abbreviations 6

Chapter 1 9
General Introduction

Chapter 2 39
Towards the Synthesis of *trans*-Fused Tricyclic Ethers Containing an Angular Methyl Group: A Selenocyclisation Based Approach

Chapter 3 65
Radical Cyclisation Mediated Synthesis of Conformationally Constrained γ-Sugar Amino Acids

Chapter 4 85
Transformation of Glucose into a Novel Carbasugar Amino Acid Dipeptide Isoster

Chapter 5 111
Claisen Self-Condensation/Decarboxylation as the Key Steps in the Synthesis of C_2-Symmetrical 1,7-Dioxaspiro[5.5]undecanes

Chapter 6 127
Summary and Future Prospects

Samenvatting 135

List of Publications 139

Curriculum Vitae 141

Nawoord 143

List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
arom.	aromatic
b	broad
BAIB	[bis-(acteoxy)-iodo] benzene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc-ON	2-(*tert*-butoxycarbonyloxy-imino)-2-phenylacetonitrile
BOP	benzotriazol-1-yloxytris-(dimethylamino)-phospho nium hexafluorophosphate
Bu	butyl
Bz	benzoyl
c	concentration
calcd	calculated
CAN	ceric (IV) ammonium nitrate
cat.	catalytic
CSA	camphorsulfonic acid
CSAA(s)	carbasugar amino acid(s)
COSY	correlated spectroscopy
C_q	quaternary carbon atom
CTX	ciguatoxin
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	double doublet of doublets
DEMS	diethylmethylsilane
DIC	diisopropylcarbodiimide
DiPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDP	2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppa	diphenylphosphoryl azide
equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
Fmoc	9-fluorenylmethyloxycarbonyl
Glu	L-glutamic acid
Gly	glycine
HATU	2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HCTU	2-(6-chloro-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
HPLC	high performance liquid chromatography
HPTLC	high performance thin layer chromatography
HRMS	high resolution mass spectrometry
i	iso
IDCP	iodonium dicollidine perchlorate
IR	infrared
isoprop.	isopropylidene
J	coupling constant
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
Leu	L-leucine
LHMDS	lithium hexamethyldisilazane
m	multiplet
M	molecular mass
M	molarity
m/z	mass to charge ratio
Me	methyl
Ms	methanesulfonyl
MS	mass spectrometry
n	normal
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
NPSP	*N*-(phenylseleno)phthalimide
p	para
P	protective group
PCC	pyridinium chlorochromate
PE	petroleum ether (40-60)
Ph	phenyl
Phe	L-phenylalanine
Phth	phthaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	part per million
Pr	propyl
PyBOP	benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
pyr.	pyridine
q	quartet
quant.	quantitative
RCM	ring-closing metathesis
rt	room temperature
R_t	retention time
SAA(s)	sugar amino acid(s)
sat.	saturated
Su	succinimide
t	tertiary
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIS	triisopropylsilane
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tr	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl
Tyr	L-tyrosine
UV	ultraviolet
Z	benzyloxycarbonyl

Chapter 1

General Introduction

A wide array of natural products are characterised by the presence of carbohydrate entities. Apart from oligo- and polysaccharides, these include glycolipids and glycoproteins.[1] Together, these glycoconjugates play a role in many different biological processes. Organic chemists are faced with the challenge to prepare suitable quantities of specific glycoconjugates, and their synthetic analogues, in order to unravel these processes. Fortunately, the monosaccharide building blocks, of which glycoconjugates are assembled, are in most cases available in large quantities and glycoconjugate synthetic studies are largely devoted to the development of efficient strategies to interconvert and oligomerise these monosaccharides.[2] The accessibility of monosaccharides as cheap chiral starting materials that are endowed with multiple functional groups has inspired organic chemists to use them as starting material in the total synthesis of a wide range of complex natural products, compounds that, other than glycoconjugates, do not necessarily contain carbohydrate entities in their structure.[3] As such, carbohydrates are important components of the chiral pool from which organic

chemists may choose their starting point. Moreover, many synthetic studies have appeared over the decades in which monosaccharides have been transformed into compounds that resemble the structure and/or function of natural carbohydrates and glycoconjugates.[4,5] These carbohydrate mimics include compounds that find application as glycosidase and glycosyltransferase inhibitors in the study of the biosynthesis and processing of glycoconjugates. Another fruitful line of research is the design of compounds that emulate secondary structural features of glycoconjugates. In this introductionary chapter, selected examples of the individual research aims outlined above are presented. Further, a brief outline of the contents of the research chapters in this thesis is given.

The potential of organic chemistry in the preparation of both naturally occurring oligosaccharides and synthetic analogues is well illustrated by synthetic studies involving heptasaccharide **1a** (Figure 1), isolated from the mycelial cell walls of *Phytophtora megasperma*.[6] This so-called phytoalexin elicitor, the terminal glucose of which is reduced to the corresponding glucitol moiety, is found to be a key intermediate in the interaction between the host plant and guest bacteria and fungi. Starting from readily available 1,2-anhydroglucose **2** (Scheme 1), Timmers *et al*. prepared both methyl heptaglucoside **1b**[7] and mimetic **1c**,[8] in which the interglycosidic linkages in the backbone pentasaccharide are replaced by amide bonds (Figure 1).

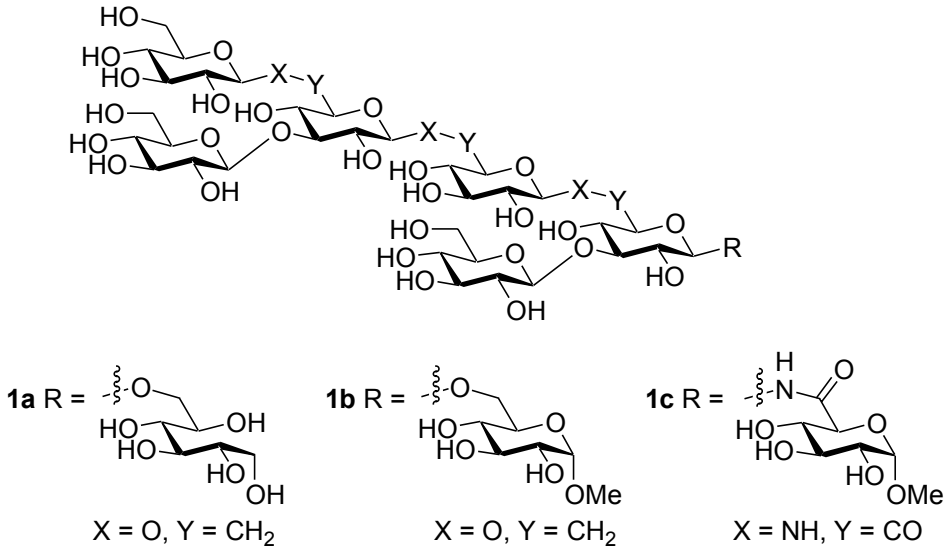
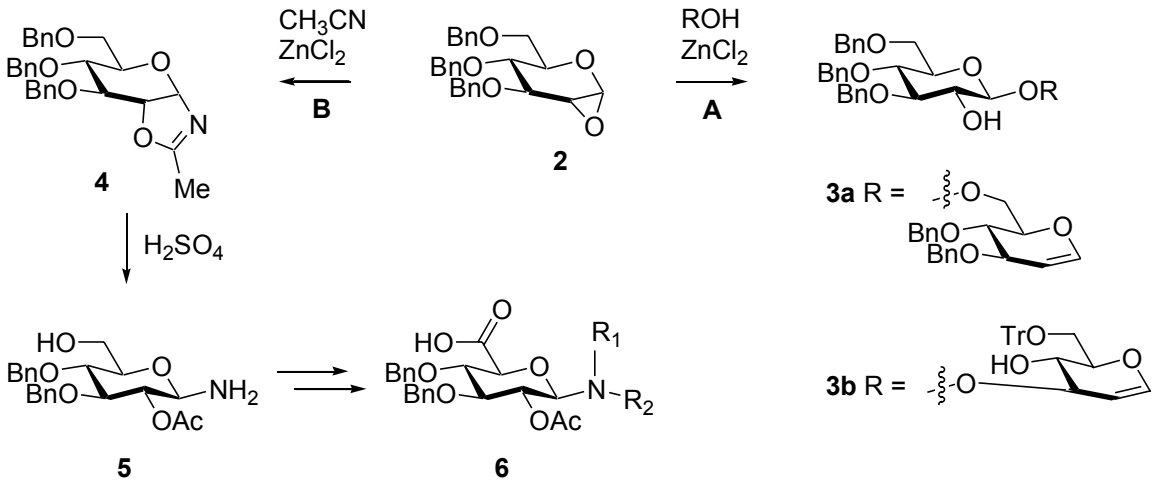


Figure 1

Key step in both synthetic sequences is the efficient and selective ring-opening of epoxide **2** in the presence of zinc chloride either by an aglycon glucoside (route A, Scheme 1) or by acetonitrile (route B).[9] Biological evaluation revealed that methyl heptasaccharide **1b** is as effective as glucitol **1a** in inducing phytoalexin accumulation in soybean, whereas the conformationally constrained sugar amino acid analogue **1c** has virtually no activity at all.



Scheme 1

In the field of oligosaccharide and glycoconjugate synthesis many efficient strategies have been developed.[1,2] Key in this research area is the ability to install the proper interglycosidic linkages with respect to regio- and stereospecificity. The majority of glycosylation procedures involve activation of the anomeric position of a suitable protected donor glycoside. The acetal is formed by displacement of the anomeric leaving group by the free hydroxyl of the acceptor. With the aim to synthesise biologically relevant trisaccharides Codée *et al.*[10] recently described a novel sequential glycosylation procedure combining the use of 1-hydroxyl- and thiodonors (Figure 2). The method is based on Ph_2SO/Tf_2O-mediated dehydrative condensation (I) of 1-hydroxyl donors (**7**) with thioglycosides (**8**) to afford thiodisaccharides. In the next glycosylation event (II), this thiodisaccharide can be activated with the same sulfonium triflate activator system to furnish a trisaccharide.

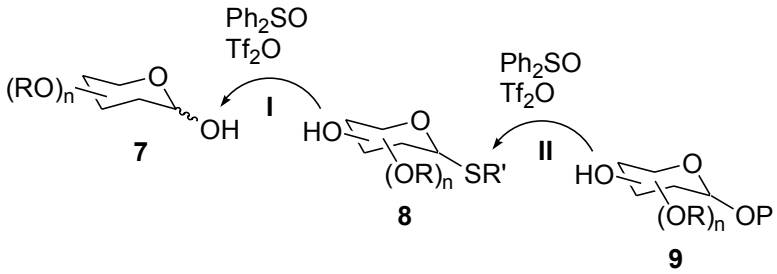
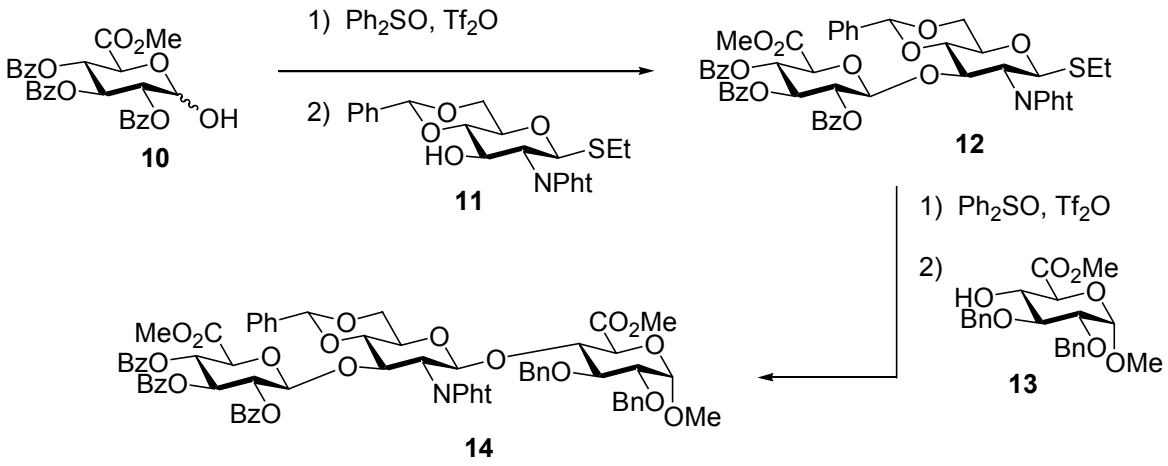


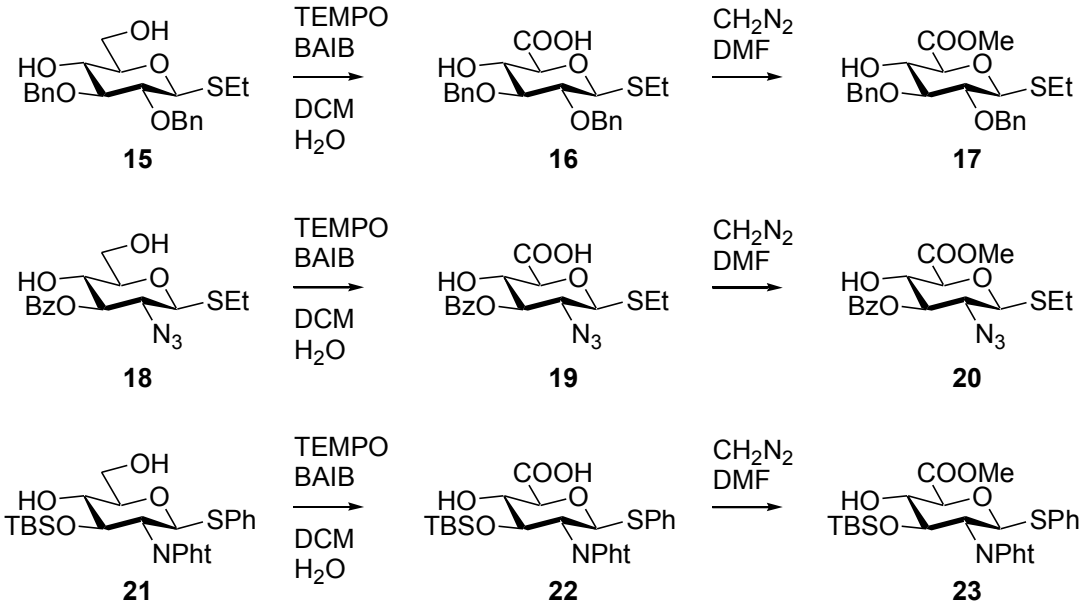
Figure 2

The scope of this sequential glycosylation strategy was nicely illustrated by the efficient assembly of a hyaluronan trisaccharide (**14**) in a stepwise procedure (Scheme 2). First glucuronic acid building block **10** was pre-activated and chemoselectively coupled to thio glucosamine **11** resulting in disaccharide **12**. Successive coupling with another



Scheme 2

glucuronic acid building block (**13**) afforded protected hyaluronan trisaccharide **14**. Key to the above studies was the accessibility of (partially) protected donor- and acceptor uronic acid derivatives. Van den Bos *et al.*[11] presented an elegant strategy in which the primary alcohol function in a series of carbohydrate-derived diols, including thioglycosides **15**, **18** and **21** (Scheme 3), is selectively oxidised to the corresponding uronic acids **16**, **19** and **22** through the action of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) and [bis-(acetoxy)-iodo]benzene (BAIB). Treatment with diazomethane furnishes thioglycosides **17**, **20** and **23**, suited for further elaboration in oligosaccharide synthesis.



Scheme 3

Carbohydrates are often used as chiral precursors in the synthesis of natural products. The class of polycyclic ether marine natural products presents an interesting and challenging synthetic target due to their structural complexity, biological activities and scarcity.[12] After its isolation and structural elucidation in 1981, the potent neurotoxin brevetoxin B (**24**, Figure 3) was reported as the first example of a marine polycyclic ether.[13] The first total synthesis of brevetoxin B was accomplished by the group of Nicoloau in 1995.[14] In a convergent approach they made use of several carbohydrates to construct parts of the polycyclic ether framework.

The interesting properties of polycyclic ethers have insprired many scientists. However, general and modular approaches towards the synthesis of polycyclic ethers are so far still lacking. This is mainly caused by the range of variations in ring size and substitution pattern of the individual ether rings. Leeuwenburgh *et al.*[15] disclosed an elegant procedure to construct fused cyclic ethers via a radical cyclisation approach of

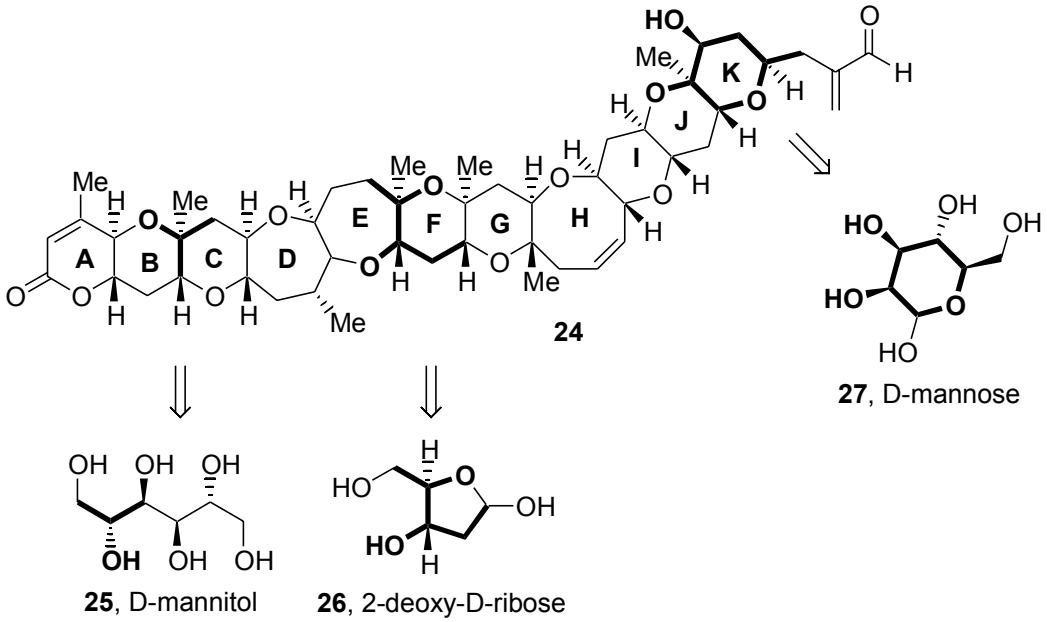
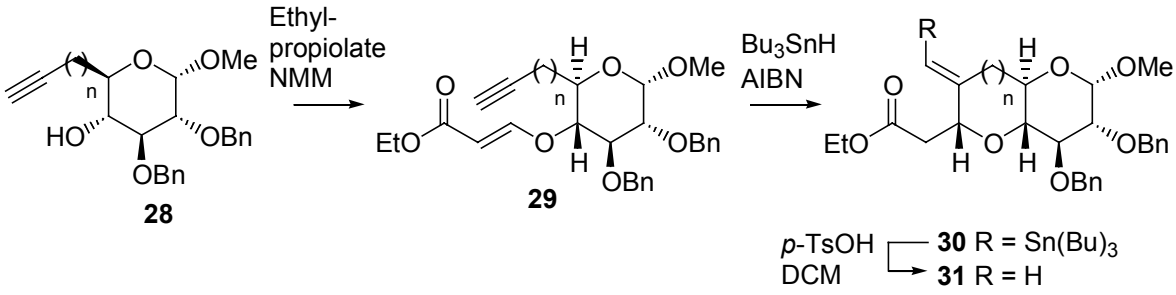


Figure 3

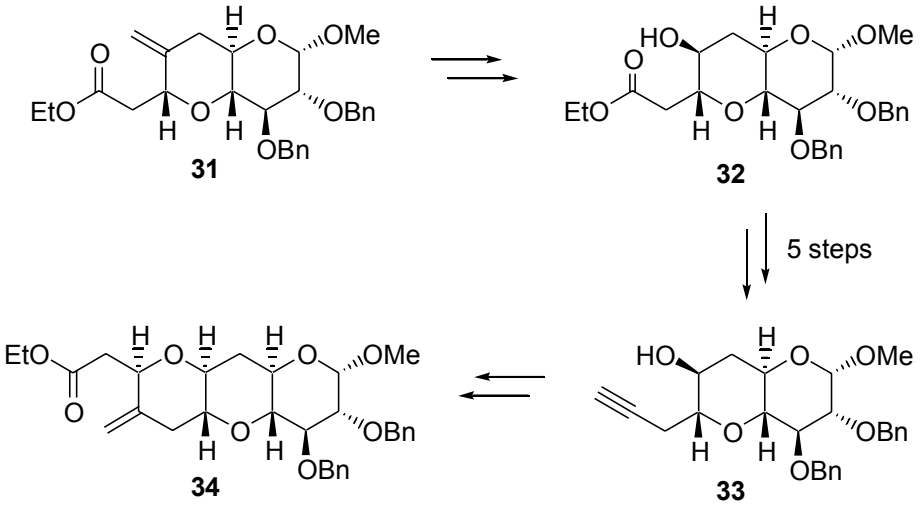
sugar-derived β-(alkynyloxy)-acrylates (Scheme 4). Accordingly, functionalised bicyclic ethers of various ring sizes (**31**, n = 0-3) were prepared. The synthesis commenced with a hetero Michael addition of suitably protected carbohydrate-derived alkynols (**28**) to ethyl propiolate. Next, the resulting ene-yne intermediates (**29**) were subjected to a tributyltin radical mediated cyclisation followed by acidic destannylation to furnish the set of bicyclic ethers.



Scheme 4

The efficiency of this methodology was nicely demonstrated in the construction of a *trans*-fused tricyclic ether in an iterative fashion. Thus, ozonolysis of the exocyclic

alkene (**31**, n =1) followed by reduction of the resulting ketone afforded alcohol **32** (Scheme 5). In a five step procedure, ester **32** was transformed into the requisite acetylene. Now alkynol **33** was subjected to the three step hetero Michael addition/radical cyclisation/reductive destannylation protocol as discussed above to yield tricyclic system **34**.



Scheme 5

Another class of compounds widely distributed in nature are the polyhydroxylated alkaloids.[16] These imino- or azasugars, in which the ring oxygen in pyranoses or furanoses is replaced by a nitrogen atom, are carbohydrate analogues which closely resemble the parent natural sugar. They can be classified into five structural categories: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes which are presented in Figure 4. Representative examples of each of these classes respectively are nojirimycin (**35**),[17] 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP, **36**),[18] castanospermine (**37**),[19] alexine (**38**)[20] and calystegine B_2 (**39**).[21] The first alkaloid isolated from nature, nojirimycin,[17a] was found to be a potent inhibitor of α-and β-glucosidases as might be expected from its close structural resemblance with glucose. Since the discovery of nojirimycin in 1966, many naturally occurring iminosugars have been identified and found to possess glycosidase inhibitor activity.[22]

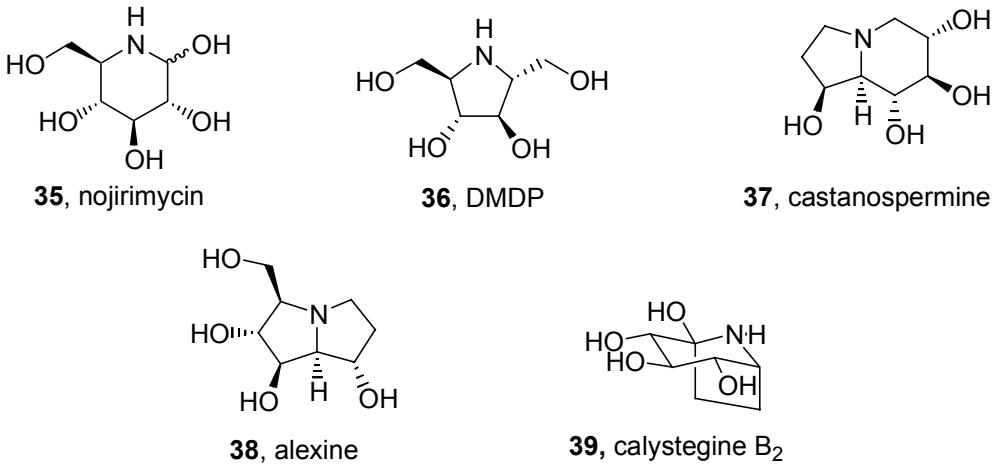
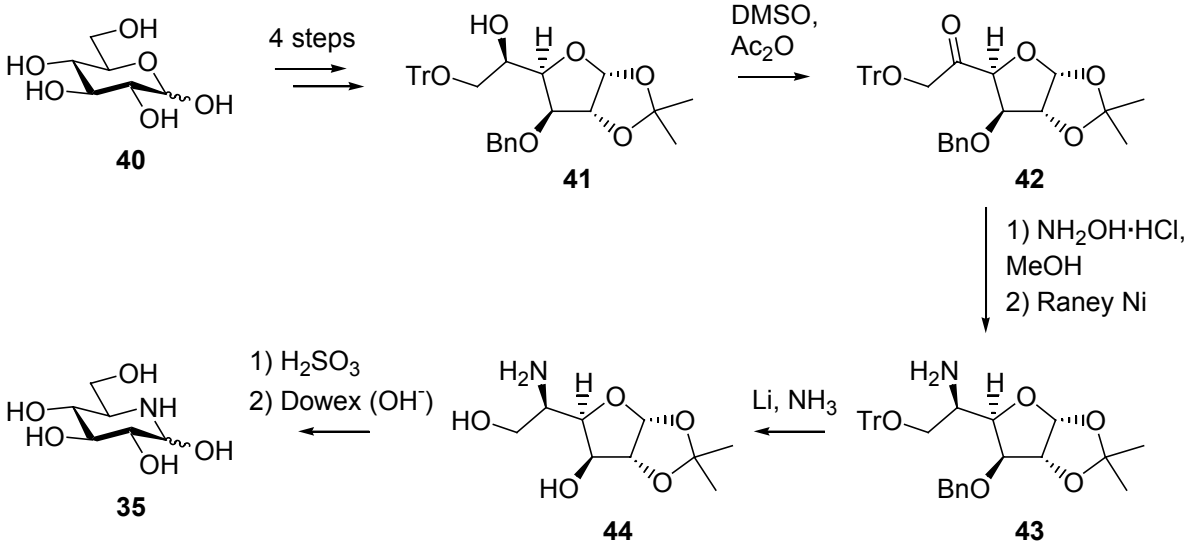


Figure 4

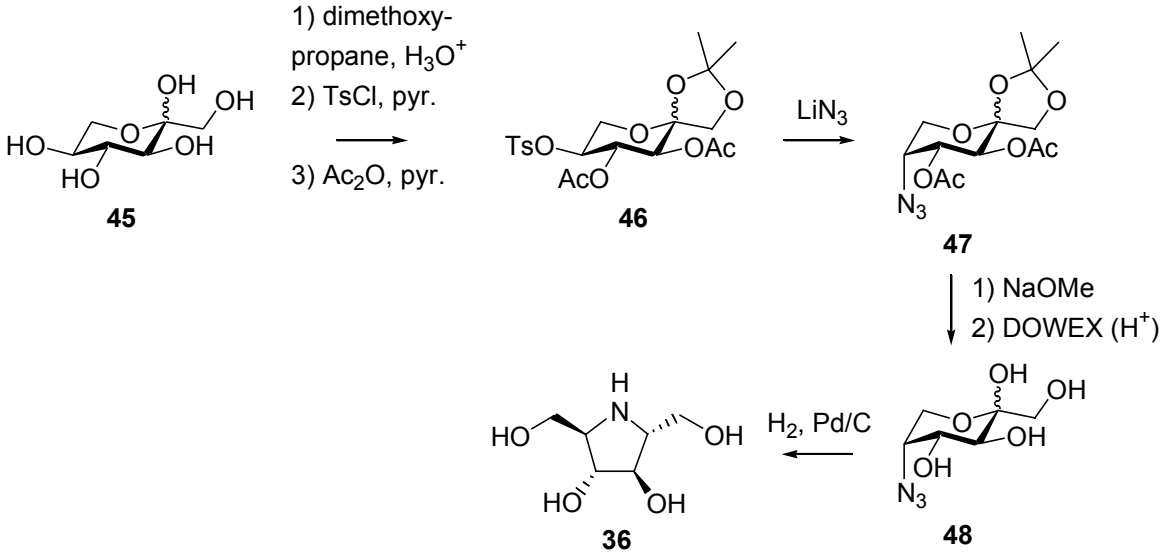
In many of the numerous reported synthetic strategies towards iminosugars,[23] the key step concerns incorporation of the nitrogen atom into a monosaccharide derivative as is exemplified by the first synthesis of nojirimycin, reported by Inouye and co-workers.[17b] Starting with glucose (**40**) the amine function was incorporated with overall retention of configuration at the C-5 position as key in the total synthesis (Scheme 6).



Scheme 6

DMDP **36** and many of its analogues show very interesting biological activities in different glycosidase mediated processes.[18] In 1985 the first synthesis of **36** was reported

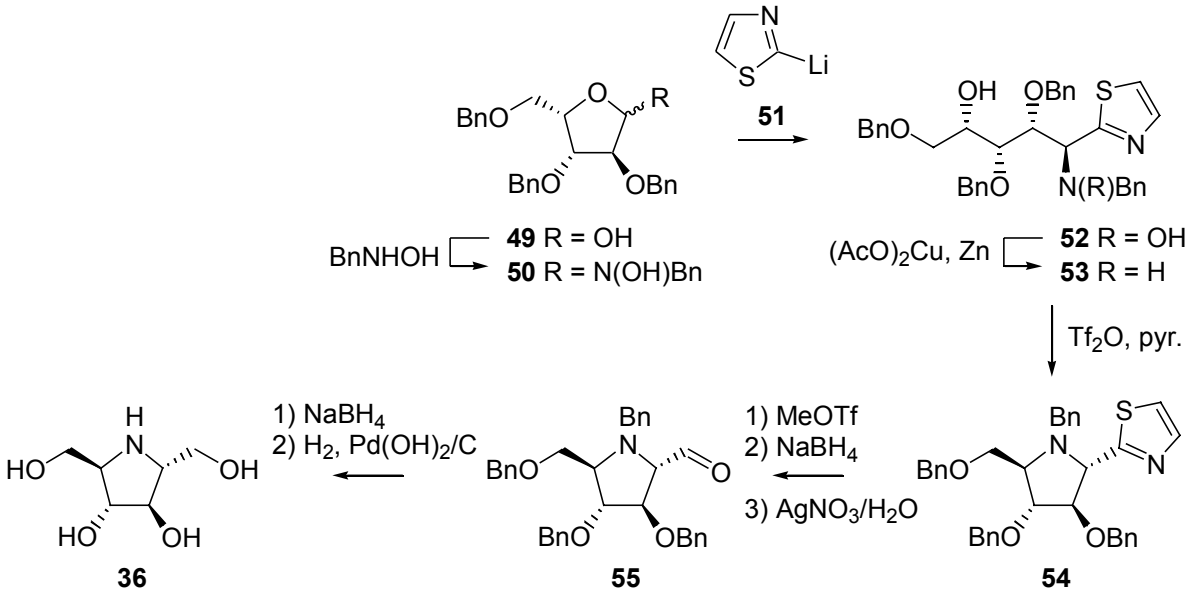
starting from L-sorbose (**45**, Scheme 7),[24] which contains the desired stereochemistry at the C-3 and C-4 positions. Bisacetate **46** was obtained in three steps from L-sorbose. Introduction of an azide function, subsequent removal of the protective groups followed by hydrogenation to liberate the amine resulted in the formation of DMDP.



Scheme 7

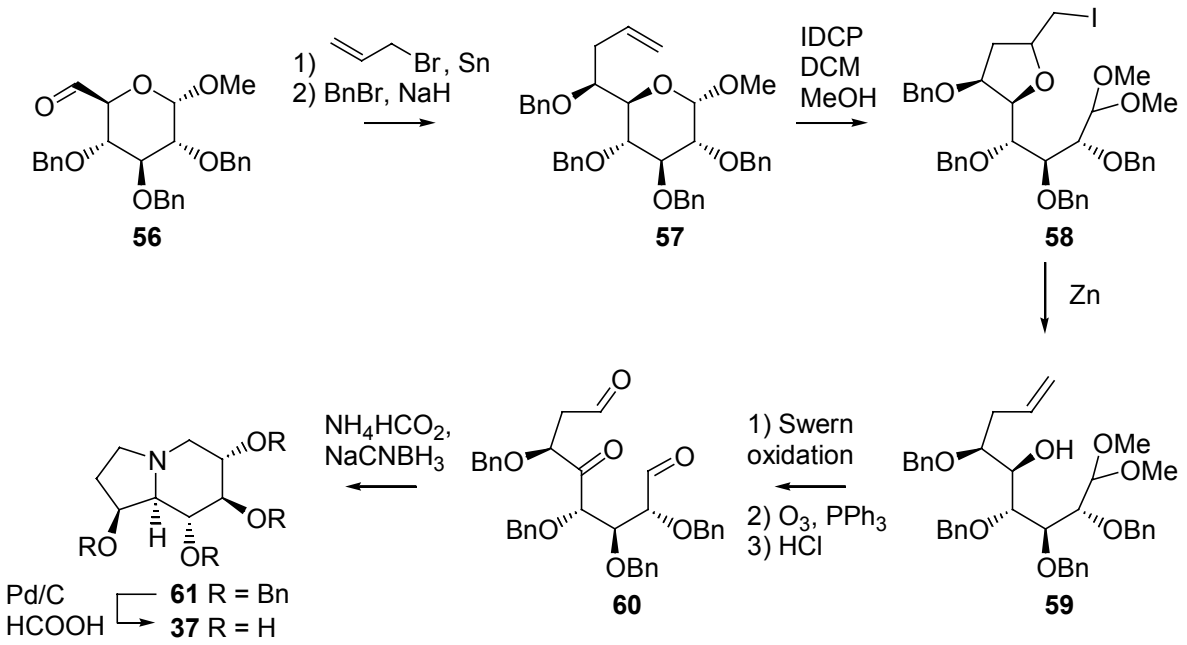
Dondoni and co-workers[25] devised a general procedure towards functionalised pyrrolidine iminosugars starting from furanoses (Scheme 8). This strategy commences with a nitrone addition followed by thiazole addition and ring-closure with inversion of stereochemistry. To attain DMDP, protected L-xylofuranose (**49**) was transformed into **50** using *N*-benzylhydroxylamine at elevated temperature. Treatment of **50** with 2-lithiothiazole (**51**) gave, after separation of the isomers, the open chain derivative **52**. Reduction of the hydroxylamine function in **52** was achieved using a Zn-Cu couple. Next, ring-closure of amine **53** proceeded with inversion of configuration upon activation of the free hydroxyl with triflic anhydride, providing pyrrolidine **54**. Cleavage of the thiazole ring, followed by reduction of the resulting aldehyde intermediate **55** and removal of the benzyl ethers eventually afforded **36**.

An elegant synthesis of castanospermine (**37**) was reported by Mootoo and co-workers[26] who made use of a triple reductive amination strategy to incorporate the



Scheme 8

tertiary amine function (Scheme 9). The requisite tricarbonyl intermediate (**60**) was obtained from glucose-derived aldehyde **56** by the following sequence of events: tin-mediated addition of an allyl anion, followed by benzylation of the major product, then



Scheme 9

iodocyclisation under the agency of iodonium dicollidine perchlorate (IDCP) in CH_2Cl_2/MeOH and reductive elimination with zinc furnished dimethylacetal **59**. Swern oxidation, ozonolysis and liberation of the aldehyde gave dialdehydo ketone **60** which upon treatment with ammonium formate and sodium cyanoborohydride yielded perbenzylated castanospermine **61**. Hydrogenolysis of the benzyl ethers in **61** provided castanospermine **37**.

Madsen and Skaanderup devised a short and efficient general strategy to prepare polyhydroxylated nortropanes (calystegines B_2, B_3 and B_4, Figure 5).[27] They took full advantage of the predisposed arrangement of the hydroxyl functions of the corresponding carbohydrate starting materials.

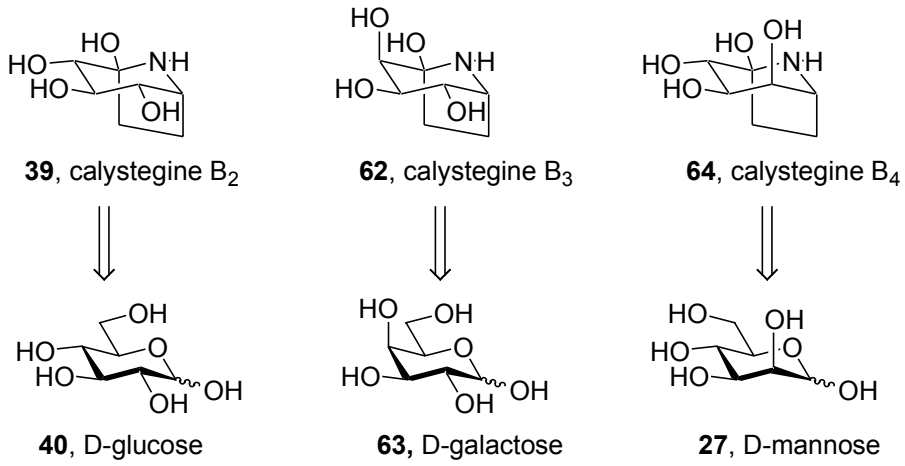
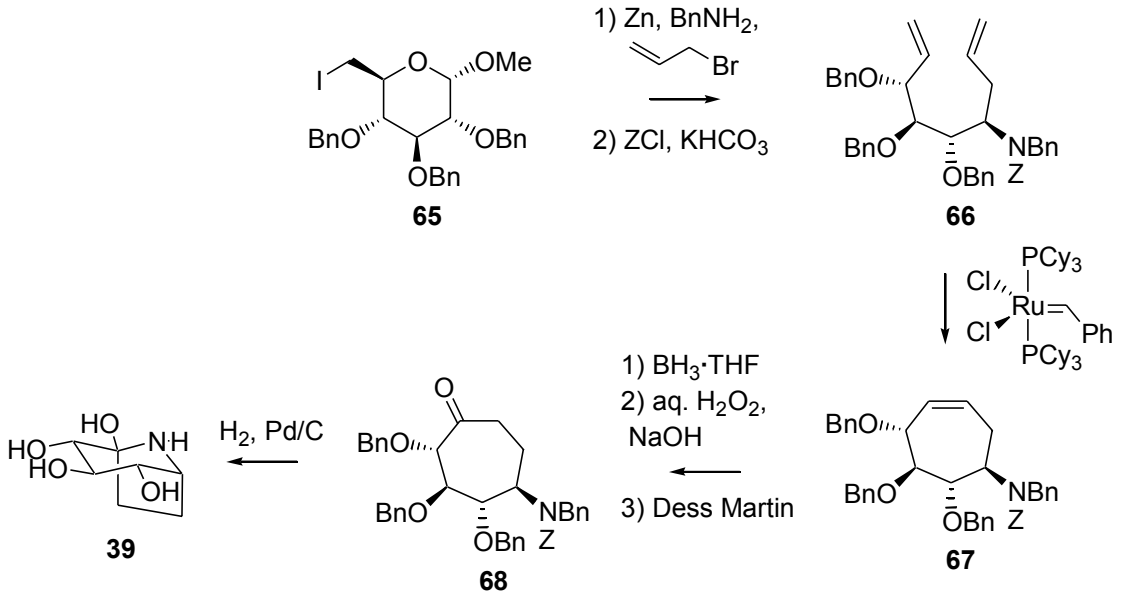


Figure 5

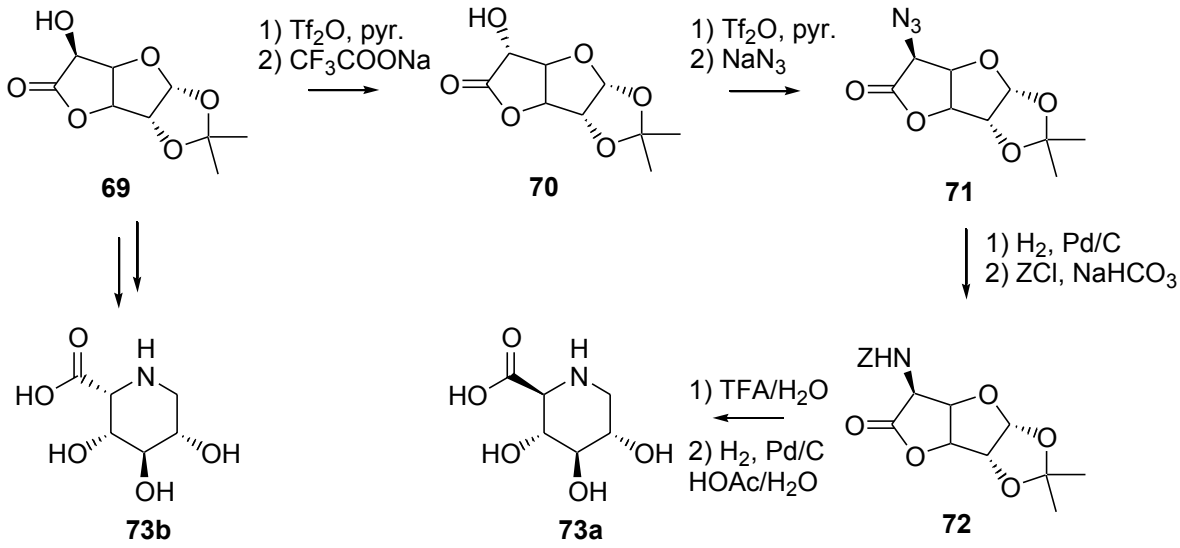
Key steps in the synthesis of the polyhydroxylated seven-membered carbocyclic cores include a zinc mediated domino reaction followed by olefin ring-closing metathesis (RCM), as is exemplified for calystegine B_2 (Scheme 10).[28]

The naturally occurring trihydroxy pipecolic acid (**73a**), isolated from the seeds of *Baphia racemose*,[29] was shown to be a glucuronidase and iduronidase inhibitor. Fleet and co-workers[30] synthesised amino acid **73a** starting from D-glucuronolactone **69** with overall retention of configuration at the C5-position (Scheme 11). Thus, **69** was converted into a triflate followed by treatment with sodium trifluoroacetate to give L-idose derivative **70**.



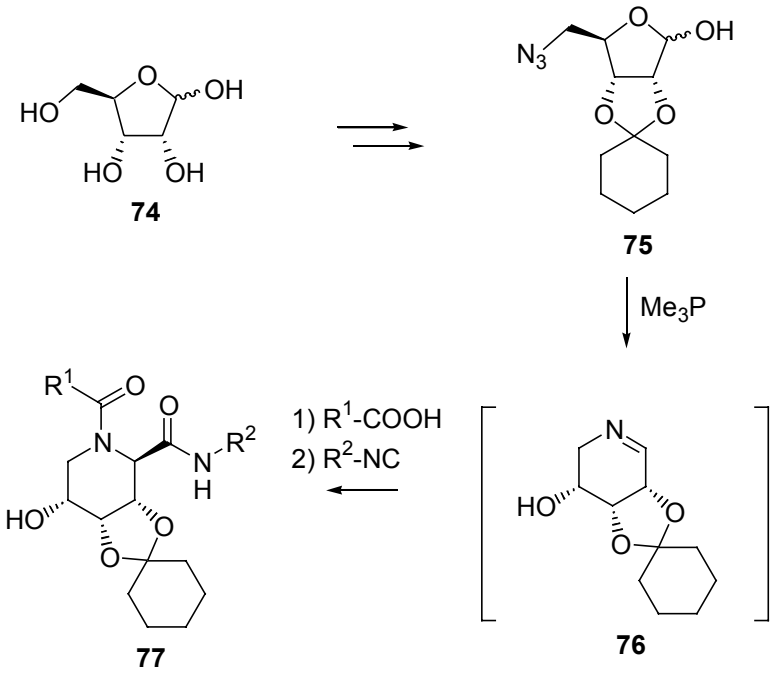
Scheme 10

Again installation of a triflate followed by nucleophilic displacement with sodium azide afforded gluco-azide **71**. Reduction of the azide and subsequent protective group manipulations furnished **73a**. With a single inversion of configuration, the 2*R*-isomer (**73b**) of the naturally occurring polyhydroxy pipecolic acid was prepared starting from **69** in an analogy to the sequence of reactions described going from **70** to **73a**.



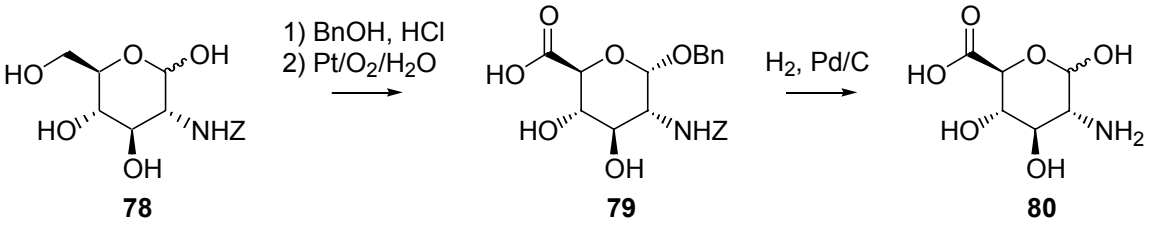
Scheme 11

Recently Timmer *et al*.[31] developed a new and efficient multicomponent reaction giving access to polyhydroxylated pipecolic acid amides starting from ribose-derived azido hemiacetal (**75**, Scheme 12). In a one-pot process imine **76** is generated via a Staudinger/aza-Wittig sequence of events, after which an Ugi three-component reaction with a series of isocyanates and carboxylic acids provided a small library of trihydroxypipecolic acids **77** in yields varying between 22% and 78%.



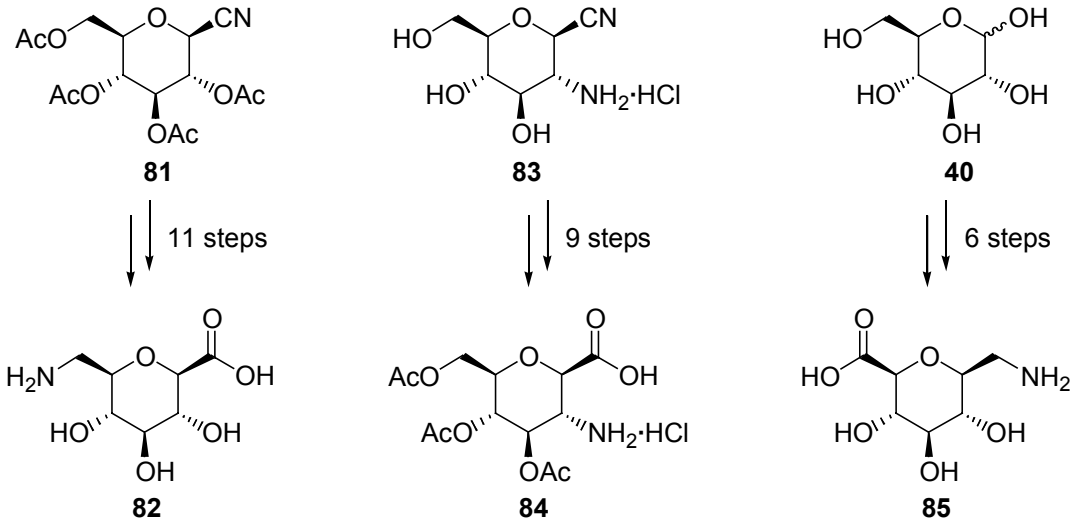
Scheme 12

Carbohydrate derivatives which contain an amine and a carboxylate function can be classified as sugar amino acids (SAAs).[5] SAAs, such as neuraminic acid[32] and muramic acid,[33] are largely found in nature as structural elements but they also play an important role as constituents of certain complex nucleoside antibiotics,[34] which exhibit inhibitory activity against fungi and/or bacteria. Heyns and Paulsen reported[35] in 1955 the first synthesis of an unnatural SAA (**80**) in three steps starting from a glucosamine building block (**78**, Scheme 13).



Scheme 13

In 1975 Fuchs and Lehmann[36] reported the synthesis of a novel set of SAAs (e.g. **82**, Scheme 14) and were the first to recognise that these compounds combine both carbohydrate and amino acid properties. They proposed the use of SAAs as monomers to construct polysaccharide analogues through amide bonds. However, it was not until 1996 that the first structure of an oligosaccharide mimic in which glycosidic linkages were replaced by amide bonds (**84**) was analysed in depth with respect to its structural behaviour.[37] Kessler *et al*.[38] reported the synthesis of SAA **85**, the enantiomer of **82** which was previously prepared by Fuchs and Lehmann.

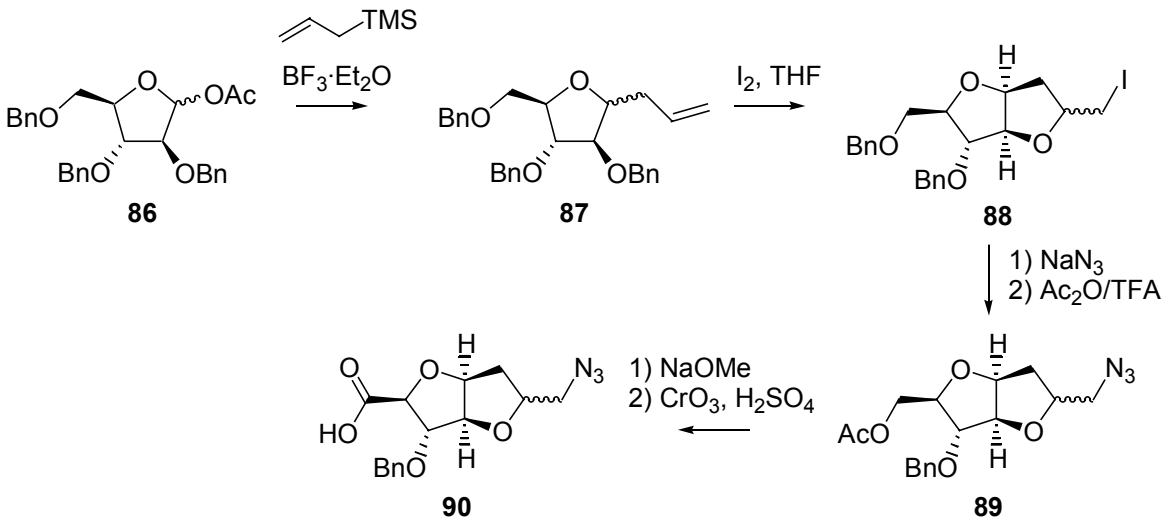


Scheme 14

In recent years, many examples of synthetic SAAs have appeared in the literature. These SAAs are used in various areas of research, in the creation of both peptide and carbohydrate mimics. Some relevant examples of synthetic SAAs and their routes of

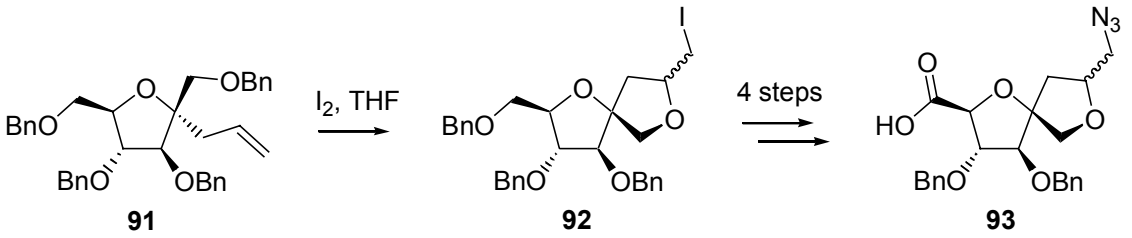
preparation are listed in Schemes 15-19. SAAs, like carbohydrates, often exist as an equilibrium between a mixture of several specific conformers depending on the substitution pattern of the carbohydrate framework. Recently, research in the field of glyco- and peptidomimetics have focussed on the design and synthesis of unnatural rigidified SAAs to urge a conformational bias. These so-called locked SAAs can be obtained through annulation of a second ring. These compounds have found application as glyco-or peptidomimetics, inducing secondary structures in linear or cyclic oligomers.

Nicotra *et al*.[39] devised an elegant approach for the construction of spiro- and fused bicyclic furanoid SAAs. Arabinofuranose **86** was converted into C-glycoside **87** by Lewis acid mediated allylation of the anomeric acetate (Scheme 15). Upon treatment of perbenzylated **87** with iodine in DCM iodocyclisation took place providing a mixture of fused bicyclic ethers (**88**). Displacement of the iodide with an azide group followed by regioselective debenzylation of the primary hydroxyl group by acetolysis gave acetate **89**. Hydrolysis of the acetate function and Jones oxidation afforded the corresponding bicyclic azido acids **90**.



Scheme 15

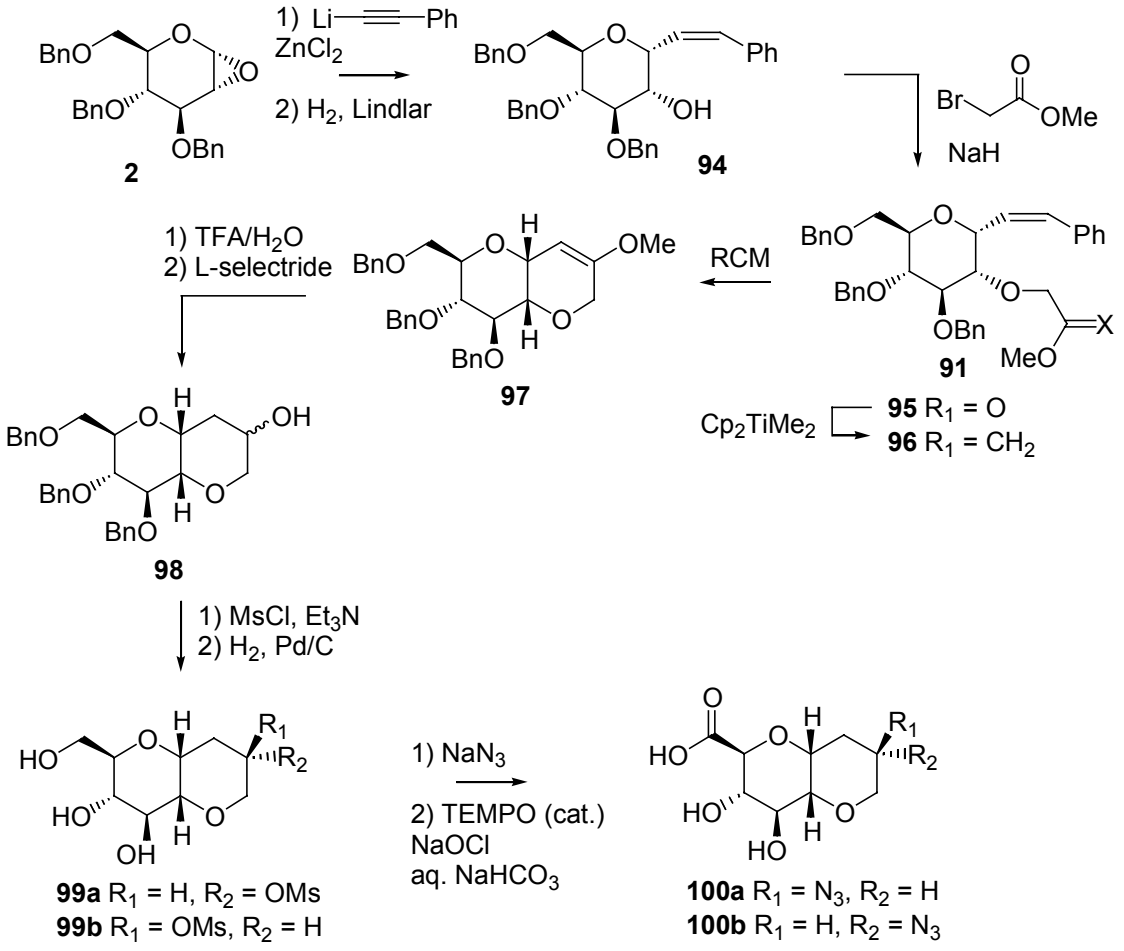
In an analogous approach making use of the iodoetherification, an epimeric mixture of two oxaspirobicyclic SAAs or spiroazidoacids (**93**) were obtained starting from fructo-C-furanoside **91** (Scheme 16).



91 **92** **93**

Scheme 16

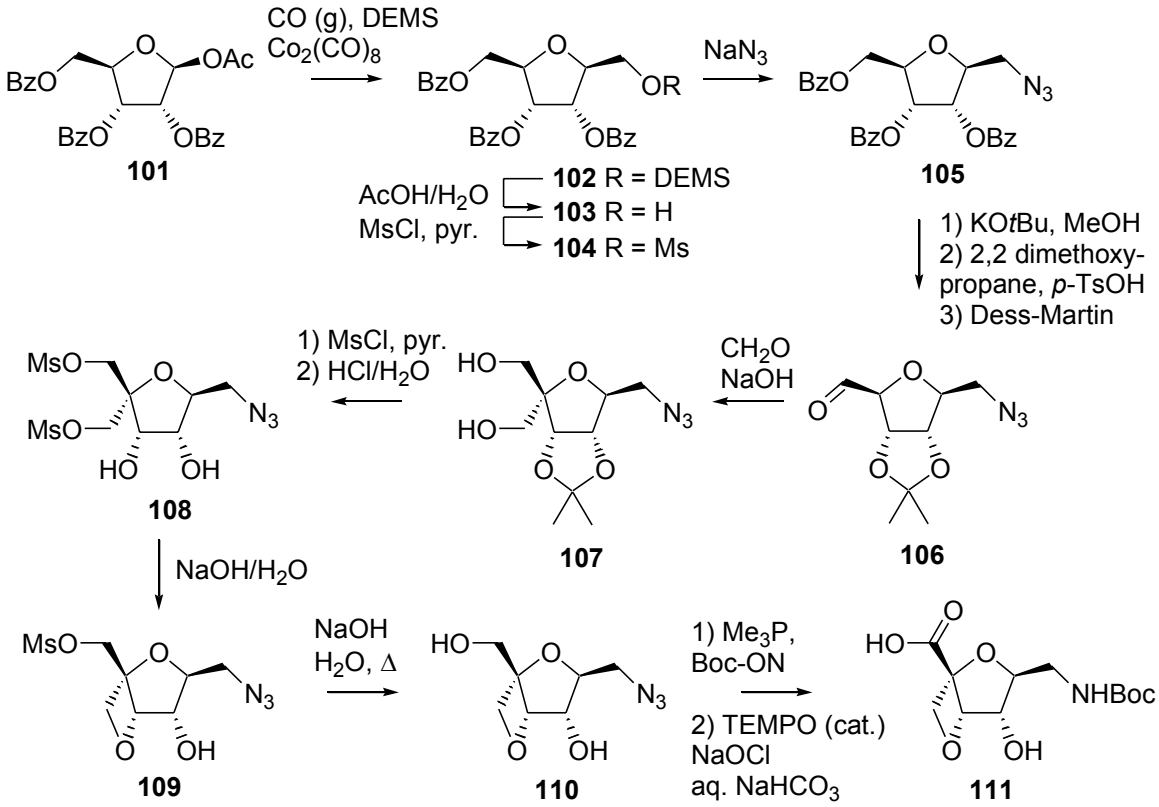
Grotenbreg *et al.*[40] described the synthesis of two pyranopyran SAAs. The synthesis commenced with the formation of C-glycoside **94**, which is readily available in a two step sequence starting from 1,2-anhydroglucitol (**2**, Scheme 17). Thus, zinc-mediated ring-opening of the epoxide with lithium phenylacetylide and partial reduction



Scheme 17

of the acetylene group gave alkene **94**. Alkylation of the free hydroxyl in compound **94** with methylbromoacetate and sodium hydride followed by olefination of methyl ester **95**, using Petasis reagent, furnished enol ether **96**. Olefin RCM of **96** afforded pyranopyran **97**. TFA-assisted hydrolysis of the enol ether **97** and subsequent reduction of the resulting ketone under the agency of L-selectride gave an epimeric mixture of alcohols (**98**). Treatment of **98** with methylsulfonyl chloride in pyridine, separation of the isomers and hydrogenolysis of the benzylethers, eventually led to the assembly of mesylates **99a** and **99b**. Nucleophilic displacement of the mesylate functions with sodium azide and selective oxidation of the primary alcohol finally furnished two constrained SAAs (**100a** and **100b**).

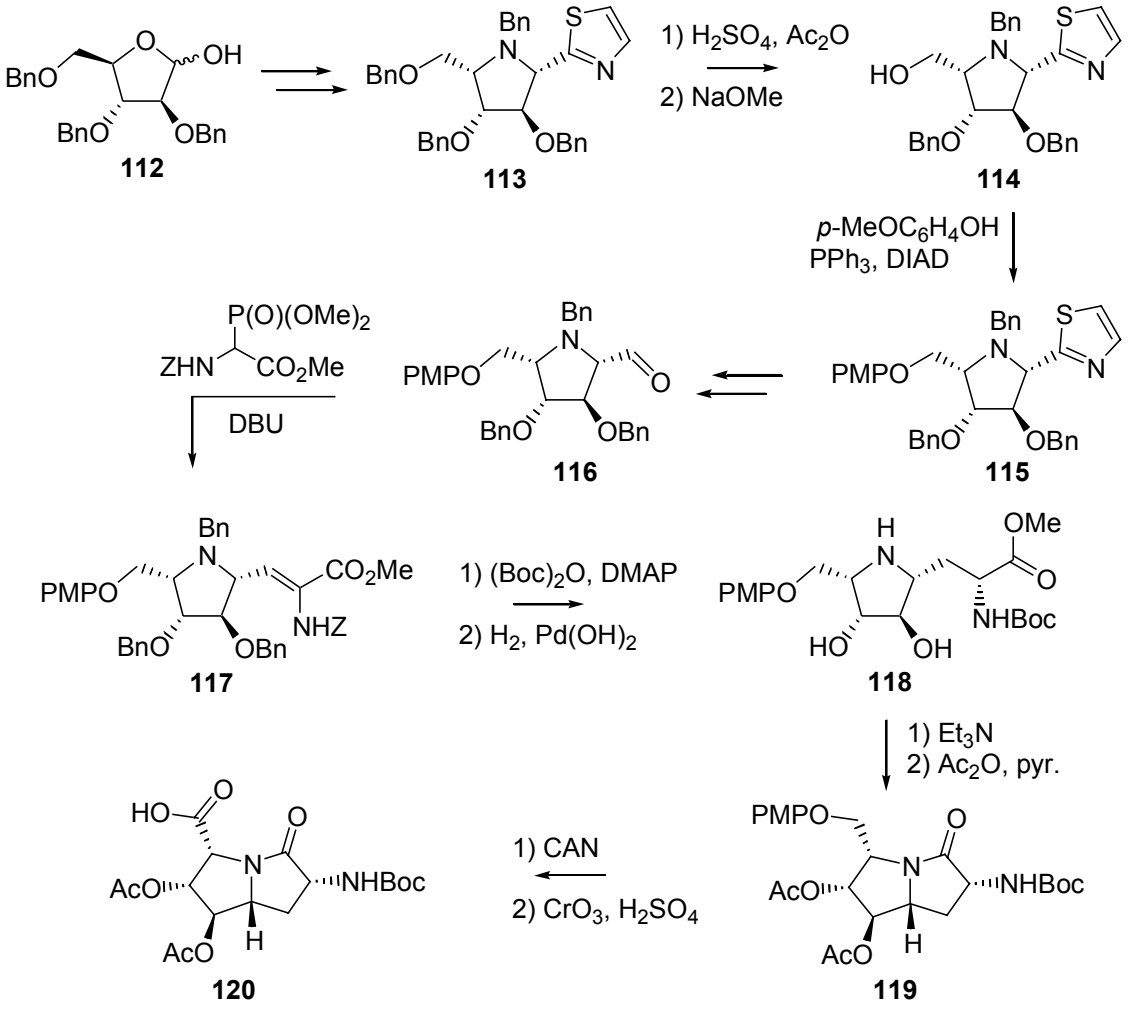
In a recent study to obtain highly constrained SAAs as dipeptide isosters, Van Well *et al*.[41] described the synthesis of novel bicyclic furanoid SAAs locked with an oxetane ring (Scheme 18). The synthesis started with carbonyl-insertion, in the presence



Scheme 18

of diethylmethylsilane (DEMS) and CO-gas, on fully protected ribofuranose **101**. Acidic removal of the silyl group, followed by mesylation and treatment with sodium azide gave compound **105**. Removal of the benzoyl protecting groups, and ensuing installation of an isopropylidene of the *cis*-diol followed by Dess-Martin oxidation of the primary hydroxyl function afforded aldehyde **106**. Treatment of **106** with formaldehyde in the presence of NaOH followed by a Cannizzaro reaction of the intermediate β-hydroxy aldehyde furnished diol **107**. Transformation of the two primary alcohol functions into mesylate groups followed by acidic removal of the acetonide afforded **108**. Ring-closure to the oxetane (**109**) was accomplished under basic conditions. Liberation of the primary alcohol with sodium hydroxide at elevated temperature provided locked furan **110**. The azide was transformed into a protected amine using a modified Staudinger reaction in the presence of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON). Finally oxidation of the primary alcohol into a carboxylic acid furnished locked SAA **111**.

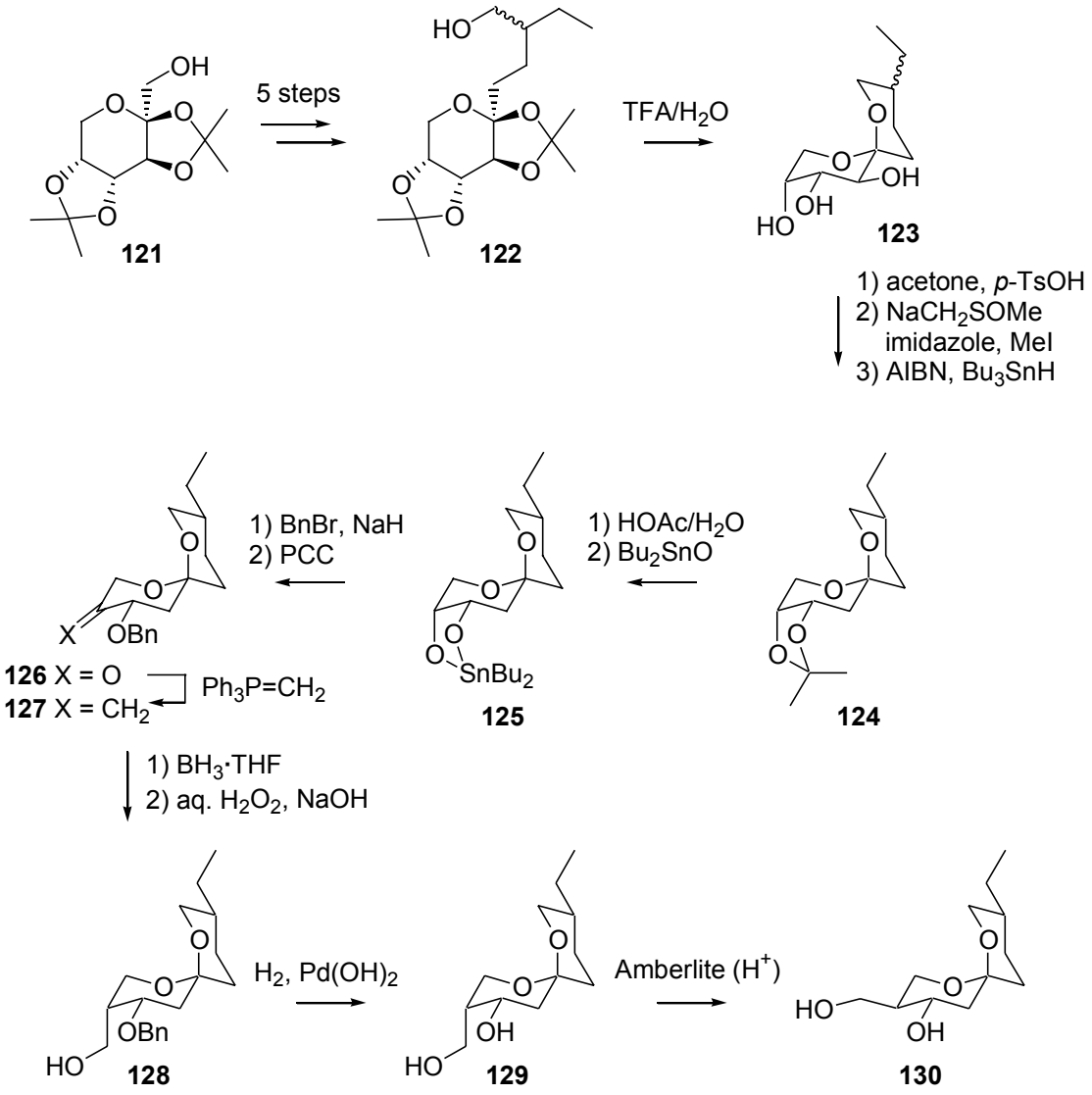
The synthesis of pyrrolizidine SAA **120** (Scheme 19), starting from a protected D-arabinofuranose, was accomplished by Dondoni *et al*.[42] D-Arabinose **112** was converted to pyrrolidine **116** using their thiazole based aminohomologation procedure previously described in Scheme 8. Next, Horner-Wadsworth-Emmons olefination of aldehyde **116** followed by saturation of the double bond and protective group manipulations provided amino acid **118**. The conformationally constrained dipeptide **120** was obtained by the following sequence of reactions. First formation of the cyclic amide was achieved under basic conditions. Next, two acetate functions were installed (**119**) followed by removal of the *p*-methoxyphenyl group and subsequent oxidation of the primary alcohol to give **120**.



Scheme 19

Spiroketals are often found as structural constituents in many biologically active compounds.[43] Spiroketals are found as simple structures in insect pheromones and are present as part of more complex compounds such as polyether marine toxins, steroids or plant metabolites. The vast majority of the spiroketal frameworks are composed of spiro[5.5], spiro[4.5] and spiro[4.4] ring systems. Talaromycins A and B (**129**, **130**, Scheme 20) are toxic metabolites isolated from the fungus *Talaromyces Stripitatas*.[44] An enantiospecific synthesis of **129** and **130** was realised by Cubero *et al*.[45] starting from diisopropylidene-D-fructopyranose **121**. In a five-step procedure chain elongation led to **122**, which after treatment with aqueous TFA furnished two spiroketals **123**. Acetonation of the *cis*-diol followed by Barton deoxygenation of the remaining hydroxyl gave compound **124**. Removal of the isopropylidene ketal, installation of a dibutylstannylidene

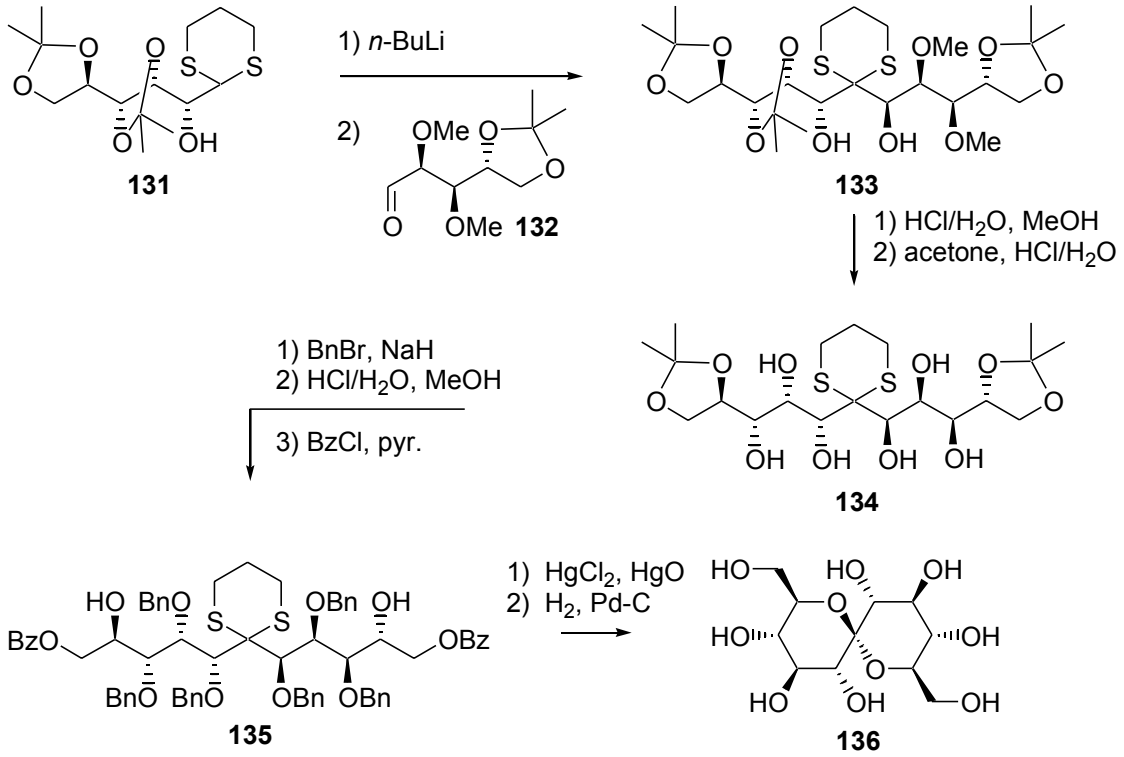
and regioselective opening of intermediate **125** with benzyl bromide followed by PCC oxidation furnished ketone **126**. Next, Wittig olefination of **126**, hydroboration of the resulting exocyclic alkene in **127** followed by hydrogenolysis of **128** afforded talaromycin A. An acid catalysed isomerisation of **129** led to the formation of talaromycin B.



Scheme 20

An interesting class of spiroketals, not identified in nature, are the perhydroxylated 1,7-dioxaspiro[5.5]undecanes. Redlich *et al.*[46] reported a general

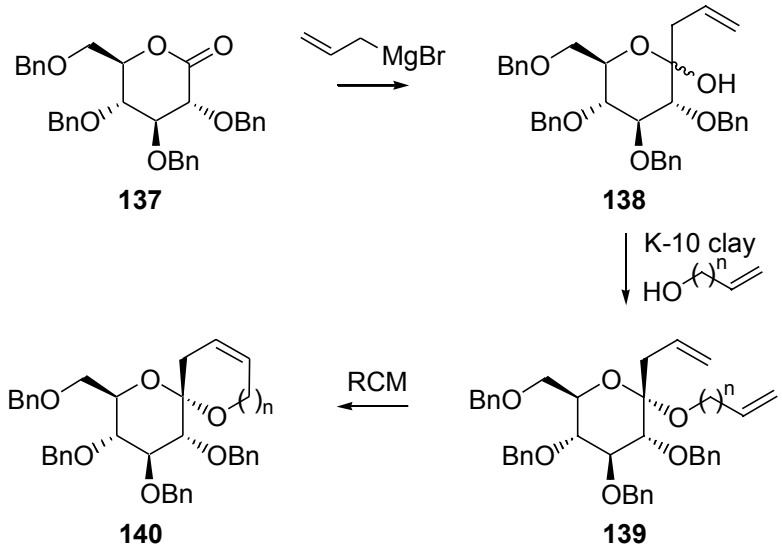
approach towards the synthesis of a set of hexopyranoses linked together by a spiroketal center. According to the Corey-Seebach procedure,[47] the synthesis commenced with the coupling of a dithioacetal with an open chain aldopentose as follows (Scheme 21). Reaction of the dianion of glucose-derived dithiane **131**, prepared under the agency of *n*-butyl lithium in THF, with an aldehyde, protected D-arabinose **132**, furnished thioketal **133**. The desired diol **135** was obtained after systematic manipulation of protective groups. Liberation of the masked ketone in **135**, upon treatment of the dithiane with $HgCl_2$/HgO, followed by cyclisation and subsequent hydrogenation afforded polyhydroxy spiroketal **136**.



Scheme 21

Recently Van Hooft *et al.*[48] described the asymmetric synthesis of carbohydrate-derived spiroketals following a three step procedure (Scheme 22). Grignard addition of allylmagnesium bromide to perbenzylated gluconolactone **137**, condensation of hemiketal **138** with a second terminal alkenol (n = 1-3) and subsequent ring-closure of **139** by olefin RCM led to the assembly of pyranose spiroketals **140**. The scope of this procedure was

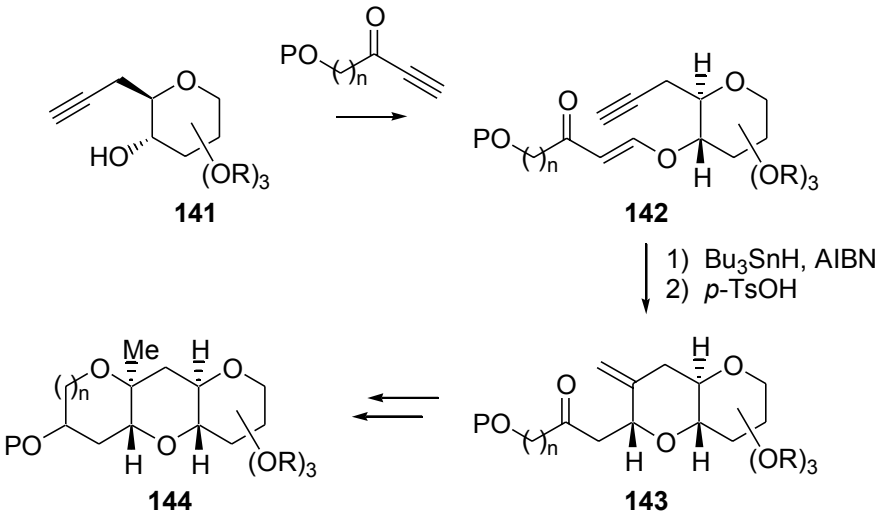
further demonstrated by variation of the Grignard reagent (allyl- or vinylmagnesium bromide) followed by the addition to different pyrano- as well as a furanolactones, in combination with changing the chain length of the alkenol. In this manner several pyranose- and furanose-derived lactones were transformed into spiroketals.[49]



Scheme 22

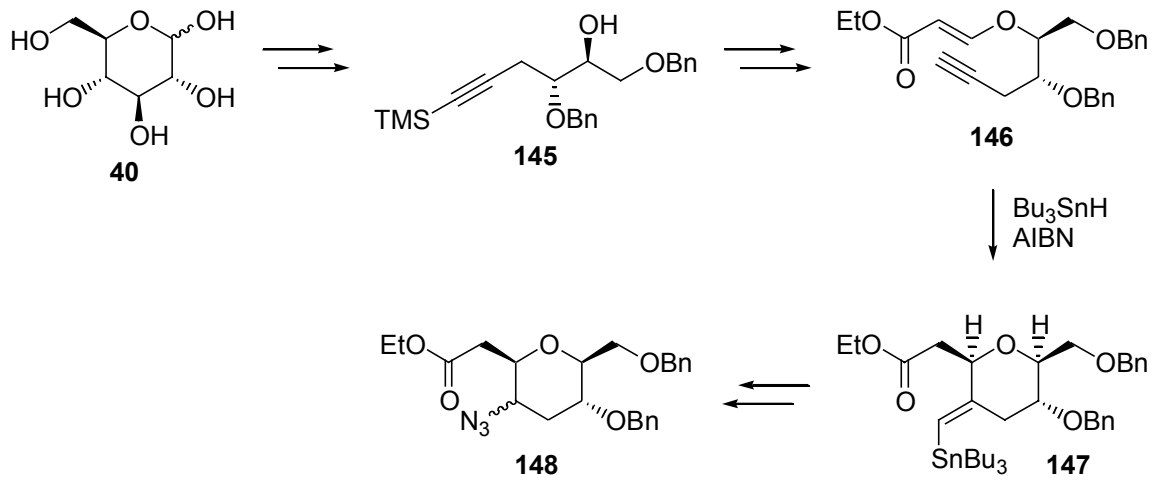
Aim and outline of the Thesis

The research described in this Thesis is directed to the implementation of monosaccharides in the construction of a variety of functionalised cyclic and oligocyclic systems. **Chapter 2** describes the construction of two *trans*-fused tricyclic ethers (**144**, n=1 or 3, Scheme 23) with a methyl group positioned at a bridgehead position. Such structural entities are often found as motif in naturally occurring polycyclic ethers. According to the tributyltin mediated radical cyclisation procedure developed by Leeuwenburgh *et al*., two glucose-derived pyranopyrans (**143**) were efficiently obtained. Next, the emphasis was directed towards cyclisation of the third ether ring and simultaneous installation of the methyl group at the bridgehead position taking advantage of the exocyclic alkene resulting from the radical cyclisation.



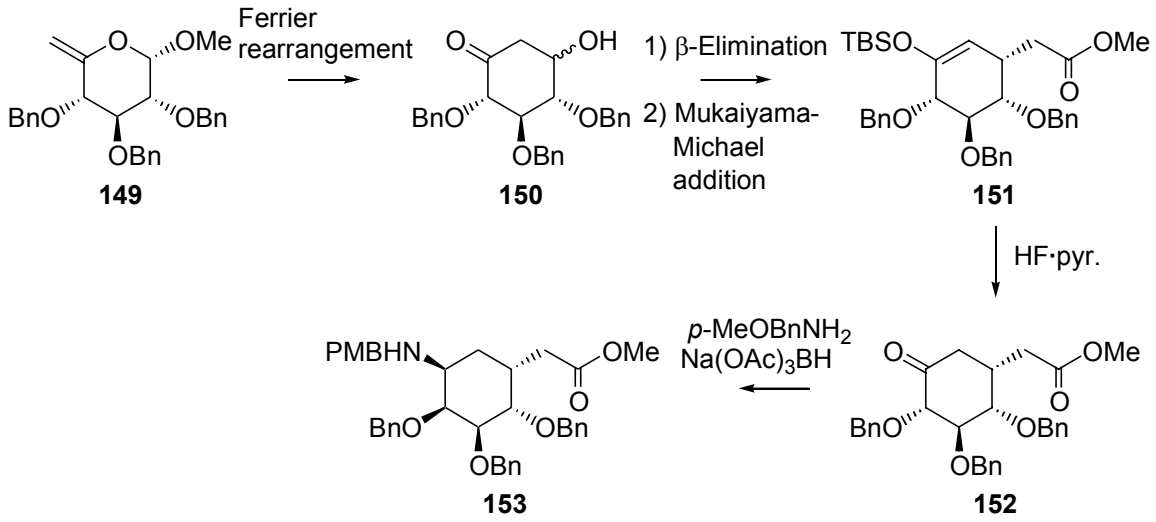
Scheme 23

The assembly of carbohydrate-based γ-amino acids using the radical cyclisation approach as key step is the subject of **Chapter 3**. Glucose-derived alkynol **145** is condensed with a propiolate and subsequently converted into enyne **146** (Scheme 24). The tributyltin mediated ring-closure of **146** proceeded smoothly to give cyclic ether **147**. Introduction of the amine functionality proved feasible by exploiting the exocyclic vinylstannane moiety, resulting from the radical cyclisation, leading to the formation of two protected γ-SAAs **148**.



Scheme 24

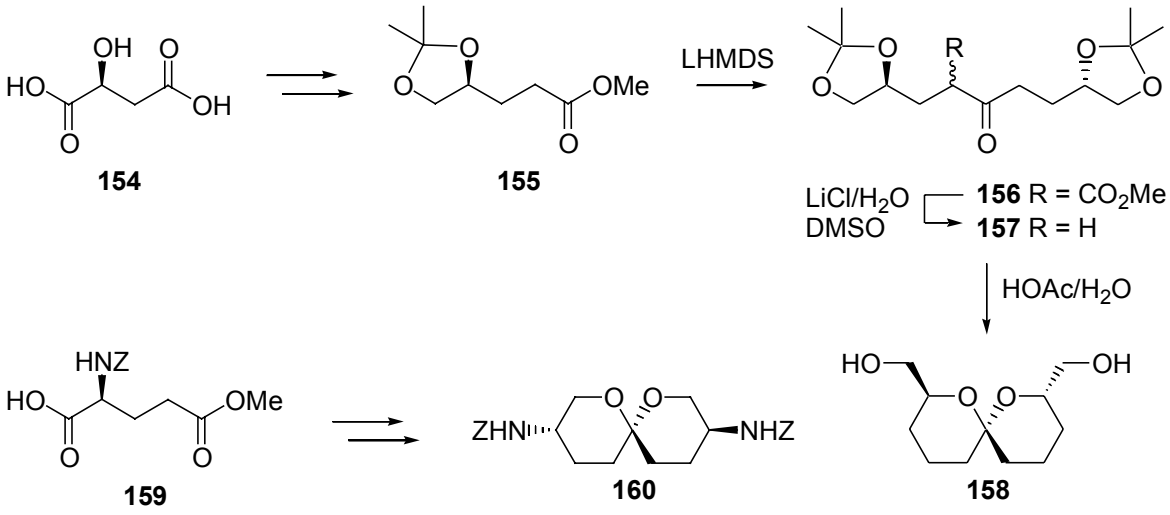
The transformation of D-glucose into a carbasugar amino acid (CSAA), a novel class of conformationally restricted SAAs, is described in **Chapter 4**. The Ferrier-rearrangement proved to be a convenient method to convert glucose-derived enopyranoside **149** into cyclitol **150** (Scheme 25). At this stage, several synthetic pathways were explored to install the amine and carboxylate functionalities. β-Elimination of the hydroxy group in **150** afforded an enone which was subjected in the next step to a Mukaiyama-Michael addition to give ester **151**. Hydrolysis of the silyl enol ether in **151** followed by installation of the amino function at the resulting ketone **152** gave protected CSAA **153**.



Scheme 25

Chapter 5 reports a convenient method for the synthesis of functionalised C_2-symmetrical 1,7-dioxaspiro[5,5]undecanes, such as **158** and **160**, using acid-catalysed spiroketalisations of substituted dihydroxyketones (Scheme 26). A two step Claisen self-condensation and decarboxylation procedure are the key steps in this synthetic route. The synthesis of spiroketal **158** commenced with the conversion of (*S*)-malic acid (**154**) into suitably protected ester **155**. Claisen self-condensation, upon treatment of ester **155** with lithium hexamethyldisilazane (LHMDS), readily afforded β-ketoesters **156**. Decarboxylation of the methyl esters under Krapcho conditions then smoothly furnished the requisite dihydroxyketone (**157**), which, upon acidic removal of the isopropylidene

moieties followed by cyclisation, led to the formation of C_2-symmetrical spiroketals **158**. In a similar approach, partially protected glutamic acid **159** was converted into spiroketal **160**, containing protected amine functions



Scheme 26

Chapter 6 summarises the results described in this Thesis. In addition several future prospects concerning its contents will be discussed.

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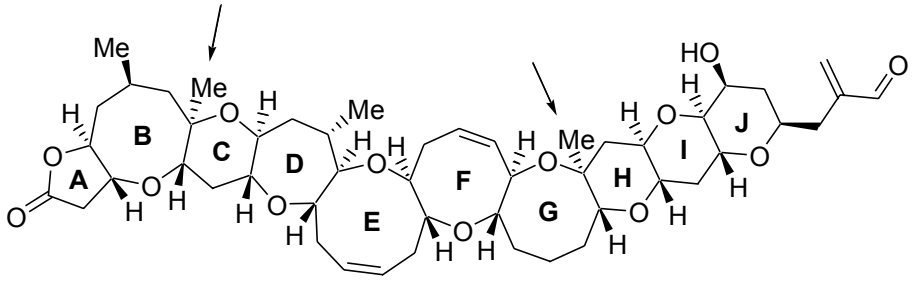
Chapter 2

Towards the Synthesis of *trans*-Fused Tricyclic Ethers Containing an Angular Methyl Group: A Selenocyclisation Based Approach

Introduction

The first example of a marine toxin featuring *trans*-fused polycyclic ethers, brevetoxin B, was isolated from cultured cells of the dinoflagellate *Gymnodinium breve* and fully characterised in 1981.[1] Since then, these molecules have received a great deal of attention due to their biological potency, natural scarcity and molecular architecture.[2] The intriguing complex structure of these polyethers is exemplified by brevetoxin A (**1**, Figure 1) and gambierol (**2**). Brevetoxin A is a member of the brevetoxin family also produced by the dinoflagellate *Gymnodinium breve*.[3] The algae that secrete this class of compounds often form large blooms. Commonly known as "red tides" these blooms occur along the coast of Florida and the Gulf of Mexico.[4] The potent neurotoxic capacity of the brevetoxins is associated with neurotoxic shellfish poisoning often responsible for massive fish mortality and human intoxication.[5] Gambierol,[6] maitotoxin[7] and ciguatoxin CTX3C[8] (a congener of the ciguatoxin family), isolated from cultures of the marine dinoflagellate *Gambierdiscus toxicus*, are the toxic constituents implicated in human

Figure 1



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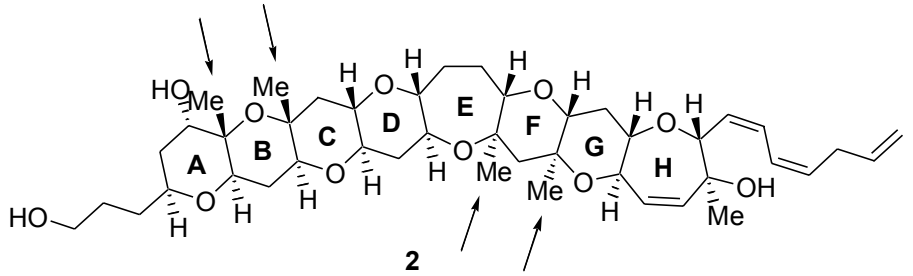


2

seafood poisoning (called ciguatera).[9] Another type of toxic polyethers obtained from this marine organism are the gambieric acids A-D[10] which are the most potent antifungal substances known.

Pharmacological studies on ciguatoxins and brevetoxins revealed that they exert their biological activity by binding to the voltage sensitive sodium channels, depolarising the cell membrane and promoting sodium ion influx into the cell.[11] Isolation and further studies on the biological activities of these toxins are hampered due to the low content in marine organisms. Therefore, synthetic access to the compounds would be highly desirable. The challenging structure of marine polycyclic ethers, from an organic chemistry point of view, further explains the numerous synthetic studies towards these compounds reported since their initial discovery.[12]

Throughout the past two decades many convergent strategies have been developed towards the construction of polycyclic ether frameworks. In 1995 the group of Nicolaou was the first to complete the total synthesis of a polycylic ether marine toxin, brevetoxin B.[13] Shortly thereafter (1998), they reported the total synthesis of brevetoxin A.[14] Other groups accomplished total syntheses of ciguatoxin CTX3C (Hirama and co-

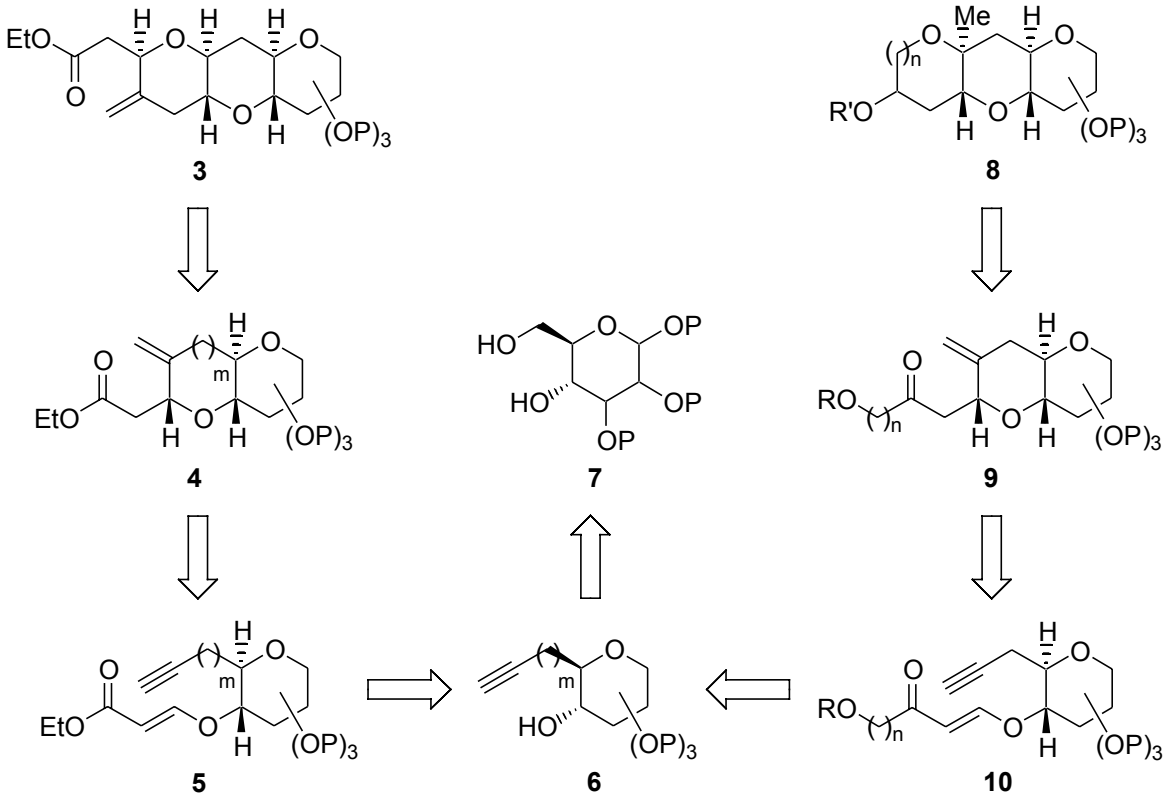
workers,[15] 2001) and gambierol (Sasaki and co-workers,[16] 2002). Despite these impressive accomplishments, successful examples of powerful and efficient modular approaches are still scarce.

As part of the ongoing challenge to assemble medium-sized polyether fragments, and in view of the repetitive nature of these structures, several groups have developed iterative procedures.[17] Main focus in these concepts entails the development of efficient and general intramolecular heterocyclisations in conjunction with high degrees of stereocontrol. The most frequent synthetic strategies applied are based on formation of C-O bonds via attack of an oxygen atom on an activated carbon center. Alternatively, a variety of transformations are studied to effectively construct carbon-carbon bonds to obtain oxacycles of different sizes and substitution patterns in a general fashion. The realisation of such an ideal method is difficult. Apart from the variation in ring sizes, the presence of angular methyl groups (indicated with arrows in Figure 1) seriously hampers the realisation of such an method.

Leeuwenburgh *et al*.[18] demonstrated an efficient method for the preparation of *trans*-fused bicyclic ethers (**4**, Scheme 1) of various ring sizes (m = 0-3). In addition, a *trans*-fused tricyclic tetrahydropyran (**3**) was constructed via an iterative procedure. The key step involved tributyltin mediated radical cyclisation of carbohydrate-derived β-(alkynyloxy)acrylates (**5**).

With the aim to broaden the scope of the radical cyclisation protocol towards the synthesis of natural polycyclic ethers, the potential to install an angular methyl functionality in a suitably derivatised radical cyclisation product was investigated. To this end, the exocyclic alkene moiety in intermediates **9** (n=1,3) obtained from **10** via the radical cyclisation approach, were designed for ensuing installation of an angular methyl group via intramolecular selenocyclisation[19] (**8**, n=1,3). In this Chapter, the feasibility of this strategy is presented.

Scheme 1

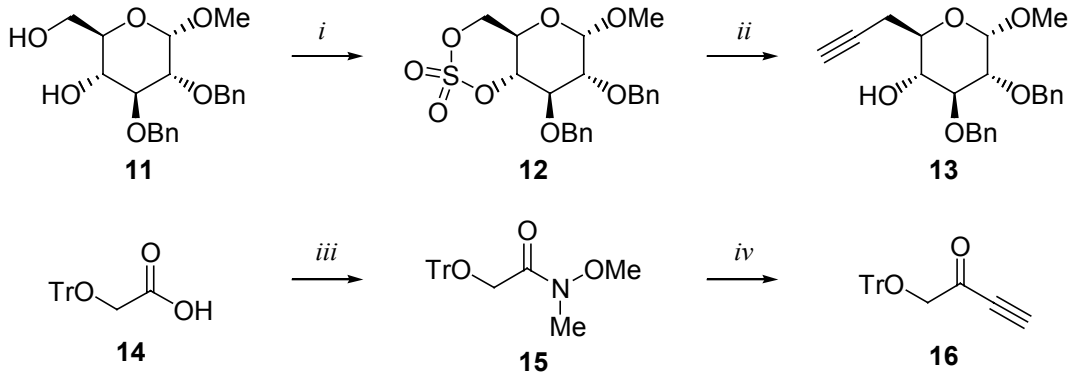


Results and discussion

Retrosynthetic analysis (see Scheme 1) reveals that installation of the angular methyl groups at the bridgehead positions in **8** (n=1,3) can be achieved through intramolecular cyclisation of hydroxyalkenes **9** (R=H). These bicyclic ethers are readily available by radical cyclisation of β-alkynyloxy acrylates **10**. In turn enynes **10** can be obtained via Michael addition of a carbohydrate-derived acetylene (**6**) to an α,β-unsaturated ketone.

First, the synthesis of a bicyclic ether **9** (n=1) was undertaken. The synthesis of the requisite building blocks, alkyne **13** and ynone **16**, is outlined in Scheme 2. Treatment of known diol **11**[20] with thionyl chloride followed by oxidation resulted in the formation of the corresponding cyclic sulfate **12** in a 90% overall yield. Opening of the cyclic sulfate with lithium acetylide and acidic removal of the remaining 4-*O*-sulfate furnished Michael donor **13** in a yield of 98%.

Scheme 2

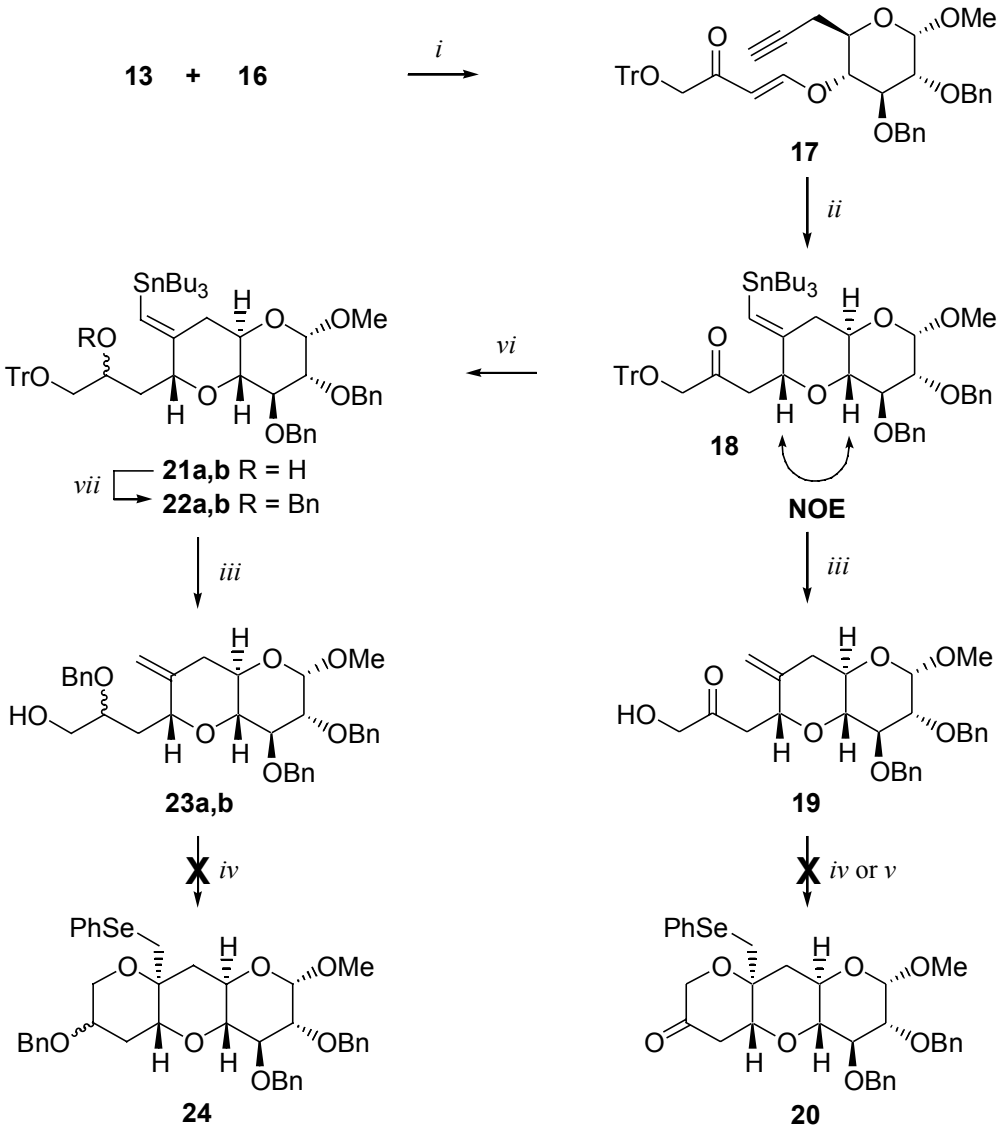


Reagents and conditions: *i*) a) $SOCl_2$ (1.5 equiv.), NMM (1.5 equiv.), CH_2Cl_2, 0 °C to rt, 30 min. b) $NaIO_4$ (2.0 equiv.), $RuCl_3$ (cat.), $MeCN/CH_2Cl_2/H_2O$ (2:2:3), 20 min, 90% (2 steps). *ii*) a) LiC≡CH ethylene diamine complex (3.0 equiv.), DMSO, rt, 15 min. b) H_2SO_4/H_2O (pH<2), 50 °C, 18 h, 98% (2 steps). *iii*) a) PyBOP (1.0 equiv.), DiPEA (1.1 equiv.), CH_2Cl_2, rt, 5 min. b) $Me(MeO)NH_2Cl$ (1.2 equiv.), DiPEA (1.2 equiv.), 16 h, 87%. *iv*) HC≡CMgBr (1.5 equiv.), THF, 0 °C to rt, 4 h, 79%.

Michael acceptor **16** was synthesised starting from known protected glycolic acid **14**[21] (Scheme 2). Conversion of the carboxylate into Weinreb amide **15** (87%) followed by alkylation with ethynylmagnesiumbromide proceeded smoothly to furnish ynone **16** in a 79% yield.

At this stage, attention was focussed on the formation of pyrano-pyran **18** (Scheme 3). Michael addition of the free hydroxyl in **13** with ynone **16**, under the influence of a catalytic amount of *N*-methylmorpholine (NMM), gave enone **17**. Radical cyclisation of compound **17** under the agency of tributyltinhydride and AIBN yielded *trans*-fused bicyclic ether **18** (71%). The stereochemistry of the newly formed tertiary center was firmly established by NOE experiments, showing the required 1,3-diaxial relationship of the indicated bridgehead hydrogens (Scheme 3). Under acidic conditions, cleavage of the tributylstannyl group was effected, liberating the exocyclic alkene. Simultaneously, the trityl ether was hydrolysed, yielding **19** in 72% yield. Formation of the third ring (**20**), starting from alkene **19**, under the influence of *N*-(phenylseleno)phthalimide (NPSP)[19] could not be accomplished. Selenocyclisation using phenylselenylchloride did not proceed either.

Scheme 3



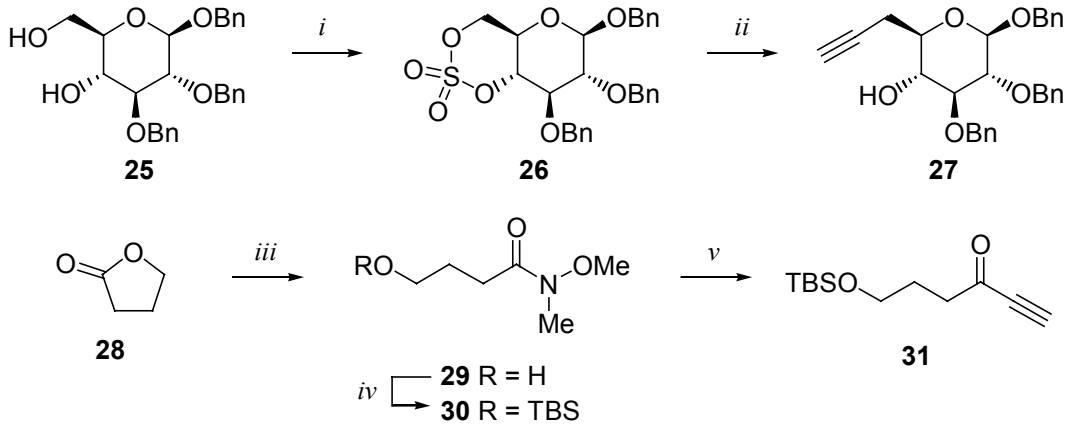
Reagents and conditions: *i*) NMM (0.5 equiv.), CH_2Cl_2, rt, 16 h, 62% (quant. relative to recovered **13**). *ii*) Bu_3SnH (2.0 equiv.), AIBN (0.25 equiv.), toluene, 80 °C, 18 h, 71%. *iii*) *p*-TsOH (2.8 equiv.), CH_2Cl_2, rt, 18 h, 72% (**19**), 80% (**23**). *iv*) NPSP (1.3 equiv.), CSA (0.1 equiv.), CH_2Cl_2, 0 °C to rt, 22 h. *v*) pyr. (0.75 equiv.), PhSeCl (1.75 equiv.), CH_2Cl_2, rt, 23 h. *vi*) $NaBH_4$ (2.4 equiv.), MeOH, rt, 1.5 h, 73%. *vii*) BnBr (1.3 equiv.), NaH (1.3 equiv.), DMF, 0 °C to rt, 18 h, 73%.

As it was reasoned that enolate formation in **19** prevented ring-closure, reduction of the ketone and protection of the alcohol were performed first. Ketone **18** was reduced

with sodium borohydride to yield alcohols **21** in 73% (1:1 mixture of diastereoisomers). Protection of the hydroxyl group in **21** as its benzyl ether, followed by separation of the mixture gave fully protected bicyclic ethers **22** in 73% overall yield. Treatment of both isomers of **22** with *p*-toluenesulfonic acid, as described for the preparation of compound **19**, furnished hydroxyalkenes **23**. To bring about the desired selenocyclisation, compound **23** was submitted to NPSP. Unfortunately, no tricyclic ether **24** was obtained. As a consequence, it was decided to abort further attempts.

Next, ring-closure of bicyclic ether **9** (n=3) was explored as follows. Known tri-*O*-benzyl glucose **25**[22] (Scheme 4) was transformed into the corresponding cyclic sulfate **26** (92% over two steps). Treatment of **26** with lithium acetylide, as described for the transformation of **11** into **13**, gave alkyne **27** in a 83% yield. Michael acceptor **31** proved to be accessible in a three-step synthesis starting from γ-butyrolactone **28**. Thus lactone **28** was converted into Weinreb amide **29** using trimethylaluminum[23] followed by protection of the primary hydroxyl as the TBS-ether to give **30**. Grignard reaction of amide **30** with ethynylmagnesium bromide furnished ynone **31** in 90% yield.

Scheme 4



Reagents and conditions: *i*) a) $SOCl_2$ (1.5 equiv.), NMM (1.5 equiv.), CH_2Cl_2, 0 °C, 4 h. b) $NaIO_4$ (2.1 equiv.), $RuCl_3$ (cat.), $MeCN/CH_2Cl_2/H_2O$ (3:3:5), rt, 1 h, 92% (2 steps). *ii*) LiC≡CH ethylene diamine complex (3.0 equiv.), DMSO, rt, 5 min. b) H_2SO_4/H_2O (pH<2), 50 °C, 18 h, 83% (2 steps). *iii*) $Me(MeO)NH_2Cl$ (3.0 equiv.), Me_3Al (3.0 equiv.), -78 °C to rt, 18 h, 70%. *iv*) TBSCl (1.2 equiv.), pyr., rt, 15 h, 90%. *v*) HC≡CMgBr (1.5 equiv.), THF, 0 °C to rt, 2 h, 90%.

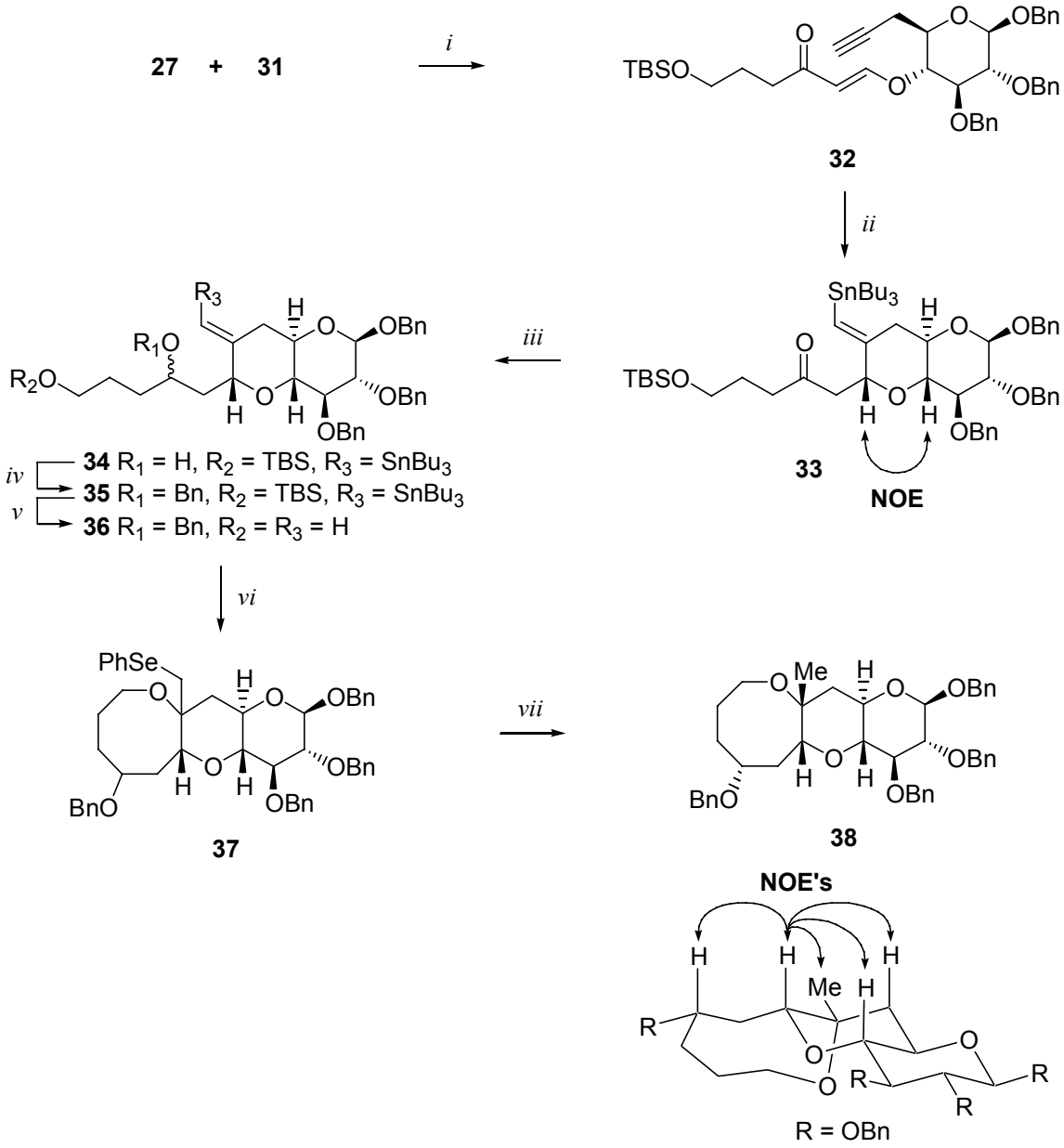
Hetero-Michael addition of alcohol **27** to α,β-unsaturated ketone **31** (Scheme 5), under the influence of base, gave enyne **32** in 59% (88% relative to recovered **27**). The tributyltin mediated radical cyclisation of **32**, as described for the conversion of **17** into **18**, furnished bicyclic ether **33** in 85% yield. Reduction of the ketone moiety followed by protection of the resulting alcohol as the corresponding benzyl ether gave vinyltin derivative **35**.

Acidic removal of the tributyltin moiety along with the TBS protective group yielded cyclisation precursor **36** in 84%. Cyclic ether formation of alkene **36** under the agency of NPSP did proceed, affording **37** in a modest yield of 48% (62% relative to recovered starting material). The configuration of the new chiral center in **37** could not be assigned unambiguously based on COSY and NOESY NMR analysis. Liberation of the methyl function in **37** was achieved by reductive removal of the phenylseleno group, leading to the formation of **38** in a yield of 71%. At this stage the absolute stereochemistry of tricyclic ether **38** was established by NMR analysis. The configuration of the angular position was assigned unequivocally through an observed NOE between the methyl group and the angular proton, revealing a 1,2 *cis*-relationship.

Conclusion

In this Chapter, a radical cyclisation strategy was shown to be a successful method for the construction of *trans*-fused pyrano-pyrans with an exocyclic methylene group. The thus obtained bicyclic ethers were used as structural motifs to explore the possibility to synthesise tricyclic ethers with an angular methyl group as present in several marine toxins. However, the conducted selenocyclisations proved to be rather cumbersome. Attempts to construct a pyrano-pyrano-pyran were abortive, whereas the synthesis of an eight membered ring did proceed, albeit with the undesired *syn*-geometry.

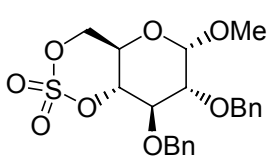
Scheme 5



Reagents and conditions: *i*) NMM (0.1 equiv.), CH_2Cl_2, rt, 24 h, 59% (88% relative to recovered **27**). *ii*) Bu_3SnH (2.0 equiv.), AIBN (0.25 equiv.), toluene, 80 ^oC, 15 h, 85%. *iii*) $NaBH_4$ (2.4 equiv.), $MeOH/CH_2Cl_2$ (1:4), rt, 2.5h, 82% (**34a : 34b** 2:1), *iv*) BnBr (1.3 equiv.), NaH (1.2 equiv.), DMF, 0 ^oC, 22 h, 78%. *v*) *p*-TsOH (2.3 equiv.), CH_2Cl_2, rt, 2.5 h (84%), *vi*) NPSP (1.25 equiv.), *p*-TsOH (cat.), CH_2Cl_2, 0 ^oC to rt, 24 h, 48% (62% relative to recovered **36**), *vii*) Bu_3SnH, AIBN, toluene, 90 ^oC, 2.5 h, 71%.

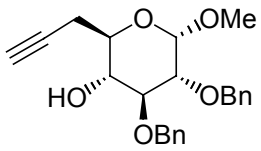
Experimental section

General methods and materials. Acetone, 1,2-dichloroethane, dichloromethane, dimethyl formamide, dimethyl sulfoxide, 1,4-dioxane, ethanol, *n*-hexane, pyridine and toluene (Biosolve) were stored over molecular sieves (4Å). Acetonitrile and methanol (HPLC grade) (Biosolve) were stored over molecular sieves (3Å). Diethyl ether and tetrahydrofuran (Biosolve) were distilled from $LiAlH_4$ prior to use. Eluents ethyl acetate, petroleum ether (40-60) and toluene (Riedel-de Haën) were of technical grade and distilled prior to use. All other chemicals were used as received. All reactions were performed under an inert atmosphere and at ambient temperature unless stated otherwise. Prior to reactions that require anhydrous conditions, traces of water from starting material and reagents were removed by coevaporation with toluene or 1,2-dichloroethane. All solvents were removed by evaporation under reduced pressure. Reactions were monitored by TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) or HPTLC aluminum sheets (Merck, silica gel 60, F254). Compounds were visualised by UV-absorbtion (254 nm) where applicable and by spraying with 20% H_2SO_4 in ethanol followed by charring at ~150 ^oC or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% sulfuric acid followed by charring at ~150 ^oC. Acetylenes and olefins were visualised by spraying with a solution of $KMnO_4$ (2%) and K_2CO_3 (1%) in water. Column chromatography was performed on silica gel (Merck, 40-60 μm). Optical rotations ($[\alpha]_D^{20}$) were measured on a Propol automatic polarimeter (sodium D line, λ = 589 nm). ^1H- and ^{13}C-APT-NMR spectra were recorded on a Jeol JNM-FX-200 (200/50.1 MHz), a Bruker 300 WM-300 (330/75 MHz), a Bruker AV 400 (400/100 MHz) or a Bruker DMX-600 (600/150 MHz) spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Coupling constants (*J*) are given Hz. Where indicated, NMR-peak assingments were made using COSY and NOESY experiments. Infrared spectra were recorded on a Shimadzu FTIR-8300 and data are reported in cm^{-1}. Mass spectra were recorded on a PE/Sciex API 165 instrument with an ion spray interface. High resolution mass spectra were recorded on a Finnigan LTQ-FT (Thermo electron). LC-MS analysis was conducted on a Jasco system (detection simultanously at 214 nm and 254 nm) equipped with an Alltima C-18 analytical column (Alltech, 4.6 mm × 150 mm, 5μm particle size). Preperative HPLC was performed on a BioCad Vision (Applied Biosystems, Inc.) using a Alltima C-18 column (Alltech, 10.0 mm × 250 mm, 5μm particle size).

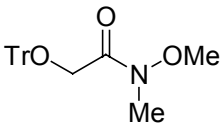


Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 4,6-cyclic sulfate (12): Known diol **10**[20] (7.57 g, 20.2 mmol) was dissolved in DCM (150 mL) and cooled to 0 ^oC. NMM (3.33 mL, 30.3 mmol, 1.5 equiv.) and $SOCl_2$ (2.21 mL, 30.3 mmol, 1.5 equiv.) were added dropwise and the mixture was allowed to reach rt. After 30 min the reaction was quenched upon addition of water and extracted with Et_2O. The organic layer was separated and the aqueous layer was extracted once more with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude sulfite was dissolved in a mixture of

MeCN/DCM/water (2:2:3, 140 mL) followed by the addition of $NaIO_4$ (8.66 g, 40.5 mmol, 2.0 equiv.) and a catalytic amount of $RuCl_3$. After stirring for 20 min, the reaction mixture was diluted with EtOAc, washed with water, sat. aq. NH_4Cl and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE 1:3) the yield cyclic sulfate **12** (7.92 g, 18.2 mmol, 90%) as a white crystalline solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.38-7.33 (m, 10H, CH_{arom}), 4.83 (d, 1H, J = 10.2 Hz, CH Bn), 4.81 (s, 2H, CH_2 Bn), 4.63 (d, 1H, J = 10.2 Hz, CH Bn), 4.60-4.40 (m, 4H), 4.20-3.98 (m, 2H), 3.51 (dd, 1H, J = 8.8 Hz, J = 3.7 Hz, H-2), 3.40 (s, 3H, CH_3 OMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.6, 137.4 (2× C_q Bn), 128.4, 128.2, 128.0, 127.8 (CH_{arom}), 98.9 (C-1), 84.3, 78.6, 76.8, 60.3 (C-2, C-3, C-4, C-5), 75.4, 73.8, 72.0 (2× CH_2 Bn, C-6), 55.9 (CH_3 OMe).

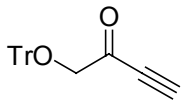


Methyl 2,3-di-*O*-benzyl-6-deoxy-6-*C*-ethynyl-α-D-glucopyranoside (13): To a suspension of lithium acetylide ethylene diamine complex (5.57 g, 54.5 mmol, 3.0 equiv.) in DMSO (70 mL) under an argon atmosphere was added dropwise a solution of cyclic sulfate **12** (7.92 g, 18.2 mmol) in DMSO (40 mL). After 15 min TLC analysis (EtOAc/PE 1:1) showed complete disappearance of starting material. The reaction mixture was acidified to pH 2 (CAUTION! Exothermic reaction) by slow addition of 80% aq. H_2SO_4 and heated to 50 °C. After stirring for 18 h, the TLC analysis (EtOAc/PE 1:1) revealed the formation of a higher running spot and the reaction was diluted with water and extracted four times with Et_2O. The combined ether layers were dried ($MgSO_4$), filtered and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/PE 1:9) gave alkyne **13** (6.78 g, 17.7 mmol, 98%) as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35-7.30 (m, 10H, CH_{arom}), 5.03 (d, 1H, J = 11.7 Hz, CH Bn), 4.76 (d, 1H, J = 12.4 Hz, CH Bn), 4.69 (d, 1H, J = 11.7 Hz, CH Bn), 4.63 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.63 (d, 1H, J = 12.4 Hz, CH Bn), 3.80-3.43 (m, 4H, H-2, H-3, H-4, H-5), 3.40 (s, 3H, CH_3 OMe), 2.64 (dt, 1H, $J_{6a,5}$ = $J_{6a,8}$ = 2.9 Hz, $J_{6a,6b}$ = 17.2 Hz, H-6a), 2.47 (ddd, 1H, $J_{6b,8}$ = 2.9 Hz, $J_{6b,5}$ = 6.2 Hz, $J_{6b,\ 6a}$ = 17.2 Hz, H-6b), 2.23 (d, 1H, $J_{OH,4}$ = 2.2 Hz, OH), 1.99 (t, 1H, $J_{8,6a}$ = $J_{8,6b}$ = 2.9 Hz, H-8). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.3, 137.6 (2× C_q Bn), 128.0, 127.6, 127.5, 127.4, 126.4 (CH_{arom}), 97.5 (C-1), 80.8, 79.4, 71.9, 68.4 (C-2, C-3, C-4, C-5), 80.0 (C-7), 74.9, 72.6 (2× CH_2 Bn), 69.8 (C-7), 54.6 (CH_3 OMe), 20.9 (C-6). MS (ESI): *m/z* 405.3 $[M+Na]^+$, 787.6 $[2M+Na]^+$.

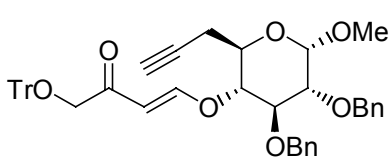


***N*-Methoxy-*N*-methyl-2-trityloxy-acetamide (15):** To a solution of acid **14** (3.22 g, 10.1 mmol), dissolved in DCM (60 mL), was added PyBOP (5.27 g, 10.1 mmol, 1.0 equiv.) and DiPEA (1.20 mL, 11.1 mmol, 1.1 equiv.). After stirring for 5 min, $Me(MeO)NH_2Cl$ (1.19 g, 12.1 mmol, 1.2 equiv.) and DiPEA (1.31 mL, 12.1 mmol, 1.2 equiv.) were added. After stirring for 16 h, TLC analysis (EtOAc/PE 1:1) showed the reaction had gone to completion. Next the mixture was poured into water and the organic layer separated. After extraction of the aqueous phase with DCM, the organic fractions were combined, washed against sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. Purification of the resdiue by silica gel column chromatography

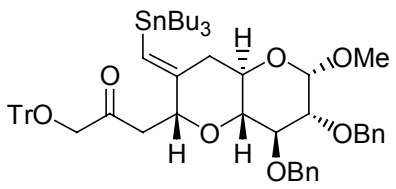
(EtOAc/PE 1:4 to 1:2) afforded Weinreb amide **15** (3.18 g, 8.80 mmol, 87%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.54-7.48 (m, 6H, CH_{arom}), 7.35-7.19 (m, 9H, CH_{arom}), 3.90 (s, 2H, CH_2), 3.43 (s, 3H, CH_3 NMe), 3.12 (s, 3H, CH_3 OMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 169.6 (CO C-1), 143.0 (C_q Tr), 129.5, 128.8, 127.3, 126.6, 125.9, 125.1 (CH_{arom}), 86.6 (C_q OTr), 60.5 (CH_2 C-2), 59.8 (CH_3 OMe), 31.6 (CH_3 NMe). MS (ESI): *m/z* = 384.1 $[M+Na]^+$, 400.1 $[M+K]^+$, 745.4 $[2M+Na]^+$.



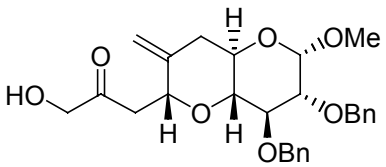
1-Trityloxy-but-3-yn-2-one (16): A solution of amide **15** (3.20 g, 8.86 mmol) in THF (90 mL) was cooled to 0 °C. Ethynyl magnesiumbromide (26.6 mL, 0.5 M solution in THF, 13.3 mmol, 1.5 equiv.) was added and the mixture was allowed to reach rt. After 4 h, TLC analysis (EtOAc/PE 1:1) showed complete conversion of starting material into a higher running spot. The reaction mixture was poured into asat. aq. NH_4Cl solution and extracted with Et_2O. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. After purification of the residue by column chromatography (EtOAc/PE 1:19 to 1:6) ynone **16** (2.29 g, 7.0 mmol, 79%) was obtained as an off white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.50-7.46 (m, 6H, CH_{arom}), 7.35-7.24 (m, 9H, CH_{arom}), 3.90 (s, 2H, H-1), 3.30 (s, 1H, H-4). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 183.6 (C-3), 143.0 (C_q Tr), 98.0 (C_q OTr), 87.5 (C-4), 81.1 (C-2), 70.6 (C-1). MS (ESI): *m/z* = 349.3 $[M+Na]^+$, 675.3 $[2M+Na]^+$.



Methyl 2,3-di-*O*-benzyl-6-deoxy-6-*C*-ethynyl-4-*O*-((*E*)-3-oxo-4-trityloxy-butene)-α-D-glucopyranoside (17): To a solution of alkyne **13** (0.486 g, 1.27 mmol) and ynone **16** (0.622, 1.91 mmol, 1.5 equiv.) in DCM (15 mL) under an argon atmosphere was added NMM (69 µL, 0.64 mmol, 0.5 equiv.). After stirring for 16 h the reaction mixture was concentrated, the residue was purified by column chromatography (EtOAc/toluene 1:39) giving compound **17** (0,562 g, 0.79 mmol, 62%) as light yellow oil together with recovered starting material **13** (0.18g, 0.47 mmol). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.67 (d, 1H $J_{1',2'}$ = 12.4 Hz, H-1'), 7.46-7.18 (m, 25H, CH_{arom}), 6.17 (d, 1H, $J_{2',1'}$ = 12.4 Hz, H-2'), 4.83 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.80 (d, 1H, *J* = 12.4 Hz, CH Bn), 4.65 (d, 1H, *J* = 12.4 Hz, CH Bn), 4.64 (d, 1H, *J* = 10.2 Hz, CH Bn), 4.62 (d, 1H, $J_{1,2}$ = 2.9 Hz, H-1), 3.98-3.84 (m, 3H, H-3, H-4, H-5), 3.71 (s, 2H, CH_2 H-4'), 3.55 (dd, 1H, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 8.9 Hz, H-2), 3.40 (s, 3H, CH_3 OMe), 2.62-2.20 (m, 2H, 2× H-6), 1.98 (t, 1H, $J_{8,6a} = J_{8,6b}$ = 2.6 Hz, H-8). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 196.6 (C-3'), 163.5 (C-1'), 143.0 (C_q Tr), 137.4 (2× C_q Bn), 128.8, 128.6, 128.2, 128.2, 128.1, 128.0, 127.6, 126.9 (CH_{arom}), 103.6 (C-2'), 97.7 (C-1) 87.1 (C_q OTr), 83.8, 79.1, 79.0, 66.3 (C-2, C-3, C-4, C-5), 78.6 (C-7), 75.3, 72.9 (2× CH_2 Bn), 71.0 (C-8), 69.0 (C-4'), 55.0 (CH_3 OMe), 20.8 (C-6). MS (ESI): *m/z* = 731.6 $[M+Na]^+$, 747.2 $[M+K]^+$.

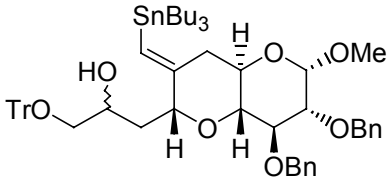


(1*S*, 3*R*, 6*R*, 8*S*, 9*R*, 10*R*)-9,10-Bis-benzyloxy-4-((*E*)-tributylstannanylmethylene)-8-methoxy-3-(2-oxo-3-trityloxy-propyl)-2,7-dioxabicyclo[4.4.0]decane (18): A degassed solution of enyne **17** (0.562 g, 0.79 mmol) in toluene (7.5 mL) was heated to 80 °C. A degassed solution of AIBN (32.6 mg, 0.198 mmol, 0.25 equiv.) and Bu_3SnH (0.426 mL, 1.59 mmol, 2.0 equiv.) in toluene (7.5 mL) was added dropwise over 7.5 h to the former solution. After the addition, heating was maintained for an additional period of 10 h. Evaporation of the volatiles and purification of the residue by column chromatography (EtOAc/PE 1:9) gave bicyclic ether **18** (0.562 g, 0.562 mmol, 71%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41-7.22 (m, 25H, CH_{arom}), 5.61 (s, 1H, CH Sn), 4.82 (d, 1H, J = 12.2 Hz, CH Bn), 4.66 (d, 1H, J = 10.9 Hz, CH Bn), 4.65 (d, 1H, J = 12.2 Hz, CH Bn), 4.56 (d, 1H, J = 10.9 Hz, CH Bn), 4.52 (d, 1H, $J_{8,9}$ = 3.7 Hz, H-8), 4.34 (dd, 1H, $J_{3,1a'}$ = 5.4 Hz, $J_{3,1b'}$ = 7.5 Hz, H-3), 3.84 (d, 1H, $J_{3a',3b'}$ = 16.6 Hz, H-3a'), 3.77 (t, 1H, $J_{10,1}$ = $J_{10,9}$ = 9.2 Hz, H-10), 3.77 (d, 1H, $J_{3b',3a'}$ =16.6 Hz, H-3b'), 3.46 (dd, 1H, $J_{9,8}$ = 3.7 Hz, $J_{9,10}$ = 9.2 Hz, H-9), 3.46 (m, 1H, H-6), 3.36 (s, 3H, CH_3 OMe), 3.22 (t, 1H, $J_{1,6}$ = $J_{1,10}$ = 9.2 Hz, H-1), 2.89 (dd, 1H, $J_{1a',3}$ = 5.2 Hz, $J_{1a',1b'}$ =15.8 Hz, H-1a'), 2.83 (dd, 1H, $J_{1b',3}$ = 7.8 Hz, $J_{1b',1a'}$ = 15.8 Hz, H-1b'), 2.47 (dd, 1H, $J_{5a,6}$ = 4.6 Hz, $J_{5a,5b}$ = 12.4 Hz, H-5a), 2.32 (t, 1H, $J_{5b,5a}$ = 12.4 Hz, H-5b), 1.47 (m, 6H, CH_2Sn), 1.28 (sextet, 6H, J = 7.0 Hz, 3× CH_2 Bu), 0.91 (t, 6H, J = 8.0 Hz, 3× CH_2Sn Bu), 0.87 (t, 9H, J = 7.3 Hz, 3× CH_3 Bu). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 205.9 (CO C-2'), 150.5 (C_q C-4), 143.0 (C_q OTr), 138.7, 138.2 (2× C_q Bn), 128.5, 128.2, 128.0, 127.8, 127.7, 127.2 (CH_{arom}), 123.5 (CHSn), 98.8 (C-8), 87.2 (C_q Tr), 82.8, 79.1, 78.6, 76.5, 67.7 (C-1, C-3, C-6, C-9, C-10), 75.1, 73.7 (2× CH_2 Bn), 70.3 (C-3'), 54.9 (CH_3 OMe), 41.7, 41.2 (C-5, C-1'), 29.0 (CH_2 Bu), 27.1 (CH_2 Bu), 13.5 (CH_3 Bu), 10.2 (CH_2Sn). MS (ESI): *m/z* = 1023.5 $[M+Na]^+$.

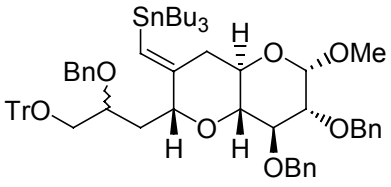


(1*S*, 3*R*, 6*R*, 8*S*, 9*R*, 10*R*)-9,10-Bis-benzyloxy-3-(3-hydroxy-2-oxo-propyl)-8-methoxy-4-methylene-2,7-dioxabicyclo [4.4.0] decane (19): To a solution of compound **18** (1.43 g, 1.43 mmol) in DCM (10 mL) was added *p*-TsOH (0.764 g, 4.02 mmol, 2.8 equiv.). After stirring for 18 h, sat. aq. $NaHCO_3$ was added and the mixture diluted with Et_2O. The organic layer was separated and washed once more with water. The ether layer was dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:2) yielded alkenol **19** (0.480 g, 1.02 mmol, 72%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 10H, CH_{arom}), 4.94 (s, 1H, =C*H*H), 4.82 (d, 1H, J = 12.2 Hz, CH Bn), 4.80 (s, 1H, =CH*H*), 4.71 (s, 2H, CH_2 Bn), 4.65 (d, 1H, J = 12.2 Hz, CH Bn), 4.53 (d, 1H, $J_{8,9}$ = 3.8 Hz, H-8), 4.30 (bs, 3H, H-3, H-3a', H-3b'), 3.81 (t, 1H, $J_{10,1}$ = $J_{10,9}$ = 9.4 Hz, H-10), 3.50 (m, 1H, H-6), 3.49 (dd, 1H, $J_{9,8}$ = 3.7 Hz, $J_{9,10}$ = 9.4 Hz, H-9), 3.37 (s, 3H, CH_3 OMe), 3.25 (t, 1H, $J_{1,6}$ = $J_{1,10}$ = 9.4 Hz, H-1), 3.11 (bs, 1H, OH), 2.81 (dd, 1H, $J_{5a,6}$ = 9.2 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 2.73 (dd, 1H, $J_{5b,6}$ = 4.1 Hz, $J_{5b'5a}$ = 15.0 Hz, H-5b), 2.63 (dd, 1H, $J_{1a',3}$ = 4.8 Hz, $J_{1a',1b'}$ = 12.6 Hz, H-1a'), 2.27 (t, 1H, $J_{1b',1a'}$ = 12.6 Hz, H-1b'). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 207.9 (C-2'), 142.7 (C-4), 138.6, 138.1 (2× C_q Bn), 128.4, 128.3, 128.1, 127.9, 127.8, 127.5 (CH_{arom}), 110.5 (=CH_2), 98.8 (C-

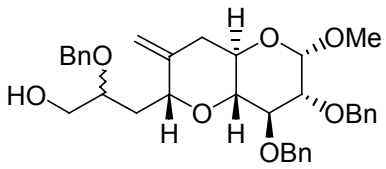
8), 82.4 (C-1), 79.0 (C-10), 79.0 (C-9), 75.3, 73.7 (2× CH_2 Bn), 74.9 (C-3), 69.2 (C-3'), 67.0 (C-6), 55.3 (CH_3 OMe), 40.7 (C-1'), 38.5 (C-5). MS (ESI): *m/z* = 491.3 $[M+Na]^+$, 959.7 $[2M+Na]^+$.



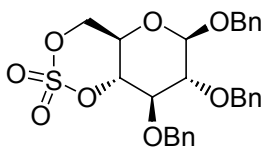
(1*S*, 3*R*, 6*R*, 8*S*, 9*R*, 10*R*)-9,10-Bis-benzyloxy-4-((*E*)-tributylstannanylmethylene)-3-(2-hydroxy-3-trityloxy-propyl)-8-methoxy-2,7-dioxabicyclo[4.4.0]decane (21): To a solution of ketone **18** (0.832 g, 0.832 mmol) in MeOH (20 mL) were added a few drops of DCM. To this solution was added $NaBH_4$ (0.078 g, 2.06 mmol, 2.4 equiv.) and the mixture was stirred for 1.5 h. The reaction was quenched by addition of sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (EtOAc/PE 1:15) yielded two diastereoisomers, **21a** (0.313 g, 0.311 mmol, 37%) and **21b** (0.302 g, 0.301 mmol, 36%). Analytical data of compound **21a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46-7.23 (m, 25H, CH_{arom}), 5.76 (s, 1H, CHSn), 4.81 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.79 (d, 1H, *J* = 10.5 Hz, CH Bn), 4.72 (d, 1H, *J* = 10.5 Hz, CH Bn), 4.66 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.52 (d, 1H, $J_{8,9}$ = 3.6 Hz, H-8), 4.13 (m, 1H, H-2'), 3.84 (t, 1H, $J_{10,1} = J_{10,9}$ = 9.4 Hz, H-10), 3.81 (m, 1H, H-3), 3.50 (dd, 1H, $J_{9,8}$ = 3.6 Hz, $J_{9,10}$ = 9.4 Hz, H-9), 3.47 (m, 1H, H-6), 3.36 (m, 4H, CH_3 OMe, OH), 3.18 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.3 Hz, H-1), 3.16 (m, 2H, H-3a', H-3b'), 2.47 (dd, 1H, $J_{5a,6}$ = 4.8 Hz, $J_{5a,5b}$ = 12.3 Hz, H-5a), 2.26 (t, 1H, $J_{5b,5a}$ = 12.3 Hz), 2.07 (dt, 1H, $J_{1a',3}$ = 3.6 Hz, $J_{1a',1b'}$ = 14.3 Hz, H-1a'), 1.81 (m, 1H, H-1b'), 1.46 (M, 6H, 3× CH_2 Bu), 1.30 (m, 6H, 3× CH_2 Bu), 0.92 (t, 6H, *J* = 7.9 Hz, 3× CH_2Sn Bu), 0.87 (t, 9H, *J* = 7.3 Hz, 3× CH_3 Bu). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 151.4 (C-4), 143.7 (C_q Tr), 138.6, 138.1 (2× C_q Bn), 128.6, 128.3, 128.0, 127.7, 127.5, 126.9 (CH_{arom}), 123.3 (CHSn), 98.7 (C-8), 86.4 (C_q OTr), 82.3, 79.2, 79.1, 76.6, 68.1, 67.5 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.4, 73.6 (2× CH_2 Bn), 67.7 (C-3'), 54.9 (CH_3 OMe), 41.5 (C-5), 34.4 (C-1'), 30.1, 27.1 (2× CH_2 Bu), 13.5 (CH_3 Bu), 10.1 (CH_2Sn Bu). Analytical data of compound **21b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46-7.21 (m, 25H, CH_{arom}), 5.77 (s, 1H, CHSn), 4.82 (d, 1H, *J* = 12.3 Hz, CH Bn), 4.80 (d, 1H, *J* = 10.6 Hz, CH Bn), 4.72 (d, 1H, *J* = 10.6 Hz, CH Bn), 4.66 (d, 1H, *J* = 12.3 Hz, CH Bn), 4.52 (d, 1H, $J_{8,9}$ = 3.6 Hz, H-8), 4.11 (m, 1H, H-2'), 3.81 9t, 1H, $J_{10,1} = J_{10,9}$ = 9.4 Hz, H-10), 3.79 (m, 1H, H-3), 3.50 (dd, 1H, $J_{9,8}$ = 3.6 Hz, $J_{9,10}$ = 9.4 Hz, H-9), 3.47 (m, 1H, H-6), 3.36 (bs, 4H, CH_3 OMe, OH), 3.17 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.4 Hz, H-1), 3.15 (m, 2H, H-3a', H-3b'), 2.46 (dd, 1H, $J_{5a,6}$ = 4.7 Hz, $J_{5a,5b}$ = 12.3 Hz, H-5a), 2.26 (dd, 1H, $J_{5b,6}$ = 5.9 Hz, $J_{5b,5a}$ = 12.3 Hz, H-5b), 2.07 (dt, *J* = 3.6 Hz, $J_{1a',1b'}$ = 14.2 Hz, H-1a'), 1.78 (ddd, 1H, *J* = 8.5 Hz, *J* = 9.7 Hz, $J_{1b',1a'}$ = 14.2 Hz, H-1b'), 1.28 (m, 12H, 6× CH_2 Bu), 0.92 (t, 6H, *J* = 7.9 Hz, 3× CH_2Sn Bu), 0.87 (t, 9H, *J* = 7.2 Hz, 3× CH_3 Bu). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 150.7 (C-4), 143.9 (C_q Tr), 138.2, 138.0 (2× C_q Bn), 128.6, 128.3, 128.2, 128.0, 127.6, 126.8 (CH_{arom}), 124.0 (CHSn), 98.6 (C-8), 86.3 (C_q OTr), 81.7, 80.0, 79.5, 78.8, 70.1, 67.9 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.6, 73.4 (2× CH_2 Bn), 67.0 (C-3'), 54.9 (CH_3 OMe), 41.2 (C-5), 34.9 (C-1'), 29.0, 27.1 (2× CH_2 Bu), 13.5 (CH_3 Bu), 10.1 (CH_2Sn Bu).



(1*S*, 3*R*, 6*R*, 8*S*, 9*R*, 10*R*)-9,10-Bis-benzyloxy-3-(2-benzyloxy-3-trityloxy-propyl)-4-((*E*)-tributylstannan-yl-methylene)-8-methoxy-2,7-dioxabicyclo[4.4.0]decane (22a,b): To a solution of alcohol **21a** (0.313 g, 0.311 mmol) in DMF (2 mL) was added BnBr (48 µL, 0.40 mmol, 1.3 equiv.) and the resulting mixture was cooled to 0 °C. After the addition of NaH (0.017 g 60% dispersion in mineral oil, 0.40 mmol, 1.3 equiv.), the mixture was allowed to reach rt. After stirring for 18 h, TLC analysis (EtOAc/PE 1:6) showed complete conversion of starting material into a higher running spot. MeOH was added slowly to destroy excess NaH followed by addition of water and Et_2O. The organic layer was separated, washed with water, brine and dried ($MgSO_4$). Purification by silica gel column chromatography (EtOAc/PE 1:19) afforded **22a** (0.248 g, 0.227 mmol, 73%) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47-7.21 (m, 30H, CH_{arom}), 5.81 (s, 1H, CHSn), 4.80 (d, 1H, *J* = 12.6 Hz, CH Bn),4.70 (d, 1H, *J* = 11.6 Hz, CH Bn), 4.67 (d, 1H, *J* = 12.6 Hz, CH Bn), 4.65 (d, 1H, *J* = 11.6 Hz, CH Bn), 4.62 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.54 (d, 1H, $J_{8,9}$ = 3.6 Hz, H-8), 4.46 (d, 1H, *J* = 11.9 Hz), 3.83 (m, 1H, H-2'), 3.77 (t, 1H, $J_{10,1} = J_{10,9}$ = 9.2 Hz, H-10), 3.41 (dd, 1H, $J_{9,8}$ = 3.6 Hz, $J_{9,10}$ = 9.2 Hz, H-9), 3.41 (m, 2H, H-3, H-6), 3.35 (s, 3H, CH_3 OMe), 3.32 (dd, 1H, $J_{3a',2'}$ = 2.9 Hz, $J_{3a',3b'}$ = 10.2 Hz, H-3a'), 3.08 (dd, 1H, $J_{3b',2'}$ = 4.3 Hz, $J_{3b',3a}$'= 10.2 Hz, H-3b'), 2.85 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.2 Hz, H-1), 2.40 (dd, 1H, $J_{5a,6}$ = 4.8 Hz, $J_{5a,5b}$ = 12.4 Hz, H-5a), 2.15 (ddd, 1H, *J* = 4.3 Hz, *J* = 9.4 Hz, $J_{1a',1b'}$ = 13.8 Hz, H-1a'), 2.11 (t, 1H, $J_{5b,5a}$ = 12.4 Hz, H-5b), 2.00 (ddd, 1H, *J* = 5.1 Hz, *J* = 9.7 Hz, $J_{1b',1a'}$ = 13.8 Hz, H-1b'), 1.45 (m, 6H, 3× CH_2 Bu), 1.28 (m, 6H, 3× CH_2 Bu), 0.92-0.84 (m, 15H, 3× CH_2 Bu, 3× CH_3 Bu). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 151.2 (C-4), 143.9 (C_q Tr), 138.9, 138.6, 138.2 (3× C_q Bn), 128.7, 128.2, 128.0, 127.7, 127.5, 127.1, 126.8 (CH_{arom}), 123.3 (CHSn), 98.7 (C-4), 86.2 (C_q OTr), 82.6, 79.3, 78.5, 76.9, 75.8, 68.1 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.1, 73.5, 71.9 (3× CH_2 Bn), 63.5 (C-3'), 54.9 (CH_3 OMe), 41.4 (C-5), 33.5 (C-1'), 29.0, 27.2 (2× CH_2 Bu), 13.6 (CH_3 Bu), 10.1 (CH_2Sn Bu). Compound **21b** (0.303 g, 0.302 mmol) was converted into compound **22b** (0.204 g, 0.188 mmol, 0.205 mmol, 68%) as described for the synthesis of **22a**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.23 (m, 30H, CH_{arom}), 5.71 (s, 1H, CHSn), 4.97 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.89 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.84 (d, 1H, *J* = 12.3 Hz, CH Bn), 4.69 (d, 1H, *J* = 12.3), 4.67 (d, 1H *J* = 11.2 Hz, CH Bn), 4.57 (d, 1H, $J_{8,9}$ = 3.8 Hz, H-8), 4.48 (d, 1H, *J* = 11.2 Hz, CH Bn), 4.09 (m, 1H, H-2'), 3.98 (d, 1H, $J_{3,1a'} = J_{3,1b'}$ = 11.8 Hz, H-3), 3.91 (t, 1H, $J_{10,1} = J_{10,9}$ = 9.4 Hz, H-10), 3.54 (dd, 1H, $J_{9,8}$ = 3.8 Hz, $J_{9,10}$ = 9.4 Hz, H-9), 3.50 (m, 1H, H-6), 3.28 (s, 3H, CH_3 OMe), 3.26 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.4 Hz, H-1), 3.24 (m, 1H, H-3a'), 3.17 (dd, 1H, $J_{3b',2}$'= 3.4 Hz, $J_{3b',3a'}$ = 9.5 Hz, H-3b'), 2.48 (dd, 1H, $J_{5a,6}$ = 4.6 Hz, $J_{5a,5b}$ = 12.3 Hz, H-5a), 2.31 (t, 1H, $J_{5b,5a}$ = 12.3 Hz, H-5b), 1.97 (m, 1H, H-1a'), 1.67 (m, 1H, H-1b'), 1.44 (m, 6H, 3× CH_2 Bu), 1.29 (m, 6H, 3× CH_2 Bu), 0.90 (t, 6H, *J* = 8.3 Hz, 3× CH_2Sn Bu), 0.86 (t, 9H, *J* = 7.3 Hz, 3× CH_3 Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.7 (C-4), 144.0 (C_q Tr), 139.0, 138.2, 138.2 (3× C_q Bn), 130.4, 128.7, 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 126.8 (CH_{arom}), 123.1 (CHSn), 98.8 (C-8), 86.5 (C_q OTr), 82.4 (C-1), 79.5 (C-10), 79.3 (C-9), 76.5 (C-3), 75.7 (C-2'), 75.4, 73.6, 73.5 (3× CH_2 Bn), 68.4 (C-6), 67.2 (C-3'), 54.9 (CH_3 OMe), 41.6 (C-5), 34.6 (C-1'), 29.0, 27.2 (2× CH_2 Bu), 13.6 (CH_3 Bu), 10.2 (CH_2Sn Bu).

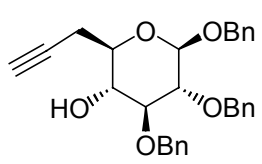


(1*S*, 3*R*, 6*R*, 8*S*, 9*R*, 10*R*)-9,10-Bis-benzyloxy-3-(2-benzyloxy-3-hydroxy-propyl)-8-methoxy-4-methylene-2,7-dioxabicyclo[4.4.0] decane (23): Alcohol **22a** (0.119 g, 0.109 mmol) was dissolved in DCM (2 mL) to which was added *p*-TsOH (0.058 g, 0.31 mmol, 2.8 equiv.). After stirring the mixture for 18 h, TLC analysis (EtOAc/PE 1:3) showed complete consumption of starting material into a lower running spot. After addition of Et_2O, sat. aq. $NaHCO_3$ and water, the organic phase was separated and washed with brine, dried ($MgSO_4$) and concentrated. Column chromatography (EtOAc/PE 1:9 to 1:3) gave alkene **23a** (0.049 g, 0.087 mmol, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.22 (m, 15H, CH_{arom}), 4.90 (bs, 2H, $=CH_2$), 4.77 (d, 1H, J = 12.2 Hz, CH Bn), 4.75 (d, 1H, J = 10.9 Hz, CH Bn), 4.71 (d, 1H, J = 10.9 Hz, CH Bn), 4.61 (d, 1H, J = 12.2 Hz, CH Bn), 4.55 (d, 1H, J = 11.7 Hz, CH Bn), 4.50 (d, 1H, $J_{8,9}$ = 3.7 Hz, H-8), 4.47 (d, 1H, J = 11.7 Hz, CH Bn), 3.80 (t, 1H, $J_{10,1} = J_{10,9}$ = 9.3 Hz, H-10), 3.80 (m, 2H, H-3, H-2'), 3.73 (dd, 1H, $J_{3a',2'}$ = 3.7 Hz, $J_{3a',3b'}$ = 11.7 Hz, H-3a'), 3.57 (dd, 1H, $J_{3b',2'}$ = 4.8 Hz, $J_{3b',3a'}$ = 11.7 Hz, H-3b'), 3.50 (ddd, J = 4.9 Hz, J = 9.6 Hz, J = 11.7 Hz, H-6), 3.46 (dd, 1H, $J_{9,8}$ = 3.7 Hz, $J_{9,10}$ = 9.4 Hz, H-9), 3.35 (s, 3H, CH_3 OMe), 3.17 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.4 Hz, H-1), 2.59 (dd, 1H, $J_{5a,6}$ = 4.8 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 2.19 (t, 1H, $J_{5b,6} = J_{5b,5a}$ = 12.4 Hz, H-5b), 2.08-1.97 (m, 2H, H-1a', H-1b'). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 143.6 (C-4), 138.5, 138.2, 138.1 (3× C_q Bn), 128.4, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 110.4 ($=CH_2$), 98.8 (C-8), 82.3, 79.4, 79.2, 76.6, 74.9, 67.5 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.4, 73.7, 71.2 (3× CH_2 Bn), 63.0 (C-3'), 55.2 (CH_3 OMe), 38.9 (C-5), 31.8 (C-1'). MS (ESI): *m/z* = 561.4 $[M+H]^+$, 583.4 $[M+Na]^+$, 1143.8 $[2M+H]^+$. Alcohol **22b** (0.117 g, 0.107 mmol) was converted into alkene **23b** (0.052 g, 0.093 mmol, 87%) according to the procedure described for the synthesis of **23a**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.23 (m, 15H, CH_{arom}), 4.90 (m, 4H, $=CH_2$, CH_2 Bn), 4.81 (d, 1H, J = 12.1 Hz, CH Bn), 4.67 (d, 1H, J = 12.1 Hz, CH Bn), 4.55 (d, 1H, $J_{8,9}$ = 3.7 Hz, H-8), 4.48 (d, 1H, J = 11.4 Hz, CH Bn), 4.41 (d, 1H, J = 11.4 Hz, CH Bn), 3.92 (d, 1H, $J_{3,1a'} = J_{3,1b'}$ = 10.8 Hz, H-3), 3.88 (t, 1H, $J_{10,1} = J_{10,9}$ = 9.4 Hz, H-10), 3.81 (m, 2H, H-2', H-3a'), 3.54 (m, 2H, H-6, H-3b'), 3.53 (dd, 1H, $J_{9,8}$ = 3.7 Hz, $J_{9,10}$ = 9.4 Hz, H-9), 3.38 (s, 3H, CH_3 OMe), 3.19 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.4 Hz, H-1), 2.62 (dd, 1H, $J_{5a,6}$ = 4.9 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 2.23 (t, 1H, J = 12.2 Hz, H-5b), 2.09 (ddd, 1H, $J_{1a',2'}$ = 2.2 Hz, $J_{1a',3}$ = 9.4 Hz, $J_{1a',1b'}$ = 14.2 Hz, H-1a'), 1.90 (t, 1H, $J_{OH,3a'} = J_{OH,3b'}$ 6.1 Hz, OH), 1.70 (ddd, 1H, $J_{1b',3}$ = 3.2 Hz, $J_{1b',2'}$ = 10.8 Hz, $J_{1b',1a'}$ = 14.2 Hz, H-1b'). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 143.8 (C-4), 139.0, 138.6, 138.2 (3× C_q Bn), 128.8, 128.4, 128.2, 128.1, 127.8, 127.6, 127.5, 127.3 (CH_{arom}), 110.1 ($=CH_2$), 98.7 (C-8), 82.0, 79.6, 79.3, 76.9, 74.9, 67.7 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.3, 73.5, 72.7 (3× CH_2 Bn), 64.7 (C-3'), 55.2 (CH_3 OMe), 39.0 (C-5), 31.8 (C-1'). MS (ESI): *m/z* = 583.4 $[M+Na]^+$, 599.3 $[M+K]^+$.

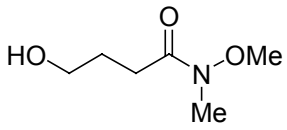


Benzyl 2,3 di-*O*-benzyl-β-D-glucopyranoside 4,6-cyclic sulfate (26): Known tri-O-benzyl glucose **25**[22] (4.12 g, 9.14 mmol) was dissolved in DCM (60 mL) and cooled to 0 °C. To this solution were added NMM (1.51 mL, 13.7 mmol, 1.5 equiv.) and $SOCl_2$ (1.00 mL, 13.7 mmol, 1.5 equiv.). After stirring for 4 h

at 0 °C the mixture was quenched by addition of water and diluted with Et_2O. The aqueous layer was separated and washed with Et_2O. The organic layers were combined, dried ($MgSO_4$) and concentrated. The crude sulfite was dissolved in a mixture of MeCN/DCM/water (3:3:5, 60 mL) followed by the addition of $NaIO_4$ (3.89 g, 18.9 mmol, 2.1 equiv.) and a catalytic amount of $RuCl_3$ (61 mg). After stirring for 1 h the dark mixture was diluted with EtOAc and washed with water. The organic phase was separated, washed against sat. aq. NH_4Cl and brine. The organic layer was dried ($MgSO_4$) and concentrated and the residue was purified by column chromatography (EtOAc/PE 1:4 to 1:3) to yield cyclic sulfate **26** (4.30 g, 8.38 mmol) as a pale white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.44-7.31 (m, 15H, CH_{arom}), 5.05-4.56 (m, 10H, H-1, H-4, 2× H-6, 3× CH_2 Bn), 3.86-3.72 (m, 2H, H-3, H-5), 3.60 (m, 1H, H-2). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.6,137.3,136.4 (3× C_q Bn), 128.5, 128.3, 128.1, 128.0, 127.9 (CH_{arom}), 102.8 (C-1), 84.0, 81.2, 79.2 (C-2, C-3, C-4), 75.3, 75.2, 71.7, 71.7 (3× CH_2 Bn, C-6), 64.0 (C-5). MS (ESI): *m/z* = 535.1 $[M+Na]^+$, 1047.5 $[2M+Na]^+$.

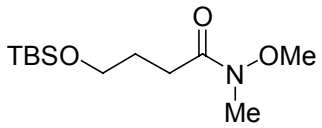


Benzyl 2,3-di-*O*-benzyl-6-deoxy-6-*C*-ethynyl-β-D-glucopyranoside (27): According to the procedure described for the synthesis of **13**, cyclic sulfate **26** (4.30 g, 8.38 mmol) was consumed after stirring for 5 min. After careful acidification and ensuing hydrolysis (15 h) and work up, the residue was purified by silica gel column chromatography (EtOAc/PE 1:3) giving alkyne **27** (6.78 g, 17.7 mmol, 98%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.40-7.32 (m, 15H, CH_{arom}), 4.99 (d, 1H, J = 10.2 Hz, CH Bn), 4.97 (d, 1H, J = 11.7 Hz, CH Bn), 4.72 (d, 1H, J = 10.9 Hz, CH Bn), 4.71 (d, 1H, J = 10.2 Hz, CH Bn), 4.70 (d, 1H, J = 11.7 Hz, CH Bn), 4.68 (d, 1H, J = 10.9 Hz, CH Bn), 4.53 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 3.57-3.31 (m, 4H, H-2, H-3, H-4, H-5), 2.74 (dt, 1H, $J_{6a,5} = J_{6a,8}$ = 2.9 Hz, $J_{6a,6b}$ = 16.8 Hz, H-6a), 2.53 (ddd, 1H, $J_{6b,8}$ = 2.9 Hz, $J_{6b,5}$ = 6.6 Hz, $J_{6b,6a}$ = 16.8 Hz, H-6b), 2.21 (d, 1H, $J_{OH,4}$ = 2.2 Hz, OH), 2.04 (t, 1H, $J_{8,6a} = J_{8,6b}$ = 2.9 Hz, H-8). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.3, 138.0, 136.9 (3× C_q Bn), 128.1, 128.0, 127.9, 127.7, 127.6, 127.4 (CH_{arom}), 101.8 (C-1), 83.9, 81.6, 73.2, 72.4 (C-2, C-3, C-4, C-5), 80.2 (C-7), 75.1, 74.4, 70.7 (3× CH_2 Bn), 69.7 (C-8), 21.4 (C-6). MS (ESI): *m/z* = 481.1 $[M+Na]^+$.

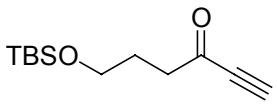


4-Hydroxy-*N*-methoxy-*N*-methyl-butyramide (29): To a solution of $Me(MeO)NH_2Cl$ (3.90 g, 40.0 mmol, 3.0 equiv.) in DCM (25 mL) at –78 °C under an argon atmosphere was added Me_3Al (20 ml, 2.0 M solution in toluene). The mixture was stirred for 30 min at –78 °C after the resulting clear solution was allowed to reach rt overnight. After 18 h, the solution was cooled to 0 °C and γ-butyrolactone (0.96 mL, 13.33 mmol) was added dropwise. The resulting suspension was warmed to rt followed by stirring for 1 h untill all salts were dissolved. After 4.5 h, TLC analysis (EtOAc/PE 1:1) indicated complete conversion of starting material into a lower running spot. The reaction was cooled again to 0 °C and quenched by careful addition of 1N HCl (50 mL). Next the aqueous layer was separated and extracted with DCM (3 times). The combined organic layers were washed against brine, dried ($MgSO_4$) and concentrated to yield amide **29**

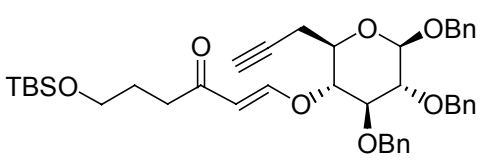
(1.37 g, 9.30 mmol, 70%) as an oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.70 (s, 3H, CH_3 OMe), 3.63 (t, 2H, J = 5.8 Hz, 2× H-4), 3.18 (s, 3H, CH_3 NMe), 2.56 (dd, 2H, J = 6.6 Hz, J = 7.3 Hz, 2× H-2), 1.86 (m, 2H, 2× H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.6 (C-1), 60.7 (C-4), 60.3 (CH_3 OMe), 31.2 (CH_3 NMe), 27.7, 26.6 (C-2, C-3). MS (ESI): *m/z* = 170.1 $[M+Na]^+$.



4-(*tert*-Butyl-dimethyl-silanyloxy)-*N*-methoxy-*N*-methyl-butyramide (30): Amide **29** (1.37 g, 9.30 mmol) was dissolved in pyridine (50 mL) and TBSCl (1.68 g, 11.2 mmol, 1.2 equiv.) was added. After stirring for 15 h, TLC analysis (EtOAc/PE 1:3) revealed complete conversion of starting material into a higher running spot. The reaction was quenched by addition of MeOH and all volatiles were removed under reduced pressure. The residue was dissolved in Et_2O and washed against water, the organic layer separated washed against brine. The organic layer was dried ($MgSO_4$), concentrated followed by purification using silica gel column chromatography (EtOAc/PE 1:4) to obtain silyl ether **30** (2.18 g, 8.33 mmol) in a yield of 90%. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.68 (s, 3H, CH_3 OMe), 3.67 (dd, 2H, J = 5.8 Hz, J = 6.6 Hz, 2× H-4), 3.18 (s, 3H, CH_3 NMe), 2.51 (t, 2H, J = 7.3 Hz, 2× H-2), 1.84 (m, 2H, 2× H-3), 0.89 (S, 9H, 3× CH_3 *t*-Bu), 0.05 (s, 6H, 2× SiMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.5 (C-1), 61.5 (C-4), 60.3 (CH_3 OMe), 31.4 (CH_3 NMe), 27.3, 26.9 (C-2, C-3), 25.2 (CH_3 *t*-Bu), 17.5 (C_q *t*-Bu), -6.1 (CH_3 SiMe).

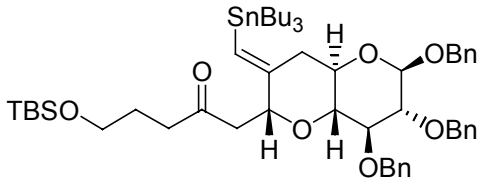


6-(*tert*-Butyl-dimethyl-silanyloxy)-hex-1-yn-3-one (31): According to the procedure described for the synthesis of **16**, amide **30** (0.793 g, 3.03 mmol) was converted (4 h) into ynone **31** (0.615 g, 2.72 mmol) in a yield of 90%. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.56 (t, 2H, J = 5.8 Hz, 2× H-6), 3.23 (s, 1H, H-1), 2.59 (t, 2H, J = 7.3 Hz, 2× H-4), 1.80 (m, 2H, 2× H-5), 0.81 (s, 9H, 3× CH_3 *t*-Bu), -0.03 (s, 6H, 2× CH_3 SiMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 186.6 (C-3), 81.2 (C-1), 78.3 (C-2), 61.4 (C-6), 41.7 (C-4), 26.5 (C-5), 25.6 (CH_3 *t*-Bu), 17.9 (C_q *t*-Bu), -5.7 (CH_3 SiMe).

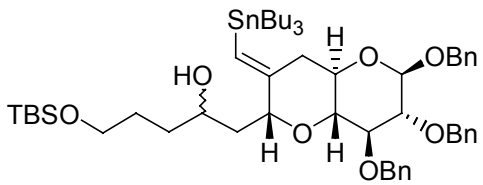


Benzyl 2,3-di-*O*-benzyl-4-*O*-((*E*)-6-(*tert*-butyl-dimethyl-silanyloxy)-3-oxo-hex-1-ene)-6-deoxy-6-*C*-ethynyl-β-D-glucopyranoside (32): To a solution of alkyne **27** (1.60 g, 3.49 mmol) and ynone **31** (1.21 g, 5.35 mmol, 1.5 equiv.) in DCM (30 mL) under an argon atmosphere was added NMM (38.3 µL, 0.349 mmol, 0.1 equiv.). After 24 h the mixture was concentrated and purified by column chromatography (acetone/PE 1:9) to yield enyne **32** (1.41 g, 2.07 mmol, 59%) as a colorless oil and recovered alkyne **27** (0.516 g, 1.13 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 1H, $J_{1',2'}$ = 12.3 Hz, H-1'), 7.39-7.18 (m, 15H, CH_{arom}), 5.70 (d, 1H, $J_{2',1'}$ = 12.3 Hz, H-2'), 4.97 (d, 1H, J = 10.8 Hz, CH Bn), 4.93 (d, 1H, J = 10.5 Hz, CH Bn), 4.79 (d, 1H, J = 10.6 Hz, CH Bn), 4.71 (d, 1H, J = 10.8 Hz, CH Bn), 4.67 (d, 1H, J = 10.5 Hz, CH Bn), 4.56 (d, 1H, J = 10.6 Hz, CH Bn), 4.52 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1), 3.90 (t, 1H, $J_{3,1}$ = $J_{3,2}$ = 9.0 Hz, H-3), 3.60-3.47 (m, 5H, H-2, H-4, H-

5, H-6a', H-6b'), 2.65 (dt, 1H, $J_{6a,8}$ = 2.8 Hz, $J_{6a,6b}$ = 17.1 Hz, H-6a), 2.53 (m, 1H, H-6b), 2.42 (m, 1H, H-4a'), 2.32 (ddd, 1H, J = 6.3 Hz, J = 8.4 Hz, $J_{4b',4a'}$ = 16.2 Hz, H-4b'), 2.08 (t, 1H, $J_{8,6a} = J_{8,6b}$ = 2.6 Hz, H-8), 1.81-1.70 (m, 2H, H-5a', H-5b'), 0.90 (s, 9H, 3× CH_3 *t*-Bu), 0.07 (s, 6H, 2× CH_3 SiMe). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.5 (C-3'), 162.4 (C-1'), 137.9, 137.5, 136.8 (3× C_q Bn), 108.2 (C-2'), 101.9 (C-1), 83.6, 82.1, 81.7 (C-2, C-3, C-4), 78.8 (C-7), 75.5, 74.8, 70.8 (3× CH_2 Bn), 73.0 (C-5), 71.1 (C-8), 62.2 (C-6), 36.8 (C-4'), 27.4 (C-5'), 25.8 (CH_3 *t*-Bu), 21.5 (C-6), 18.2 (C_q *t*-Bu), -5.4 (CH_3 SiMe). MS (ESI): *m/z* = 685.6 $[M+H]^+$, 707.7 $[M+Na]^+$, 723.6 $[M+K]^+$.

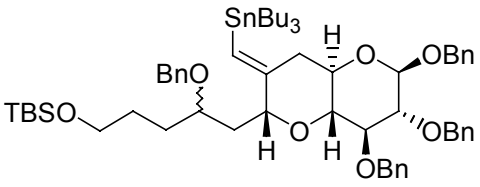


(1*S*, 3*R*, 6*R*, 8*R*, 9*R*, 10*R*)-8,9,10-Tris-benzyloxy-3-(5-*tert*-butyl-dimethyl-silanyloxy-2-oxo-pentyl)-4-((*E*)-tributylstannanylmethy-lene)-2,7-dioxabicyclo [4.4.0] decane (33): Enyne **32** (1.90 g, 2.78 mmol) was dissolved in toluene (25 mL), degassed bubbling through argon for 10 min and heated to 80 °C. A degassed solution of AIBN (114 mg, 0.696 mmol, 0.25 equiv.) and Bu_3SnH (1.49 mL, 5.56 mmol, 2.0 equiv.) in toluene (20 mL) was added dropwise over 5 h to the former solution. After the addition heating, was continued for an additional period of 15 h. Evaporation of the volatiles followed by purification of the residue using silica gel column chromatography (EtOAc/PE 0:1 to 1:9) yielded bicyclic ether **33** (2.23 g, 2.35 mmol, 85%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.27 (m, 15H, CH_{arom}), 5.72 (s, 1H, CHSn), 5.02 (d, 1H, J = 11.9 Hz, CH Bn, 4.93 (d, 1H, J = 10.8 Hz, CH Bn), 4.83 (d, 1H, J = 11.2 Hz, CH Bn), 4.80 (d, 1H, J = 10.8 Hz, CH Bn), 4.73 (d, 1H, J = 11.9 Hz, CH Bn), 4.70 (d, 1H, J = 11.2 Hz, CH Bn), 4.58 (d, 1H, $J_{8,9}$ = 7.4 Hz, H-8), 4.46 (dd, 1H, $J_{3,1a'}$ = 5.9 Hz, $J_{3,1b'}$ = 7.1 Hz, H-3), 3.61-3.50 (m, 4H, H-9, H-10, H-5a', H-5b'), 3.48 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.0 Hz, H-1), 3.16 (ddd, 1H, $J_{6,5a}$ = 4.6 Hz, $J_{6,1}$ = 9.2 Hz, $J_{6,5b}$ = 11.4 Hz, H-6), 2.87 (m, 2H, H-1a', H-1b'), 2.71 (dd, 1H, $J_{5a,6}$ = 4.6 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 2.63 (m, 2H, H-3a', H-3b'), 2.57 (m, 1H, H-5b'), 1.81 (m, 2H, H-4a', H-4b'), 1.68 (m, 6H, 3× CH_2 Bu), 1.41 (m, 6H, 3× CH_2 Bu), 0.94 (m, 24H, 3× CH_3 Bu, 3× CH_3 *t*-Bu, 3× CH_2Sn), 0.06 (s, 6H, 3× CH_3 SiMe). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.3 (C-2'), 150.3 (C-4), 138.6, 138.3, 137.2 (3× C_q Bn), 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3 (CH_{arom}), 123.6 (CHSn), 102.6 (C-8), 82.2, 81.7, 81.6, 76.9, 72.1 (C-1, C-3, C-6, C-9, C-10), 75.2, 74.8, 71.2 (3× CH_2 Bn), 62.0 (C-5'), 45.1, 41.3, 39.8, 26.6 (C-5, C-1', C-3', C-4'), 29.1, 27.2 (2× CH_2 Bu), 25.8 (CH_3 *t*-Bu), 17.4 (C_q *t*-Bu), 13.6 (CH_3 Bu), 10.2 (CH_2Sn), -5.5 (CH_3 SiMe). MS (ESI): *m/z* = 977.4 $[M+H]^+$, 999.4 $[M+Na]^+$.



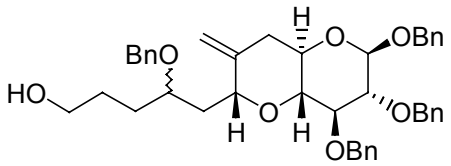
(1*S*, 3*R*, 6*R*, 8*R*, 9*R*, 10*R*)-8,9,10-Tris-benzyloxy-3-(5-*tert*-butyl-dimethyl-silanyloxy-2-hydroxy-pentyl)-4-((*E*)-tributylstannanyl-methylene)-2,7-dioxabicyclo [4.4.0] decane (34): Following the procedure described for the synthesis of **18** into **21a** and **21b**, ketone **33** (0.519, 0.532 mmol) was reduced in 2.5 h. After purification of the residue by silica gel column chromatography

(EtOAc/PE 1:9 to 1:4), two diastereoisomers **34a** (0.280 g, 0.286 mmol, 54%) and **34b** (0.144 g, 0.147 mmol, 28%) were obtained. Analytical data of compound **34a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ (7.37-7.23 (m, 15H, CH_{arom}), 5.81 (s, 1H, CHSn), 4.96 (d, 1H, J = 11.8 Hz, CH Bn), 4.92 (d, 1H, J = 10.8 Hz, CH Bn), 4.79 (d, 1H, J = 10.5 Hz, CH Bn), 4.73 (d, 1H, J = 10.5 Hz, CH Bn), 4.71 (d, 1H, J = 10.8 Hz, CH Bn), 4.67 (d, 1H, J = 11.8 Hz, CH Bn), 4.55 (d, 1H, $J_{8,9}$ = 7.4 Hz, H-8), 4.01 (m, 1H, H-3), 3.93 (m, 1H, H-2'), 3.78 (d, 1H, $J_{OH,2'}$ = 1.4 Hz, OH), 3.65 (m, 2H, H-5a', H-5b'), 3,56 (t, 1H, $J_{10,1} = J_{10,9}$ = 8.8 Hz, H-10), 3.51 (dd, 1H, $J_{9,8}$ = 7.4 Hz, $J_{9,10}$ = 8.8 Hz, H-9), 3.39 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.0 Hz, H-1), 3.13 (ddd, 1H, $J_{6,5a}$ = 4.7 Hz, $J_{6,1}$ = 9.3 Hz, $J_{6,5b}$ = 11.3 Hz, H-6), 2.64 (dd, 1H, $J_{5a,6}$ = 4.7 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 2.45 (t, 1H, $J_{5b,5a} = J_{5b,6}$ = 11.3 Hz, H-5b), 1.96 (m, 1H, H-1a'), 1.85 (1H, H-1b'), 1.74-1.52 (m, 4H, H-3a', H-3b', H-4a', H-4b'), 1.48 (m, 6H, 3× CH_2 Bu), 1.28 (m, 6H, 3× CH_2 Bu), 0.98-0.85 (m, 24H, 3× CH_3 Bu, 3× CH_3 *t*-Bu, 3× CH_2Sn), 0.06 (s, 6H, 2× CH_3 SiMe). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.6 (C-4), 138.2, 138.1, 137.1 (3× C_q Bn), 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 128.0, 127.8, 127.6, 127.4 (CH_{arom}), 124.3 (CHSn), 102.7 (C-8), 82.4, 81.5, 81.1, 80.8, 72.2, 70.6 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.6, 75.1, 71.3 (3× CH_2 Bn), 63.3 (C-5'), 41.5, 38.0, 33.9, 28.9 (C-5, C-1', C-3', C-4'), 29.1, 27.3 (2× CH_2 Bu), 25.9 (CH_3 *t*-Bu), 18.3 (C_q *t*-Bu), 13.7 (CH_3 Bu), 10.2 (CH_2Sn), -5.4 (CH_3 SiMe). MS (ESI): *m/z* = 979.8 $[M+H]^+$, 1001.5 $[M+Na]^+$. Analytical data of compound **34b**: ^{13}C-NMR (50 MHz, $CDCl_3$): δ 151.2 (C-4), 138.5, 138.3, 137.1 (3× C_q Bn), 128.3, 128.2, 128.0, 127.9, 127.5 (CH_{arom}), 123.5 (CHSn), 102.6 (C-8), 82.0, 81.7, 81.6, 77.1, 72.3, 68.1 (C-1, C-3, C-6, C-9, C-10), 75.2, 75.2, 71.2 (3× CH_2 Bn), 63.2 (C-5'), 41.5, 38.2, 34.6, 29.4 (C-5, C-1', C-3', C-4'), 29.1, 27.2 (2× CH_2 Bu), 25.8 (CH_3 *t*-Bu), 18.2 (C_q *t*-Bu), 13.6 (CH_3 Bu), 10.1 (CH_2Sn), -5.5 (CH_3 SiMe).

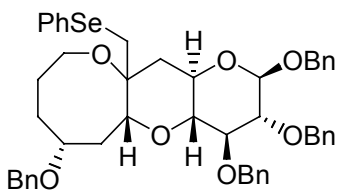


(1*S*, 3*R*, 6*R*, 8*R*, 9*R*, 10*R*)-8,9,10-Tris-benzyloxy-3-(2-benzyloxy-5-*tert*-butyl-dimethyl-silanyloxy-pentyl)-4-((*E*)-tributylstannanylmethylene)-2,7-dioxabicyclo [4.4.0]decane (35): Alcohol **34a** (0.484 g, 0.495 mmol) was dissolved in DMF (5.0 mL) and cooled to 0 °C. BnBr (75 µL, 0.643 mmol, 1.3 equiv.) was added followed NaH (24.8 mg 60%dispersion in mineral oil, 0.619 mmol, 1.25 equiv.). The reaction mixture was allowed to reach rt and after 22 h no starting material was present, as witnessed by TLC analysis (EtOAc/PE 1:9). The reaction mixture was quenched by addition of MeOH and all volatiles were removed by concentration *in vacuo*. The residue was dissolved in Et_2O, washed with water and brine. The organic layer was separated, dried ($MgSO_4$) and concentrated. After purification of the residue by column chromatography (EtOAc/ PE 1:19), fully protected bicyclic ether **35** (0.413 g, 0.387 mmol) was obtained as a colorless oil. ^{13}C-NMR (50 MHz, $CDCl_3$): δ 151.8 (C-4), 139.3, 139.3, 139.0, 137.8 (4× C_q Bn), 128.9, 128.7, 128.5, 128.2, 127.9 (CH_{arom}), 124.2 (CHSn), 103.2 (C-8), 82.9, 82.4, 82.4, 77.7, 76.6, 73.1 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.8, 75.7, 71.8, 71.3 (4× CH_2 Bn), 63.7 (C-5'), 42.3, 36.0, 30.2, 28.4 (C-5, C-1', C-3', C-4'), 29.7, 27.8 (2× CH_2 Bu), 26.5 (CH_3 *t*-Bu), 18.8 (C_q *t*-

Bu), 14.3 (CH_3 Bu), 10.8 (CH_2Sn), -4.7 (CH_3 SiMe). MS (ESI): *m/z* = 979.6 $[M+H]^+$, 999.6 $[M+Na]^+$, 1017.6 $[M+K]^+$.

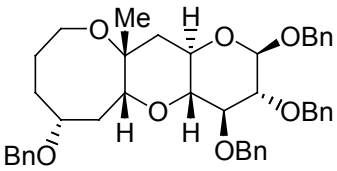


(1*S*, 3*R*, 6*R*, 8*R*, 9*R*, 10*R*)-8,9,10-Tris-benzyloxy-3-(2-benzyloxy-5-hydroxy-pentyl)-4-methylene-2,7-dioxabicyclo [4.4.0]decane (36): To a solution of compound **35** (0.413 g, 0.387 mmol) in DCM (3.0 mL) was added *p*-TsOH (0.169 g, 0.889 mmol, 2.3 equiv). After stirring for 2.5 h, the reaction was complete according to TLC analysis (EtOAc/PE 1:9). After addition of sat. aq. $NaHCO_3$ the mixture was diluted with Et_2O. The organic phase was separated, washed against sat. aq. $NaHCO_3$, water and brine. After drying ($MgSO_4$) and concentration of the organic layer, the resulting residue was purified by silica gel column chromatography (EtOAc/PE 1:9 to 2:3) to yield alkene **36** (0.217 g, 0.326 mmol) in 84%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.24 (m, 20H, CH_{arom}), 4.99 (m, 3H, CH Bn, $=CH_2$), 4.91 (d, 1H, *J* = 10.8 Hz, CH Bn), 4.81 (d, 1H, *J* = 11.2 Hz, CH Bn), 4.76 (d, 1H, *J* = 10.8 Hz, CH Bn), 4.75 (d, 1H, *J* = 11.2 Hz, CH Bn), 4.70 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.61 (d, 1H, *J* = 11.6 Hz, CH Bn), 4.58 (d, 1H, $J_{8,9}$ = 7.6 Hz, H-8), 4.49 (d, 1H, *J* = 11.6 Hz, CH Bn), 3.83 (m, 2H, H-3, H-2'), 3.59 (m, 2H, H-5a', H-5b'), 3.57 (t, 1H, $J_{10,1} = J_{10,9}$ = 9.0 Hz, H-10), 3.50 (dd, 1H, $J_{9,8}$ = 7.6 Hz, $J_{9,10}$ = 9.0 Hz, H-9), 3.34 (t, 1H, $J_{1,6} = J_{1,10}$ = 9.1 Hz, H-1), 3.20 (ddd, 1H, $J_{6,5a}$ = 4.8 Hz, $J_{6,1}$ = 9.4 Hz, $J_{6,5b}$ = 11.4 Hz, H-6), 2.80 (dd, 1H, $J_{5a,6}$ = 4.8 Hz, $J_{5a,5b}$ = 12.8 Hz, H-5b), 2.39 (t, 1H, $J_{5b,5a} = J_{5b,6}$ = 12.0 Hz, H-5b), 2.18 (ddd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, $J_{1a',1b'}$ = 13.7 Hz, H-1a'), 1.94 (ddd, 1H, *J* = 3.6 Hz, *J* = 9.6 Hz, $J_{1b',1a'}$ = 13.7 Hz, H-1b'), 1.82 (m, 1H, H-3a'), 1.76 (m, 1H, H-4a'), 1.69 (m, 2H, H-3b', H-4b'). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 143.4 (C-4), 138.5, 138.3, 137.3 (3× C_q Bn), 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 110.4 ($=CH_2$), 102.7 (C-8), 82.0, 81.9, 81.8, 75.9, 75.1, 71.7 (C-1, C-3, C-6, C-9, C-10, C-2'), 75.3, 75.2, 71.4, 70.9 (4× CH_2 Bn), 62.8 (C-5'), 39.0, 34.8, 29.7, 28.1 (C-5, C-1', C-3', C-4'). MS (ESI): *m/z* = 665.6 $[M+H]^+$, 687.6 $[M+Na]^+$, 703.5 $[M+K]^+$.



(3*R*, 5*R*, 6*R*, 7*R*, 8*S*, 10*R*,)-5,6,7,12-Tetrakis-benzyloxy-1-(phenyl-selenyl-methyl)-4,9,16-trioxatricyclo[8.6.0.0^{3,8}]hexadecane (37): Alkene **36** (0.136 g, 0.205 mmol) was dissolved in DCM (2.0 mL). A catalytic amount of *p*-TsOH was added and the resulting solution was cooled to 0 °C. After the addition of NPSP (77.3 mg, 0.256 mmol, 1.25 equiv.) the cold bath was removed. Although TLC analysis after 24 h still indicated the presense of starting material, the reaction mixture was concentrated and the residue purified by column chromatography to obtain tricyclic ether **37** (78.0 mg, 0.0951 mmol, 47%) and recovered alkene (17 mg, 0.0207 mmol).^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.60-7.51 (m, 4H, CH_{arom}), 7.38-7.23 (m, 21H, CH_{arom}), 4.95 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.91 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.86 (d, 1H, *J* = 10.7 Hz, CH Bn), 4.76 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.73 (d, 1H, *J* = 10.7 Hz, CH Bn), 4.65 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.62 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.58 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.52 (d, 1H, $J_{5,6}$ = 7.8 Hz, H-5), 4.00 (m, 1H, H-12), 3.83 (m, 2H,

H-10, H-15a), 3.66 (m, 1H, H-15b), 3.62 (t, 1H, $J_{7,6} = J_{7,8}$ = 9.0 Hz, H-7), 3.46 (dd, 1H, $J_{6,7}$ = 7.8 Hz, $J_{6,5}$ = 9.0 Hz, H-6), 3.38 (ddd, 1H, $J_{3,2a}$ = 4.3 Hz, $J_{3,8}$ = 9.3 Hz, $J_{3,2b}$ = 11.4 Hz, H-3), 3.29 (t, 1H, $J_{8,3} = J_{8,7}$ = 9.3 Hz, H-8), 3.20 (d, 1H, *J* = 12.4 Hz, CH CH_2Se), 3.10 (d, 1H, *J* = 12.4 Hz, CH CH_2Se), 2.58 (dd, 1H, $J_{2a,3}$ = 4.3 Hz, $J_{2a,2b}$ = 13.6 Hz, H-2a), 2.00 (dd, 1H, $J_{2b,3}$ = 11.4 Hz, $J_{2b,2a}$ = 13.6 Hz, H-2b), 1.94 (m, 2H, H-11a, H-13a), 1.84 (m, 1H, H-14a), 1.79 (m, 1H, H-14b), 1.72 (m, 1H, H-11b), 1.43 (m, 1H, H-13b). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 139.0, 138.9, 138.5, 137.4 (4× C_q Bn), 132.3 (C_q PhSe), 131.5, 129.2, 128.8, 128.4, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.7, 127.2, 127.6, 127.1 (CH_{arom}), 103.0 (C-5), 82.0 (C-6), 81.9 (C-8), 81.8 (C-7), 80.7 (C-10), 77.2 (C-1), 76.1 (C-12), 75.3, 75.0, 71.4, 64.1 (4× CH_2 Bn), 68.0 (C-3), 67.4 (C-15), 34.9 (C-2), 34.6 (C-11), 34.5 (CH_2Se), 31.9 (C-13), 25.7 (C-14). MS (ESI): *m/z* = 843.7 $[M+Na]^+$.



(1*R*, 3*R*, 5*R*, 6*R*, 7*R*, 8*S*, 10*S*, 12*R*)-5,6,7,12-Tetrakis-benzyloxy-1-methyl-4,9,16-trioxatricyclo[8.6.0.0^{3,8}]hexadecane (38): To a solution of compound **37** (61.0 mg, 0.0774 mmol) in toluene (1.0 mL) were added Bu_3SnH (0.100 mL, 0.372 mmol, 5.0 equiv.) and a catalytic amount of AIBN. The reaction mixture was heated for 2.5 h at 90 °C after which TLC analysis (EtOAc/PE 1:3) revealed complete consumption of starting material. Evaporation of the solvent, followed by silica gel column chromatography (EtOAc/PE 1:9 to 1:2) afforded **38** (35.0 mg, 0.0526 mmol, 71 %) as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38-7.24 (m, 20H, CH_{arom}), 4.94 (d, 1H, *J* = 11.3 Hz, CH Bn), 4.92 (d, 1H, *J* = 10.3 Hz, CH Bn), 4.86 (d, 1H, *J* = 10.8 Hz, CH Bn), 4.75 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.73 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.65 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.53 (d, 1H, $J_{5,6}$ = 7.9 Hz, H-5), 4.52 (d, 1H, *J* = 11.2 Hz, CH Bn), 4.50 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.05 (m, 1H, H-12), 3.86 (ddd, 1H, *J* = 6.2 Hz, *J* = 7.9 Hz, $J_{15a,\ 15b}$ = 12.6 Hz, H-15a), 3.66 (ddd, 1H, *J* = 6.2 Hz, *J* = 6.4 Hz, $J_{15b,15a}$ = 12.6 Hz, H-15b), 3.65 (t, 1H, $J_{7,6} = J_{7,8}$ = 9.1 Hz, H-7), 3.52 (dd, 1H, $J_{10,11a}$ = 1.5 Hz, $J_{10,11b}$ = 10.5 Hz, H-10), 3.45 (dd, 1H, $J_{6,5}$ = 7.9 Hz, $J_{6,7}$ = 8.8 Hz, H-6), 3.39 (ddd, 1H, $J_{3,2a}$ = 4.2 Hz, $J_{3,8}$ = 9.5 Hz, $J_{3,2b}$ = 11.4 Hz, H-3), 3.28 (t, 1H, $J_{8,3} = J_{8,7}$ = 9.2 Hz, H-8), 2.52 (dd, 1H, $J_{2a,3}$ = 4.2 Hz, $J_{2a,2b}$ = 13.6 Hz, H-2a), 1.99 (m, 2H, H-11a, H-13a), 1.87 (m, 1H, H-14a), 1.81 (m, 1H, H-14b), 1.71 (ddd, 1H, *J* =1.5 Hz, *J* = 9.5 Hz, $J_{11b,11a}$ = 14.5 Hz, H-11b), 1.49 (dd, 1H, $J_{2b,3}$ = 11.6 Hz, $J_{2b,2a}$ = 13.6 Hz, H-2b), 1.48 (m, 1H, H-13b), 1.22 (s, 3H, CH_3 Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 139.9, 139.0, 138.5, 137.5 (4× C_q Bn), 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 127.0 (CH_{arom}), 102.9 (C-5), 82.3 (C-10), 82.1 (C-8), 82.0 (C-6), 81.8 (C-7), 76.2 (C-12), 75.6 (C-1), 75.3, 75.0, 71.4 (3× CH_2 Bn), 67.8 (C-3), 67.4 (C-15), 63.7 (CH_2 Bn), 37.5 (C-2), 34.5 (C-11), 32.0 (C-13), 25.7 (C-14), 21.9 (CH_3 Me). MS (ESI): *m/z* = 665.5 $[M+H]^+$, 687.5 $[M+Na]^+$.

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Chapter 3

Radical Cyclisation Mediated Synthesis of Conformationally Constrained γ-Sugar Amino Acids

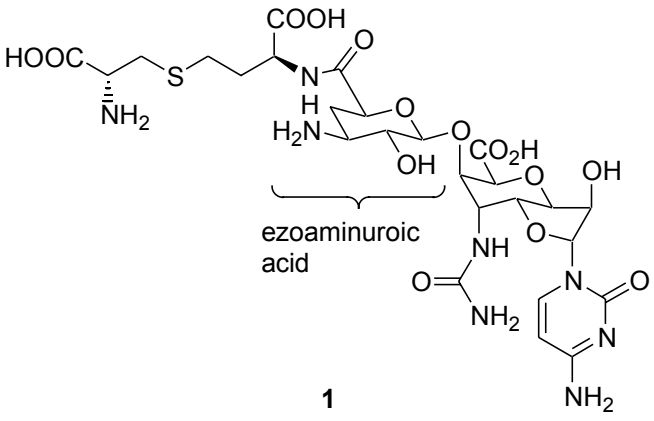
Introduction

Among the naturally occurring amino acids, α-amino acids represent the largest class. The β- and γ-amino acids,[1] the homologues with one or two methylene groups inserted, are less abundant in nature. In contrast to α-amino acids, γ-amino acids are generally not incorporated in oligomeric structures (with poly-γ-glutamic acid as a notable exception),[2] but are found either as monomer or as structural part of more complex molecules. An important structural feature of γ-amino acids is their potential to encompass heterosubstituents at the α-carbon (the carbon atom next to the carbonyl). These substituents are not encountered in α-amino acids and their peptides because such structures would be very labile.[3] As a consequence, γ-amino acids comprised of homologated proteinogenic amino acids are able to carry heteroatoms on the backbone. In 1998, the groups of Seebach[4] and Hanessian[5] have reported the synthesis and secondary structural charcteristics of γ-peptides. They discovered that γ-peptides assembled from as few as four amino acid residues already have the ability to form stable secondary

in solution. Ever since, peptide chains made up of γ-amino acids gained interest due to their capacity to form stable secondary structures such as turn structures,[6] helices,[7] and parallel or pleated sheets.[8] Furthermore, Frackenpohl *et al.*[9] have reported that γ-peptides are to a large extent resistant towards proteolytic degradation, making them interesting as potential lead structures in medicinal chemistry.

Sugar amino acids (SAAs) are carbohydrate-derived structures bearing an amino and a carboxylic acid functionality and are involved in a variety of natural processes. The most prominent example is the class of sialic acids, *N*- and *O*-acyl derivatives of neuraminic acid which are subunits of many oligosaccharides and glycoconjugates.[10] Muramic acid is another glycopeptide which is one of the main constituents of bacterial cell walls.[11] SAAs are also present in glycopeptides[12] and nucleoside antibiotics.[13] Ezoaminuroic acid (Figure 1) is one of the two γ-SAAs present in the antifungal agent ezomycin A_1 (**1**).[14] Because of their hybrid nature, both naturally occurring and synthetic SAAs have found wide application in glyco- and peptidomimetics.[15] The carbohydrate frameworks (furan and pyran rings) provide conformational rigidity with a three-dimensional arrangement of substituents. The hydroxyl functions present on the carbohydrate core can participate inducing specific secondary structures resulting from intramolecular hydrogen bonding.[16] Furthermore, the hydroxyl functions can also be

Figure 1



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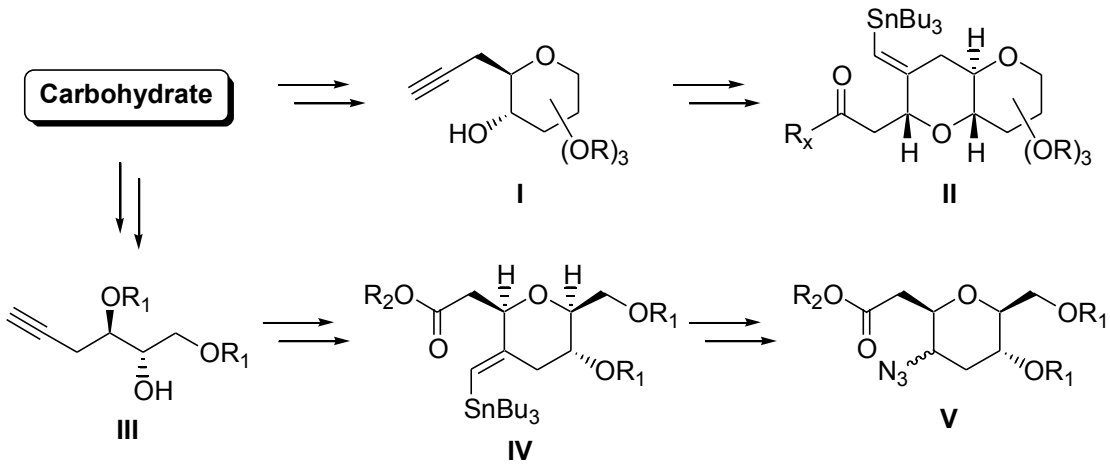
addressed to attach functional groups (e.g. α-amino acid side chains)[17] to construct building blocks for combinatorial synthesis or pharmacophore mapping library studies.[18] The high potential of SAAs as multifunctional designer building blocks, make these compounds valuable structural templates in the development of bioactive molecules.[19]

In Chapter 2, a radical cyclisation approach was described to convert carbohydrate-derived alkynols (**I**) into functionalised *trans*-fused bicyclic ethers possessing a vinylstannane moiety (**II**) (Scheme 1). This entity served as a masked angular methyl group, present at bridgehead positions in several marine toxins. It was reasoned that by making use of the exocyclic vinylstannane appended to a tetrahydropyran system (**IV**), prepared from a carbohydrate-derived alkyne (**III**), an entry into carbohydrate-based γ-amino acids (**V**) could be obtained. Installation of the amine functionality can be achieved through oxidative cleavage of the vinylstannane and ensuing synthetic transformations. Moreover, by employing a propiolate as Michael acceptor, the carboxylate function will be readily integrated. This chapter describes the viability of this approach in the synthesis of new γ-SAAs in which the radical cyclisation of a carbohydrate-derived alkynol is the key step.

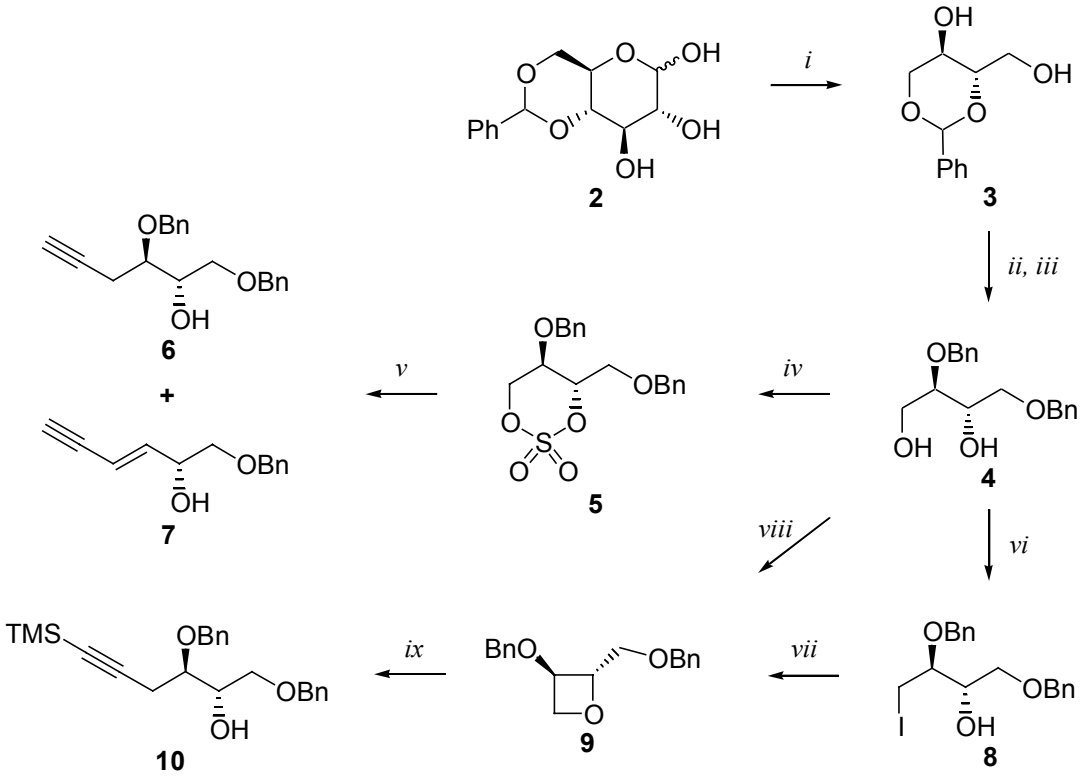
Scheme 1



Results and discussion

The first objective comprised the synthesis of the carbohydrate-derived alkynol amenable to Michael addition with ethyl propiolate. In Chapter 2, it was shown that formation of hydroxyalkynes can be achieved via nucleophilic opening of cyclic sulfates with lithiumacetylide. This approach was explored to synthesise Michael donor **6**, as outlined in Scheme 2. The initial aim was to prepare cyclic sulfate **5** from 4,6-*O*-benzylidene-D-glucose (**2**).[20] Periodate oxidation of **2** followed by reduction of the resulting aldehyde gave 1,3-*O*-benzylidene-L-erythritol (**3**). Benzylation of the hydroxyl groups in **3** followed by removal of the benzylidene acetal gave diol **4**. Treatment of **4** with $SOCl_2$ followed by ruthenium catalysed oxidation of the sulfite smoothly furnished **5** in 85% yield. Opening of the cyclic sulfate with lithium acetylide ethylene diamine complex in DMSO proceeded sluggishly and resulted in an inseparable mixture of alkynol **6** together with elimination product **7** as witnessed by NMR and mass-spectrometry. Clearly the strong acidic conditions required to remove the transiently formed sulfate after alkyne addition promoted β-elimination of the 3-*O*-benzyl ether with formation of enyne derivative **7** as a result. In search of an alternative procedure it was reasoned that installation of the acetylene moiety could be achieved by nucleophilic displacement of a leaving group in a compound derived from diol **4**. Thus, treatment of **4** with triphenylphosphine, iodine and imidazole, following the protocol developed by Garegg,[21] readily afforded primary iodide **8**. Treatment of iodide **8** with lithium acetylide ethylene diamine complex, however, did not result in the formation of **6**. Instead, oxetane **9** was isolated as the sole product in 73%. Recently Trost *et al.*[22] described an elegant method to open oxetanes with lithium trimethylsilyl acetylide under the influence of a Lewis acid. Therefore it was decided to take advantage of the oxetane formation for the construction of the Michael donor (**10**). Optimised reaction conditions for the oxetane formation, using sodium hydride as base, furnished **9** in a yield 66% over two steps starting from diol **4**. Treatment of oxetane **9** with lithium trimethylsilyl acetylide and boron trifluoride etherate resulted in the formation of alkynol **10** in 77% yield.

Scheme 2

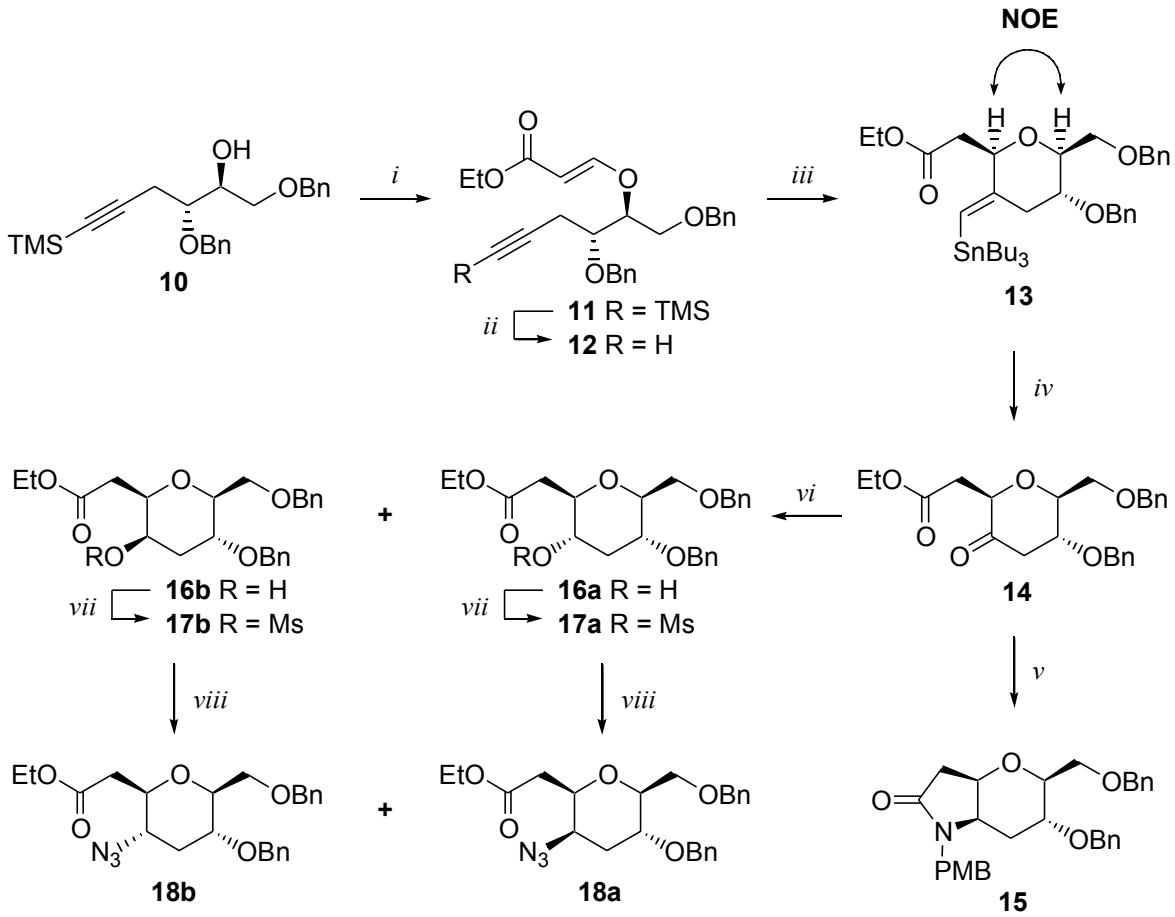


Reagents and conditions: *i*) $NaIO_4$ (3.0 equiv.), $NaHCO_3$ (4.0 equiv.), MeOH, H_2O, rt, 1 h, 88%. *ii*) BnBr (3.0 equiv.), NaH (3.0 equiv.), DMF, 0 °C to rt, 4 h, 85%. *iii*) 60% aq. HOAc, 50 °C, 4 h, 81%. *iv*) a) $SOCl_2$ (1.5 equiv.), NMM (1.5 equiv.), CH_2Cl_2, 0 °C to rt, 2 h. b) $NaIO_4$ (2.0 equiv.), $RuCl_3$ (cat.), $MeCN/CH_2Cl_2/H_2O$ (2:2:3), rt, 1.5 h, 91% (2 steps). *v*) a) LiC≡CH ethylene diamine complex (3.0 equiv.), THF, rt, 1 h. b) H_2SO_4/H_2O (pH 2), 50 °C, 18 h, 75% (2 steps). *vi*) Ph_3P (2.5 equiv.), imidazole (2.5 equiv.), I_2 (2.0 equiv.), toluene, rt, 1 h, (**8**, 42%). *vii*) LiC≡CH ethylene diamine complex (2.0 equiv.), DMSO, rt, 1.5 h, 73%. *viii*) a) see *vi*). b) NaH (1.5 equiv.), THF, 0 °C to rt, 17 h, 66% (2 steps). *ix*) TMSC≡CLi (3.0 equiv.), $BF_3{\cdot}OEt_2$ (3.0 equiv.), THF, -78 °C to rt, 16 h, 77%.

Having alkynol **10** in hand, the stage was set to perform the cyclisation protocol as described in Chapter 2. Michael addition of **10** to ethylpropiolate, using *N*-methylmorpholine (NMM) as base, afforded β-(alkynyloxy)acrylate **11** in 93% (Scheme 3). After fluoride assisted removal of the silyl group (97%), radical cyclisation of the resulting enyne **12** was executed. Submission of **12** to tributyltin hydride and AIBN generated cylic ether **13**, as the single stereoisomer, in a yield of 80%. The 3,7-*cis*-

relationship was established by NOE NMR experiments, which revealed a NOE correlation between the two axial protons. Ketone **14** was obtained in 88% via ruthenium catalysed oxidative cleavage of **13**, with excess sodium periodate as the cooxidant.[23] Conversion of the ketone moiety of **14** into an amine proved to be less

Scheme 3



Reagents and conditions: *i*) NMM (2.0 equiv.), ethyl propiolate (2.0 equiv.) CH_2Cl_2, rt, 17 h, 93%. *ii*) TBAF (2.2 equiv.), THF, rt, 5 min, 97%. *iii*) Bu_3SnH (2.0 equiv.), AIBN (0.25 equiv.), toluene, 80 °C, 5 h, 80%. *iv*) $NaIO_4$ (4.1 equiv.), $RuCl_3$ (cat.), MeCN/CH_2Cl_2/H_2O (2:2:3), rt, 1 h, 97%. *v*) *p*-MeOBnNH$_2$ (2.0 equiv.), $Na(OAc)_3BH$ (1.5 equiv.), HOAc (1.0 equiv.), 1,2-DCE, rt, 17 h, 42%. *vi*) $NaBH_4$ (1.0 equiv.), MeOH, 0 °C, 20 min, 80%. *vii*) MsCl (2.0 equiv.), pyr., CH_2Cl_2, 0 °C to rt, 6 h, 87%. *viii*) NaN_3 (5.0 equiv.), DMF, 65 °C, 24 h, 36%.

straightforward than anticipated. Subjection of **14** to reductive amination conditions (*p*-methoxybenzylamine and sodium triacetoxyboro-hydride) resulted in a complex mixture

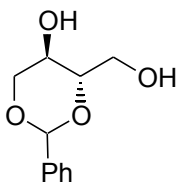
of products from which only the 3,4-*cis*-lactam **15** (41%) could be isolated. It was realised that ketones exhibit the potential to serve as template for the introduction of azides, as follows. Regioselective reduction of **14** with sodium borohydride provided alcohols **16a,b** in 80% as an inseparable mixture of diastereoisomers.[24] Treatment of the mixture of secondary alcohols with methanesulfonyl chloride and pyridine in DCM and ensuing column chromatography allowed isolation of the major diastereoisomer **17a** along with a mixture of **17a** and **17b** in an overall yield of 87%. Nucleophilic substitution of the mesylates in **17a,b** with sodium azide in DMF at elevated temperature furnished γ-SAA precursors **18a,b** in a combined yield of 36%.

Conclusion

The results presented in this chapter show that a suitable carbohydrate-derived alkynol serves as a useful precursor in a radical mediated cyclisation resulting in the formation of a highly functionalised cyclic ether. Synthesis of the requisite alkynol turned out to be the key step in this approach. Opening of the cyclic sulfate with an acetylide proceeded less straightforward than anticipated due to elimination of benzyl alcoholThe use of the 1,4-diol derived oxetane as an intermediate gave better results. Lewis acid mediated opening of this oxetane followed by Michael addition to ethylpropiolate and radical cyclisation afforded a suitably functionalised pyran system, that was further processed to furnish target γ-SAAs precursors **18**.

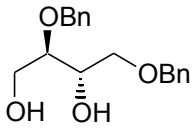
Experimental section

For general methods and materials see Chapter 2.

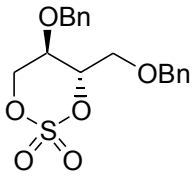


1,3-*O*-Benzylidene-L-erythritol (3): A solution of $NaHCO_3$ (15.0 g, 178.9 mmol, 4.0 equiv.) and $NaIO_4$ (28.7 g, 134.1 mmol, 3.0 equiv.) in water (300 mL) was added to a solution of 4,6-*O*-benzylidene-D-glucose (12.0 g, 44.71 mmol) in MeOH (300 mL). After stirring for 1 h TLC analysis (EtOAc) indicated complete consumption of starting material. The reaction mixture was cooled to 0 ^oC and $NaBH_4$ (6.77 g, 178.9 mmol, 4.0 equiv.) was added in small portions. After stirring for 2 h at room temperature the reaction mixture was filtered over Hyflo and the filtrate was diluted with water and EtOAc. The organic layer was separated and

the aqueous phase was extracted twice with EtOAc. The organic layers were combined, washed with a 1 M aq. Na_2SO_3 solution and brine, dried ($MgSO_4$) and concentrated. Purification of the residue was effected by silica gel chromatography (EtOAc/PE 3:7) to give diol **3** (8.30 g, 41.9 mmol, 88%). ^{1}H-NMR (200 MHz, MeOD): δ 7.48-7.27 (m, 5H, CH_{arom}), 5.45 (s, 1H, CH Ph), 4.14 (dd, 1H, $J_{1a,2}$ = 3.7 Hz, $J_{1a,1b}$ = 9.5 Hz, H-1a), 3.85 (dd, 1H, $J_{4a,3}$ = 1.5 Hz, $J_{4a,4b}$ = 11.7 Hz, H-4a), 3.72-3.50 (m, 4H, H-1b, H-2, H-3, H-4b). ^{13}C-NMR (50 MHz, MeOD): δ 139.4 (C_q Ar), 129.8, 129.0, 127.5 (CH_{arom}), 102.3 (CH Ph), 84.1 (C-3), 72.1 (C-1), 62.7 (C-4), 62.5 (C-2).

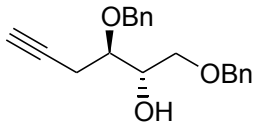


1,3-Di-*O*-benzyl-D-erythritol (4): A solution of diol **3** (9.09 g, 43.2 mmol) and BnBr (15.4 mL, 22.2 g, 130 mmol, 3.0 equiv.) in DMF (200 mL) was cooled (0 °C). NaH (5.2 g 60% dispersion in mineral oil, 130 mmol, 3.0 equiv.) was added in small portions and the mixture was allowed to reach room temperature. After stirring for 4 h TLC analysis (EtOAc/PE 1:3) revealed clean conversion of starting material. The reaction was quenched by careful addition of MeOH and the solvents were evaporated. The crude product was taken up in Et_2O and extracted with water. The organic phase was dried ($MgSO_4$), filtered and concentrated. Column chromatography (EtOAc/PE 1:9) yielded benzylated derivative of **3** (14.1 g, 36.1 mmol, 85%). This compound (1.79 g, 4.57 mmol) was dissolved in 60% aq. HOAc (20 mL) and the resulting solution was stirred for 4 h at 50 °C, concentrated and coevaporated with toluene (3x). The residue was purified by silica gel column chromatography (EtOAc/PE 1:3 to 1:1) to yield **4** (1.11 g, 3.68 mmol, 81%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.40-7.27 (m, 10H, CH_{arom}), 4.66-4.47 (m, 4H, 2× CH_2 Bn), 3.96 (m, 1H, H-2), 3.82 (m, 2H, H-4a, H-4b), 3.69-3.49 (m, 3H, H-1a, H-1b, H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.8, 137.6 (2× C_q Bn), 128.2, 127.7, 17.6 (CH_{arom}), 78.7 (C-3), 73.1, 71.8, 70.9 (C-1, 2× CH_2 Bn), 70.2 (C-2), 60.9 (C-4).

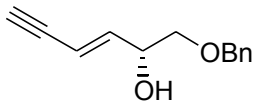


2,4-Di-*O*-benzyl-L-erythritol-1,3-*O*-cyclic sulfate (5): To a solution of diol **4** (1.50 g, 4.96 mmol) in DCM (2.5 mL) was added NMM (0.82 mL, 0.753 g, 7.44 mmol, 1.5 equiv.). After cooling to 0 °C, $SOCl_2$ (0.54 mL, 0.885 g, 7.44 mmol, 1.5 equiv.) was added dropwise. After stirring for 1 h at 0 °C the mixture was allowed to reach room temperature and stirring was continued for 1 h. The reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude sulfite was taken up in a mixture of DCM (10 mL), MeCN (10 mL) and water (15 mL), followed by the addition of $NaIO_4$ (2.12 g, 9.92 mmol, 2.0 equiv.) and a catalytic amount of $RuCl_3$. After stirring was continued for 1.5 h, TLC analysis (EtOAc/PE 1:3) indicated complete conversion of starting material. The reaction mixture was diluted with EtOAc and extracted with water. The organic phase was washed with sat. aq. NH_4Cl, brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE 1:19 to 1:9) to give sulfate **5** (1.64 g, 4.50 mmol, 91%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.38-7.20 (m, 10H, CH_{arom}), 4.76 (ddd, 1H, $J_{3,2}$ = 9.8 Hz, $J_{3,4a}$ = 3.3 Hz, $J_{3,4b}$ = 2.2 Hz, H-3), 4.64 (d, 1H, J = 12.0 Hz, CH Bn), 4.59 (d, 1H, J = 11.5 Hz, CH Bn), 4.52 (d, 1H, J = 12.0

Hz, CH Bn), 4.50 (d, 1H, J = 11.5 Hz, CH Bn), 4.44 (dd, 1H, $J_{1a,1b}$ = 11.0 Hz, $J_{1a,2}$ = 9.8 Hz, H-1a), 4.32 (dd, 1H, $J_{1b,1a}$ = 11.0 Hz, $J_{1b,2}$ = 5.2 Hz, H-1b), 4.17 (ddd, 1H, $J_{2,1a} = J_{2,3}$ = 9.8 Hz, $J_{2,1b}$ = 5.2 Hz, H-2), 3.88 (dd, 1H, $J_{4a,3}$ = 3.3 Hz, $J_{4a,4b}$ = 11.9 Hz, H-4a), 3.76 (dd, 1H, $J_{4b,3}$ = 2.2 Hz, $J_{4b,4a}$ = 11.9 Hz, H-4b). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.0, 136.4 (2× C_q Bn), 128.4, 128.3, 127.9, 127.7, 127.6 (CH_{arom}), 84.9 (C-3), 73.1, 71.5 (C-1, 2× CH_2 Bn), 66.6 (C-4), 66.2 (C-2). MS (ESI): *m/z* = 387.1 $[M+Na]^+$, 751.2 $[2M+Na]^+$.



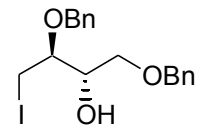
(2*S*, 3*R*)-1,3-Dibenzyloxyhex-5-yne-2-ol (6) and



(*E*)-(2*S*)-1-Benzyloxy-hex-3-en-5-yne-2-ol (7): A solution of compound **5** (0.729 g, 2.00 mmol) in THF (5.0 mL) was added slowly to a suspension of lithium acetylide ethylene diamine complex (0.553 g, 6.00 mmol, 3.0 equiv.) in THF (10 mL), under an argon atmosphere. After stirring at room temperature for 1 h, TLC analysis (EtOAc/PE 1:1) showed complete conversion of starting material into base line material. The mixture was acidified with 80% aq. H_2SO_4 (pH 2) and heated to 50 °C. After stirring for 18 h, the reaction mixture was cooled to room temperature, diluted with water and extracted four times with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated. Column chromatography (EtOAc/PE 1:9) of the residue resulted in the isolation of a mixture of compounds **6** and **7** (0.340 g, 1:3.2) in an overall yield of 75%.

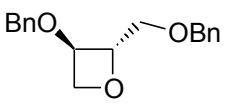
Analytical data of compound **6**: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35-7.22 (m, 10H, CH_{arom}), 4.75 (d, 1H, J = 11.0 Hz, CH Bn), 4.52 (s, 2H, CH_2Bn), 4.51 (d, 1H, J = 11.0 Hz, CH Bn), 3.92 (m, 1H, H-2), 3.71-3.55 (m, 3H, H-1, H-3), 2.61 (dt, 1H, $J_{4,3}$ = 8.0 Hz, $J_{4,6}$ = 2.2 Hz, H-4), 2.20 (t, 1H, $J_{6,4}$ = 2.2 Hz, H-6). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.8, 137.7 (2× C_q Bn), 128.3, 128.2, 127.8, 127.7 (CH_{arom}), 81.0 (C-5), 77.0 (C-3), 73.2, 72.2, 70.6 (C-1, 2× CH_2 Bn), 71.0 (C-2), 70.0 (C-6), 20.3 (C-4). MS (ESI): *m/z* = 333.1 $[M+Na]^+$, 349.0 $[M+K]^+$.

Analytical data of compound **7**: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.37-7.23 (m, 5H, CH_{arom}), 6.16 (dd, 1H, $J_{3,2}$ = 5.1 Hz, $J_{3,4}$ = 16.1 Hz, H-3), 5.78 (dd, 1H, $J_{4,6}$ = 2.2 Hz, $J_{4,3}$ = 16.1 Hz, H-4), 4.50 (s, 2H, CH_2 Bn), 4.32 (m, 1H, H-2), 3.47 (dd, 1H, $J_{1a,2}$ = 3.6 Hz, $J_{1a,1b}$ = 9.5 Hz, H-1a), 3.31 (dd, 1H, $J_{1b,2}$ = 7.3 Hz, $J_{1b,1a}$ = 9.5 Hz, H-1b), 2.88 (d, 1H, $J_{6,4}$ = 2.2 Hz, H-6), 2.81 (bs, 1H, OH). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 142.9 (C-3), 137.4 (C_q Bn), 128.3, 127.7 (CH_{arom}), 110.0 (C-4), 78.3 (C-5), 73.2 (C-1, CH_2 Bn), 70.6 (C-6), 70.3 (C-2). MS (ESI): *m/z* = 225.0 $[M+Na]^+$.



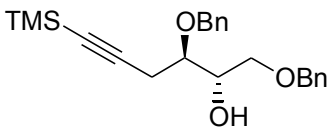
(2*S*, 3*S*)-1,3-Dibenzyloxy-4-iodo-butane-2-ol (8): To a solution of diol **4** (0.302 g, 1.00 mmol) in toluene (12 mL) were added Ph_3P (0.656 g, 2.50 mmol, 2.5 equiv.), imidazole (0.170 g, 2.50 mmol, 2.5 equiv.) and I_2 (0.508 g, 2.00 mmol, 2.0 equiv.). After stirring for 1 h, TLC analysis (EtOAc) indicated complete consumption of starting material. After

addition of a 1 M $Na_2S_2O_3$ solution the mixture was diluted with water and extracted three times with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting white solids were taken up in Et_2O followed by the slow addition of PE to precipitate triphenylphosphine oxide. After filtration of the solids, the filtrate was concentrated and purified by silica gel column chromatography (EtOAc/PE 1:19 to 1:4) affording title compound (0.170 g, 0.416 mmol, 42%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.39-7.19 (m, 10H, CH_{arom}), 4.69 (d, 1H, J = 11.0 Hz, CH Bn), 4.56 (d, 1H, J = 11.7 Hz, CH Bn), 4.49 (d, 1H, J = 11.7 Hz, CH Bn), 4.41 (d, 1H, J = 11.0 Hz, CH Bn), 3.81 (m, 1H, H-2), 3.71-3.46 (m, 4H, H-1, H-4), 3.20 (dt, 1H, $J_{3,2} = J_{3,4a}$ = 7.3 Hz, $J_{3,4b}$ = 3.7 Hz, H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.6, 137.3 (2× C_q Bn), 128.3, 127.9, 127.8 (CH_{arom}), 76.6 (C-3), 73.3, 71.8, 70.3 (C-1, 2× CH_2 Bn), 71.7 (C-2), 8.5 (C-4).



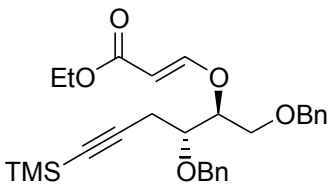
(2*S*, 3*R*)-3-benzyloxy-2-benzyloxymethyl-oxetane (9): Compound **9** prepared from **8**: A solution of iodide **8** (0.050 g, 0.121 mmol) in DMSO (1.0 mL) was added slowly to a suspension of lithium acetylide ethylene diamine complex (0.022 g, 0.243 mmol, 2.0 equiv.) in DMSO (2.0 mL), under an argon atmosphere. After stirring at room temperature for 1.5 h, TLC analysis (EtOAc/PE 1:3) revealed complete disappearance of starting material. The reaction was quenched by careful addition of water and extracted twice with Et_2O. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated to give crude oxetane **9** (0.025 g, 88.0 µmol, 73%).

Compound **9** prepared from **4**: Diol **4** (0.15 g, 0.496 mmol) was converted into iodide **8** according to the procedure described above except purification by column chromatography. The crude iodide was dissolved in THF (4.0 mL) and cooled to 0 °C. After addition of NaH (0.030 g 60% dispersion in mineral oil, 0.018 mmol, 1.5 equiv.), the reaction was allowed to reach room temperature overnight. After TLC analysis (EtOAc/PE 3:7) indicated complete conversion of starting material, the reaction was quenched by addition of sat. aq. NH_4Cl and extracted twice with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$), concentrated and purified by silica gel chromatography (EtOAc/toluene 1:9) to give oxetane **9** (0.093 g, 0.327 mmol, 66% over two steps). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 10H, CH_{arom}), 4.80 (m, 1H, H-2), 4.62 (d, 1H, J = 12.2 Hz, CH Bn), 4.60-4.48 (m, 3H, H-3, H-4), 4.54 (d, 1H, J = 12.2 Hz, CH Bn), 3.56 (dd, 1H, $J_{1a,2}$ = 4.0Hz, $J_{1a,1b}$ = 11.4 Hz, H-1a), 3.49 (dd, 1H, $J_{1b,2}$ = 4.0 Hz, $J_{1b,1a}$ = 11.4 Hz, H-1b). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.0, 137.4 (2× C_q Bn), 128.4, 128.3, 127.9, 127.6 (CH_{arom}), 88.1, 73.3 (C-2, C-3), 75.1, 73.5, 71.4, 70.5 (C-1, C-4, 2× CH_2 Bn). IR (thin film): 3031, 2871, 1496, 1454, 1363, 1207, 1123, 1028, 961, 856, 734, 696 cm^{-1}. MS (ESI): *m/z* = 307.1 $[M+Na]^+$, 569.3 $[2M+H]^+$, 591.2 $[2M+Na]^+$.

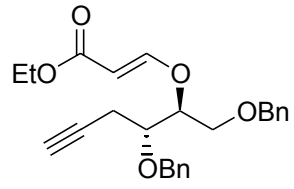


(2*S*, 3*R*)-1,3-Dibenzyloxy-6-trimethylsilanylhex-5-yne-2-ol (10): To a solution of trimethylsilylacetylene (2.0 mL, 1.38 g, 14.1 mmol, 3.0 equiv.) in THF (30 mL) at –78 °C was added *n*-butyllithium (8.80 mL 1.6

M in hexanes, 14.1 mmol, 3.0 equiv.). The reaction was stirred at –78 °C for 30 min and then warmed to 0 °C and stirred for 45 min. The mixture was cooled again to – 78 °C and boron trifluoride etherate (1.78 mL, 1.99 g, 14.1 mmol, 3.0 equiv.) was added. After stirring for 10 min a solution of compound **9** (1.33 g, 4.68 mmol) in THF (1.5 mL) was added dropwise. Stirring was continued for 4 h at –78 °C followed by stirring for another 12 h at room temperature. The reaction was quenched by addition of sat. aq. NH_4Cl and extracted three times with EtOAc. The combined organic extracts were washed with water, brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/toluene 1:99 to 1:19) afforded title compound (1.38 g, 3.61 mmol, 77%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.32-7.19 (m, 10H, CH_{arom}), 4.78 (d, 1H, J = 11.0 Hz, CH Bn), 4.54 (d, 1H, J = 11.0 Hz, CH Bn), 4.54 (s, 2H, CH_2 Bn), 3.89 (m, 1H, H-2), 3.71-3.55 (m, 3H, H-1, H-3), 2.70 (dd, 1H, $J_{4a,3}$ = 4.8 Hz, $J_{4a,4b}$ = 17.2 Hz, H-4a), 2.56 (dd, 1H, $J_{4b,3}$ = 6.2 Hz, $J_{4b,4a}$ = 17.2 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.0, 137.7 (2× C_q Bn), 128.3, 128.2, 127.8, 127.7 (CH_{arom}), 104.0 (C-5), 86.3 (C-6), 77.7 (C-3), 73.3, 72.5, 70.6 (C-1, 2× CH_2 Bn), 71.5 (C-2), 22.0 (C-4), -0.1 (CH_3 TMS). MS (ESI): *m/z* = 382.2 $[M+H]^+$, 405.2 $[M+Na]^+$.

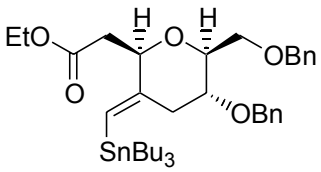


(2*S*, 3*R*)-1,3-Dibenzyloxy-2-[(*E*)-2-Ethoxycarbonyl-vinyloxy]-6-trimethylsilanylhex-5-yne (11): Alcohol **10** (1.61 g, 4.21 mmol) was dissolved in DCM (17 mL). NMM (0.93 mL, 0.85 g, 8.42 mmol, 2.0 equiv.) and ethyl propiolate (0.85 mL, 0.83 g, 8.42 mmol, 2.0 equiv.) were added. After stirring at room temperature for 17 h the mixture was concentrated and the residue purified by column chromatography (EtOAc/toluene 1:99) to give enyne **11** (1.88 g, 3.91 mmol, 93%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.55 (d, 1H, J = 12.4 Hz, C*H*=CHCO$_2$Et), 7.40-7.27 (m, 10H, CH_{arom}), 5.35 (d, 1H, J = 12.4 Hz, CH=C*H*CO$_2$Et), 4.70 (d, 1H, J = 11.3 Hz, CH Bn), 4.54 (d, 1H, J = 11.3 Hz, CH Bn), 4.53 (s, 2H, CH_2 Bn), 4.28 (dt, 1H, J = 2.9 Hz, $J_{2,1a}$ = $J_{2,1b}$ = 5.8 Hz, H-2), 4.16 (q, 2H, J = 7.3 Hz, CH_2 Et), 3.83 (dd, 1H, $J_{1a,2}$ = 5.8 Hz, $J_{1a,1b}$ = 10.9 Hz, H-1a), 3.75 (m, 1H, H-3), 3.68 (dd, 1H, $J_{1b,2}$ = 5.8 Hz, $J_{1b,1a}$ = 10.9 Hz, H-1b), 2.61 (dd, 1H, $J_{4a,3}$ = 5.8 Hz, $J_{4a,4b}$ = 16.8 Hz, H-4a), 2.51 (dd, 1H, $J_{4b,3}$ = 5.8 Hz, $J_{4b,4a}$ = 16.8 Hz, H-4b), 1.26 (t, 3H, J = 7.3 Hz, CH_3 Et), 0.16 (s, 9H, 3× CH_3 TMS). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 167.7 (C=O), 162.3 (*C*H=CHCO$_2$Et), 137.7 (C_q Bn), 128.3, 127.8, 127.7, 127.6 (CH_{arom}), 102.4 (C-6), 98.2 (CH=*C*HCO$_2$Et), 87.4 (C-5), 83.1, 75.8 (C-2, C-3), 73.4, 72.5, 68.5 (C-1, 2× CH_2 Bn), 59.7 (CH_2 Et), 22.1 (c-4), 14.3 (CH_3 Et), -0.1 (CH_3 TMS). MS (ESI): *m/z* = 481.3 $[M+H]^+$, 503.3 $[M+Na]^+$, 983.4 $[2M+Na]^+$.

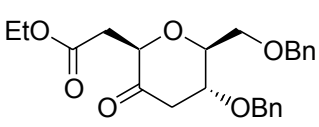


(2*S*, 3*R*)-1,3-Dibenzyloxy-2-[(*E*)-2-Ethoxycarbonyl-vinyloxy]-hex-5-yne (12): Compound **11** (0.670 g, 1.39 mmol) was dissolved in THF (8.0 mL) and TBAF (3.04 mL 1.0 M solution in THF, 2.2 equiv.) was added. After 5 min TLC analysis (1:6 EtOAc/PE) showed complete conversion of starting material into a lower running spot. Sat. aq. $NaHCO_3$ was added and the mixture was extracted twice with Et_2O. The combined organic layers were washed with brine, dried

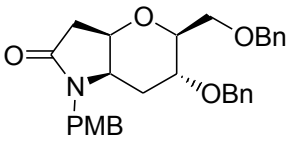
($MgSO_4$) and purified by column chromatography (1:9 EtOAc/PE) to give acetylene **12** (0.550 g, 1.35 mmol, 97%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.56 (d, 1H, J = 12.4 Hz, C*H*=CHCO$_2$Et), 7.39-7.25 (m, 10H, CH_{arom}), 5.34 (d, 1H, J = 12.4 Hz, CH=C*H*CO$_2$Et), 4.69 (d, 1H, J = 11.0 Hz, CH Bn), 4.53 (d, 1H, J = 11.0 Hz, CH Bn), 4.52 (s, 2H, CH_2 Bn), 4.27 (dt, 1H, $J_{2,3}$ = 2.9 Hz, $J_{2,1a}$ = $J_{2,1b}$ = 5.8 Hz, H-2), 4.16 (q, 2H, J = 7.3 Hz, CH_2 Et), 3.82 (dd, 1H, $J_{1a,2}$ = 5.8 Hz, $J_{1a,1b}$ = 11.0 Hz, H-1a), 3.77 (m, 1H, H-3), 3.67 (dd, 1H, $J_{1b,2}$ = 5.8 Hz, $J_{1b,1a}$ = 11.0 Hz, H-1b), 2.53 (m, 2H, H-4), 2.04 (t, 1H, $J_{6,4}$ = 2.6 Hz, H-6), 1.26 (t, 3H, J = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 167.2 (C=O), 162.0 (*C*H=CHCO$_2$Et), 137.4, 137.2 (2× C_q Bn), 128.0, 127.5, 127.3, 127.2 (CH_{arom}), 97.9 (CH=*C*HCO$_2$Et), 82.6, 75.0 (C-2, C-3), 79.5 (C-5), 73.1, 72.0, 68.2 (C-1, 2× CH_2 Bn), 70.8 (C-6), 59.3 (CH_2 Et), 20.1 (C-4), 14.0 (CH_3 Et). IR (thin film): 3294, 3031, 2870, 1702, 1640, 1624, 1497, 1454, 1368, 1324, 1286, 1199, 1130, 1071, 1028, 952, 833, 735, 696 cm^{-1}. MS (ESI): *m/z* = 431.1 [M+Na]$^+$.



(2*R*, 5*R*, 6*S*)-5-Benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-3-[(*E*)-(tributylstannanyl)-methylene]-tetrahydropyran (13): A solution of compound **12** (0.409 g, 1.00 mmol) in toluene (10 .0 mL) was degassed by bubbling through argon for 10 min and heated to 80 °C under an argon atmosphere. To this solution was added dropwise, over a period of 5 h, a degassed solution of tributyltin hydride (0.53 mL, 0.58 g, 2.00 mmol, 2.0 equiv.) and AIBN (41 mg, 0.25 mmol, 0.25 equiv.) in toluene (10 mL). After 5 h TLC analysis (EtOAc/toluene 1:9) revealed complete conversion of starting material into a higher running spot. Solvents were removed and the residue was purified by column chromatography (EtOAc/toluene 1:19) to afford title compound (0.561 g, 0.801 mmol, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 10H, CH_{arom}), 5.61 (t, 1H, J = 1.4 Hz, CHSn), 4.60 (d, 1H, J = 12.3 Hz, CH Bn), 4.57 (d, 1H, J = 11.5 Hz, CH Bn), 4.53 (d, 1H, J = 12.3 Hz, CH Bn), 4.42 (d, 1H, J = 11.5 Hz, CH Bn), 4.32 (ddd, 1H, J = 1.4 Hz, J = 5.6 Hz, J = 7.9 Hz, H-2), 4.16 (q, 2H, J = 7.2 Hz, CH_2 Et), 3.74 (dd, 1H, J = 1.7 Hz, J = 10.6 Hz, C*H*HCOBn), 3.65 (dd, 1H, J = 4.8 Hz, J = 10.6 Hz, CH*H*COBn), 3.61 (ddd, 1H, J = 1.7 Hz, J = 4.8 Hz, $J_{6,5}$ = 10.0 Hz, H-6), 3.49 (ddd, 1H, $J_{5,4a}$ = 5.2 Hz, $J_{5,4b}$ = $J_{5,6}$ = 10.0 Hz, H-5), 2.78 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, C*H*HCO$_2$Et), 2.77 (dd, 1H, $J_{4a,5}$ = 5.2 Hz, $J_{4a,4b}$ = 13.2 Hz, H-4a), 2.68 (dd, 1H, J = 8.0 Hz, J = 15.2 Hz, CH*H*CO$_2$Et), 2.34 (ddd, 1H, J = 1.4 Hz, $J_{4b,5}$ = 10.0 Hz, $J_{4b,4a}$ = 13.2 Hz, H-4b), 1.48 (m, 6H, 3× CH_2 Bu), 1.31 (m, 6H, 3× CH_2 Bu), 1.23 (t, 3H, J = 7.2 Hz, CH_3 Et), 0.90 (m, 15H, 3× CH_2Sn Bu, 3× CH_3 Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4 (C=O), 151.0 (C-3138.5, 138.2 (2× C_q Bn), 128.3, 128.2, 127.7, 127.6, 127.5, 127.4 (CH_{arom}), 121.8 (CH Cn), 80.8, 77.0, 75.3 (C-2, C-5, C-6), 73.3, 71.2, 69.5 (2× CH_2 Bn, CH_2OBn), 60.5 (CH_2 Et), 41.2, 38.0 (C-4, *C*H$_2$CO$_2$Et), 29.1, 27.2 (2× CH_2 Bu), 14.2 (CH_3 Et), 13.6 (CH_3 Bu), 10.3 (CH_2Sn Bu). IR (thin film): 3031, 2956, 2925, 2853, 1736, 1611, 1497, 1454, 1376, 1307, 1173, 1097, 1073, 1028, 733, 696 cm^{-1}. MS (ESI): *m/z* = 699.6 [M+H]$^+$, 723.4 [M+Na]$^+$, 1421.9 [2M+Na]$^+$.

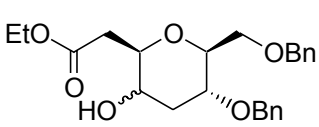


(2*R*, 5*R*, 6*S*)-5-Benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-3-oxo-tetrahydropyran (14): Sodium periodate (0.125 g, 0.586 mmol, 4.1 equiv.) was added to a solution of stannane **13** (0.100 g, 0.143 mmol) dissolved in DCM (3.0 mL), MeCN (3.0 mL) and water (4.5 mL). To this mixture was added a catalytic amount of $RuCl_3$. After stirring for 1 h, water was added and the mixture extracted with Et_2O (three times). The combined organic layers were washed against water, brine, dried ($MgSO_4$) and concentrated. Column chromatography purification (EtOAc/PE 1:9) of the residue gave ketone **14** (57 mg, 0.138 mmol, 97%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 10H, CH_{arom}), 4.61-4.53 (m, 3H, 3× CH Bn), 4.44 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.27 (dd, 1H, *J* = 4.6 Hz, *J* = 6.3 Hz, H-2), 4.14 (q, 2H, *J* = 7.1 Hz, CH_2 Et), 4.05 (ddd, 1H, $J_{5,4a} = J_{5,6} = 4.5$ Hz, $J_{5,4b} = 5.6$ Hz, H-5), 3.95 (ddd, *J* = 4.5 Hz, H-6), 3.66 (2× dd, 2H, *J* = 4.5 Hz, *J* 10.5 Hz, C*H*$_2$OBn), 2.99 (dd, 1H, $J_{4a,5} = 4.5$ Hz, $J_{4a,4b} = 15.5$ Hz, H-4a), 2.87 (dd, 1H, *J* = 4.6 Hz, *J* =16.7 Hz, C*H*HCO$_2$Et), 2.75 (dd, 1H, *J* = 6.3 Hz, *J* = 16.7 Hz, CH*H*CO$_2$Et), 2.65 (dd, 1H, $J_{4b,5} = 5.6$ Hz, $J_{4b,4a} = 15.5$ Hz, H-4b), 1.24 (t, 3H, *J* = 7.1 Hz, CH_3 Et). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 207.8 (C=O, C-3), 170.4 (C=O CO_2Et), 137.9, 137.5 (2× C_q Bn), 128.4, 128.4, 127.8, 127.7 (CH_{arom}), 79.4, 77.9, 74.0 (C-2, C-5, C-6), 73.5, 70.7, 69.9 (*C*H$_2$OBn, 2× CH_2 Bn), 60.7 (CH_2 Et), 41.5 (C-4), 35.7 (*C*H$_2$CO$_2$Et), 14.1 (CH_3 Et). IR (thin film): 2870, 1734, 1497, 1454, 1374, 1273, 1186, 1094, 1028, 735, 697 cm^{-1}. MS (ESI): *m/z* = 435.1 $[M+Na]^+$, 847.5 $[2M+Na]^+$.

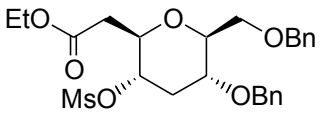


(2*S*, 3*R*, 4a*R*, 7a*R*)-3-Benzyloxy-2-benzyloxymethyl-5-(4-methoxybenzyl)-hexahydropyrano-[3,2-*b*]-pyrrol-6-one (15): To a solution of compound **14** (41.2 mg, 0.100 mmol) in 1,2-DCE (2.0 mL) were added $Na(OAc)_3BH$ (33.5 mg, 0.15 mmol, 1.5 equiv.), *p*-MeOBnNH$_2$ (26.1 µL, 27.4 mg, 0.200 mmol, 2.0 equiv.) and HOAc (5.7 µL, 1.0 equiv.). After stirring overnight at room temperature TLC analysis (EtOAc/PE 1:1) revealed complete consumption of starting material and formation of several products. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and the mixture was extracted twice with DCM. The combined organic extracts were washed with brine, dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/PE 1:3 to 1:1). From the complex mixture, title compound (20 mg, 41.1 µmol) was isolated in a yield of 41% as a white solid. ^{1}H-NMR (300 MHz, MeOD): δ 7.29-7.12 (m, 12H, CH_{arom} Bn, 2× CH_{arom} PMB), 6.81 (m, 2H, 2× CH_{arom} PMB), 4.54 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.46 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.42 (d, 1H, *J* = 15.1 Hz, CH PMB), 4.27 (d, 1H, *J* = 15.1 Hz, CH PMB), 4.18 (d, 1H, *J* = 11.7 Hz, CH Bn), 4.17 (m, 1H, H-7a), 4.05 (d, 1H, *J* = 11.7 Hz, CH Bn), 3.74 (m, 1H, H-4a), 3.70 (s, 3H, CH_3 PMB), 3.58 (m, 2H, C*H*$_2$OBn), 3.40 (ddd, 1H, *J* = 3.2 Hz, *J* = 4.4 Hz, $J_{2,3} = 7.9$ Hz, H-2), 3.21 (ddd, 1H, $J_{3,2} = 7.9$ Hz, $J_{3,4'} = 3.9$ Hz, $J_{3,4''} = 9.7$ Hz, H-3), 2.68 (dd, 1H, $J_{7',7a} = 5.3$ Hz, $J_{7',7''} = 17.1$ Hz, H-7'), 2.38 (d, 1H, $J_{7'',7'} = 17.1$ Hz, H-7''), 2.23 (ddd, 1H, $J_{4',3} = 3.9$ Hz, $J_{4',4a} = 3.9$ Hz, $J_{4',4''} = 14.3$ Hz, H-4'), 1.70 (ddd, 1H, $J_{4'',3} = 9.7$ Hz, $J_{4'',4a} = 4.9$ Hz, $J_{4'',4'} = 14.3$ Hz, H-4''). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.7 (C=O C-6), 159.0 (C_q OMe PMB), 138.2, 138.0 (2× C_q Bn), 138.2, 138.0, 129.2 (CH_{arom} PMB), 128.4, 128.3, 127.8, 127.7, 127.6 (CH_{arom} Bn), 128.8 (C_q PMB), 114.0 (CH_{arom} PMB), 79.0, 71.1, 70.5 (C-2, C-3,

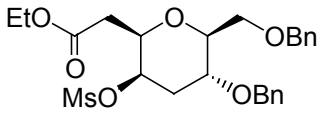
C-7a), 73.5, 71.3, 69.9 (2× CH_2 Bn, *C*H_2OBn), 56.4 (C-4a), 55.2 (CH_3 OMe), 43.5 (CH_2 PMB), 39.0 (C-7), 28.7 (C-4). MS (ESI): *m/z* = 488.4 $[M+H]^+$, 510.5 $[M+Na]^+$, 526.5 $[M+K]^+$.



(2*R*, 3*R/S*, 5*R*, 6*S*)-5-Benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-tetrahydropyran-3-ol (16a,b): A solution of compound **14** (0.230 g, 0.558 mmol) in MeOH (10 mL) was cooled to 0 °C and sodium borohydride (21 mg, 0.558 mmol, 1.0 equiv.) was added. After stirring for 20 min Et_2O was added and the mixture was washed with sat. aq. NH_4Cl, water and brine. The organic phase was collected, dried ($MgSO_4$) and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/PE 1:4 to 1:3) afforded an inseparable mixture of alcohols **16a** and **16b** (0.185 g, 0.447 mmol) in an overall yield of 80%. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.1 (C=O), 138.3, 138.0 (C_q Bn), 128.4, 128.3, 127.7, 127.6, 127.5 (CH_{arom}), 81.3, 80.4, 78.4, 76.3, 72.1, 69.6, 69.1, 67.8 (C-2, C-3, C-5, C-6), 73.4, 73.4, 71.2, 71.1, 69.4, 69.0 (CH_2 Bn, *C*H_2OBn), 60.8, 60.7 (CH_2 Et), 38.8, 38.4, 36.8, 36.4 (C-4, *C*H_2CO_2Et), 14.1 (CH_3 Et). MS (ESI): *m/z* = 415.2 $[M+H]^+$, 436.7 $[M+Na]^+$, 851.3 $[2M+Na]^+$.



(2*R*, 3*S*, 5*R*, 6*S*)-5-Benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-3-methanesulfonyloxy-tetrahydropyran (17a):

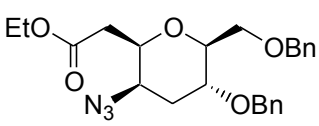


(2*R*, 3*R*, 5*R*, 6*S*)-5-Benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-3-methanesulfonyloxy-tetrahydropyran (17b): To a chilled (0 °C) solution of **16a,b** (0.185 g, 0.447 mmol) in DCM (4.5 mL) and pyridine (0.5 mL) was added dropwise mesylchloride (70 µL, 0.90 mmol, 2.0 equiv.). After stirring for 2 h at 0 °C, the reaction mixture was allowed to reach room temperature. After stirring for an additional period of 4 h, the reaction was quenched by addition of water and extracted with EtOAc. The combined organic fractions were washed with water, brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:19 to 1:9) afforded compound **17a** (0.110 g, 0.223 mmol) and a mixture of fractions **17a** and **17b** (0.082 g, 0.167 mmol) in an overall yield of 87%.

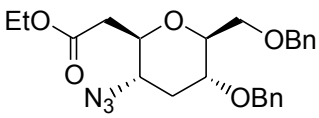
Analytical data of compound **17a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.21 (m, 10H, CH_{arom}), 4.58 (m, 2H, 2× CH Bn), 4.51 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.48 (ddd, 1H, $J_{3,2}$ = 9.5 Hz, $J_{3,4a}$ = 4.8 Hz, $J_{3,4b}$ = 11.4 Hz, H-3), 4.41 (d, 1H, *J* 11.3 Hz, CH Bn), 4.15 (q, 2H, *J* = 7.2 Hz, CH_2 Et), 3.83 (ddd, 1H, *J* = 3.0 Hz, *J* = 8.0 Hz, $J_{3,2}$ = 9.5 Hz, H-2), 3.72 (dd, 1H, *J* = 2.0 Hz, *J* = 11.0 Hz, C*H*HOBn), 3.66 (dd, 1H, *J* = 4.3 Hz, *J* = 11.0 Hz, CH*H*OBn), 3.62 (ddd, 1H, $J_{5,4a}$ = 4.7 Hz, $J_{5,4b}$ = 11.0 Hz, $J_{5,6}$ = 9.5 Hz, H-5), 3.45 (ddd, 1H, *J* = 2.0 Hz, *J* = 4.3 Hz, $J_{6,5}$ = 9.5 Hz, H-6), 3.04 (s, 3H, CH_3 Ms), 2.84 (ddd, 1H, $J_{4a,3}$ = 4.8 Hz, $J_{4a,4b}$ = 11.8 Hz, $J_{4a,5}$ = 4.7 Hz, H-4a), 2.76 (dd, 1H, *J* = 3.7 Hz, *J* = 15.7 Hz, C*H*HCO_2Et), 2.56 (dd, 1H, *J* = 8.0 Hz, *J* = 15.7 Hz, CH*H*CO_2Et), 1.77 (ddd, 1H, $J_{4b,3}$ = $J_{4b,4a}$ = $J_{4b,5}$ = 11.4 Hz, H-4b), 1.24 (t, 3H, *J* = 7.2 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 170.4 (C=O), 138.1, 137.7 (2× C_q Bn), 128.4, 128.2, 127.8, 127.7, 127.5 (CH_{arom}), 80.6, 75.8, 75.7, 71.7 (C-2, C-3, C-5, C-6), 73.3, 71.5, 68.6 (2× CH_2 Bn, *C*H_2OBn), 60.7 (CH_2

Et), 38.7 (CH_3 Ms), 37.2, 36.5 (C-4, CH_2CO_2Et), 14.1 (CH_3 Et). IR (thin film): 2934, 1734, 1455, 1362, 1337, 1281, 1202, 1175, 1097, 1028, 948, 841, 754, 699 cm^{-1}. MS (ESI): *m/z* = 493.2 $[M+H]^+$, 515.3 $[M+Na]^+$, 985.4 $[2M+H]^+$.

Analytical data of compound **17b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.21 (m, 10H, CH_{arom}), 4.97 (m, 1H, H-3), 4.63 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.55 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.54 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.43 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.15 (q, 2H, *J* = 7.1 Hz, CH_2 Et), 4.01 (ddd, 1H, *J* = 1.1 Hz, *J* = 6.8 Hz, H-2), 3.76 (dd, 1H, *J* = 2.0 Hz, *J* = 11.0 Hz, C*H*HOBn), 3.75 (ddd, 1H, $J_{5,4a} = J_{5,4b}$ = 11.0 Hz, $J_{5,6}$ = 2.0 Hz, H-5), 3.68 (dd, 1H, *J* = 5.1 Hz, *J* = 11.0 Hz, CH*H*OBn), 3.53 (ddd, 1H, $J_{6,5}$ = 2.0 Hz, *J* = 2.0 Hz, *J* = 5.1 Hz, H-6), 2.99 (s, 3H, CH_3 Ms), 2.73 (dd, 1H, *J* = 6.8 Hz, *J* = 16.8 Hz, C*H*HCO$_2$Et), 2.70 (m, 1H, H-4a), 2.62 (dd, 1H, *J* = 6.8 Hz, *J* = 16.8 Hz, CH*H*CO$_2$Et), 1.77 (ddd, 1H, $J_{4b,5}$ = 11.0 Hz, *J* = 2.8 Hz, *J* = 14.1 Hz, H-4b), 1.24 (t, 3H, *J* = 7.1 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 137.9, 137.8 (2× C_q Bn), 128.4, 128.3, 127.9, 127.9, 127.6 (CH_{arom}), 81.2, 76.6, 74.5, 68.6 (C-2, C-3, C-5, C-6), 73.5, 71.5, 69.3 (2× CH_2 Bn, CH_2COBn), 60.9 (CH_2 Et), 38.6 (CH_3 Ms), 36.3, 35.2 (C-4, CH_2CO_2Et), 14.1 (CH_3 Et). IR (thin film): 2925, 2855, 1734, 1454, 1355, 1334, 1304, 1268, 1173, 1095, 1028, 908, 854, 738, 699 cm^{-1}. MS (ESI): *m/z* = 493.3 $[M+H]^+$, 515.2 $[M+Na]^+$.



(2*R*, 3*R*, 5*R*, 6*S*)-3-Azido-5-benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-tetrahydropyran (18a):



(2*R*, 3*S*, 5*R*, 6*S*)-3-Azido-5-benzyloxy-6-benzyloxymethyl-2-ethoxycarbonylmethyl-tetrahydropyran (18b): To a solution of isomers **17a** and **17b** (78 mg, 0.159 mmol) in DMF (3.0 mL) was added sodium azide (52 mg, 0.79 mmol, 5.0 equiv.) and the mixture was heated to 65 °C. After stirring for 24 h, the solvent was removed *in vacuo* and the residue taken up in EtOAc and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated. Purification by column chromatography (PE to EtOAc/PE 1:49) afforded azide **18a** (15 mg, 34.2 μmol) and azide **18b** (10 mg, 22.8 μmol) in a combined yield of 36%.

Analytical data of compound **18a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.22 (m, 10H, CH_{arom}), 4.62 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.56 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.54 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.44 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.14 (q, 2H, *J* = 7.1 Hz, CH_2 Et), 3.93 (ddd, 1H, $J_{2,3}$ = 1.6 Hz, *J* = 6.3 Hz, *J* = 7.2 Hz, H-2), 3,85 (ddd, 1H, $J_{3,2}$ = 1.6 Hz, $J_{3,4a} = J_{3,4b}$ = 3.3 Hz, H-3), 3.73 (dd, 1H, *J* = 1.9 Hz, *J* = 11.0 Hz, C*H*HOBn), 3.69 (ddd, 1H, $J_{5,4a}$ = 4.6 Hz, $J_{5,4b}$ = 11.1 Hz, $J_{5,6}$ = 9.6 Hz, H-5), 3.65 (dd, 1H, *J* = 5.2 Hz, *J* = 11.0 Hz, CH*H*OBn), 3.49 (ddd, 1H, $J_{6,5}$ = 9.6 Hz, *J* = 1.9 Hz, *J* = 5.2 Hz, H-6), 2.72 (dd, 1H, *J* = 6.3 Hz, *J* = 16.3 Hz, C*H*HCO$_2$Et), 2.63 (dd, 1H, *J* = 7.2 Hz, *J* = 16.3 Hz, CH*H*CO$_2$Et), 2.54 (ddd, 1H, $J_{4a,3}$ = 3.3 Hz, $J_{4a,4b}$ = 13.7 Hz, $J_{4a,5}$ = 4.6 Hz, H-4a), 1.77 (ddd, 1H, $J_{4b,3}$ = 3.3 Hz, $J_{4b,4a}$ = 13.7 Hz, $J_{4b,5}$ = 11.1 Hz, H-4b), 1.25 (t, 3H, *J* = 7.1 Hz, CH_3 Et). IR (thin film): 2870, 2362, 2344, 2101, 1735, 1454, 1370, 1269, 1182, 1099, 1028, 738, 698, 668 cm^{-1}. MS (ESI): *m/z* = 440.3 $[M+H]^+$, 462.2 $[M+Na]^+$, 901.5 $[2M+H]^+$.

Analytical data of compound **18b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 10H, CH_{arom}), 4.60 (, d, 1H, *J* = 11.3 Hz, CH Bn), 4.60 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.51 (d, 1H, *J* = 12.2 Hz, CH Bn), 4.45 (d, 1H, *J* = 11.3 Hz, CH Bn), 4.15 (q, 2H, *J* = 7.1 Hz, CH_2 Et), 3.72 (dd, 1H, *J* = 2.0 Hz, *J* = 11.0 Hz, C*H*HOBn), 3.68 (dd, 1H, *J* = 4.0 Hz, *J* = 11.0 Hz, CH*H*OBn), 3.63 (ddd, 1H, $J_{2,3}$ = 10.0 Hz, *J* = 3.9 Hz, *J* = 8.0 Hz, H-2), 3.59 (ddd, 1H, $J_{5,4a}$ = 4.5 Hz, $J_{5,4b}$ = 11.0 Hz, $J_{5,6}$ = 9.4 Hz, H-5), 3.41 (ddd, 1H, $J_{6,5}$ = 9.4 Hz, *J* = 2.0 Hz, *J* = 4.0 Hz, H-6), 3.21 (ddd, 1H, $J_{3,2}$ = 10.0 Hz, $J_{3,4a}$ = 4.5 Hz, $J_{3,4b}$ = 12.0 Hz, H-3), 2.74 (dd, 1H, *J* = 3.9 Hz, *J* = 15.5 Hz, C*H*HCO$_2$Et), 2.63 (ddd, 1H, $J_{4a,3}$ = $J_{4a,5}$ = 4.5 Hz, $J_{4a,4b}$ = 12.0 Hz, H-4a), 2.50 (dd, 1H, *J* = 8.0 Hz, *J* = 15.5 Hz, CH*H*CO$_2$Et), 1.61 (ddd, 1H, $J_{4b,5}$ = 11.0 Hz, $J_{4b,3}$ = $J_{4b,4a}$ = 12.0 Hz, H-4b), 1.24 (t, 3H, *J* = 7.1 Hz, CH_3 Et). IR (thin film): 3032, 2928, 2870, 2360, 2344, 2099, 1734, 1454, 1369, 1320, 1268, 1182, 1094, 1028, 736, 698 cm^{-1}. MS (ESI): *m/z* = 462.5 $[M+Na]^+$, 901.5 $[2M+Na]^+$.

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Chapter 4

Transformation of Glucose into a Novel Carbasugar Amino Acid Dipeptide Isoster

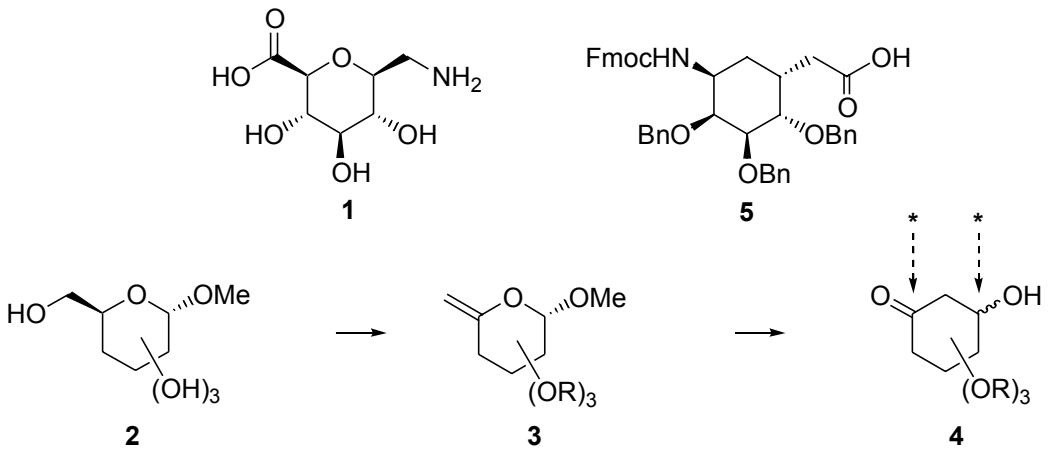
Introduction

Sugar amino acids (SAAs) are defined as carbohydrate based compounds that feature an amine and a carboxylate.[1] As such, SAAs are widely spread in nature, and neuraminic acid and *N*-acetyl muramic acid constitute important structural elements in many oligo(poly)saccharides and glycoconjugates. Interestingly, SAAs in nature are almost exclusively linked through interglycosidic bonds, not through amide bonds. The full potential of SAAs as carbohydrate-peptide hybrids was recognised first by Kessler and coworkers,[2,3] who disclosed an efficient synthesis of D-glucose-derived SAA **1** (Figure 1) and its incorporation in a series of linear and cyclic oligopeptide structures. Inspired by the work of the Kessler group, many researchers have become actively involved in SAA-related research. SAA homooligomers have been generated with the aim to attain oligosaccharide mimics that have the interglycosidic linkages replaced by amide bonds.[4] Cyclic SAA homooligomers have been prepared[5,6] with the ultimate goal to develop cyclodextrin analogous receptor molecules.[7] The hybrid nature of SAAs

comes to the fore in the multitude of reported applications in which they replace selected amino acid residues in biologically relevant oligopeptides. Here the aim is two-fold: the nature of the parent carbohydrate (the furan or pyran ring) in combination with the positioning of the amine and carboxylate may impart a desired secondary structure on the target oligopeptide, whereas the residual functionalities on the furan/pyran core may be used to introduce additional desirable properties to the peptide.[8]

In conjunction with the growing interest in the application of SAAs, recent years have witnessed numerous reports describing synthetic strategies towards new SAAs.[9] Next to aiming for control over the relative positioning of the amine- and carboxylate functionalities (as in α, β, γ, δ and ε SAAs), research objectives in these studies include the development of constrained SAAs, for instance through annulation of a second ring system,[10] but also the preparation of linear SAA counterparts.[11] Rather remarkably, given the extensive research efforts involving SAAs, reported examples of SAA building blocks in which the ring oxygen is replaced by either nitrogen[12] or carbon[13] are scarce. This is surprising especially when considering the numerous strategies available for transforming a carbohydrate in either an aminosugar[14] or a carbasugar.[15] Based on these observations, it is justifiable to establish synthetic routes towards ring-modified SAA analogues (Scheme 1).

Scheme 1



Carbohydrates are widely used as starting material in the synthesis of carbohydrate mimics (both carba- and imino analogues) and represent an obvious choice in planning a synthetic route towards carbasugar amino acids (CSAAs). Indeed many strategies for the transformation of monosaccharides into their corresponding cyclitols (functionalised hydroxylated cyclohexane derivatives) have been reported. Of these, the Ferrier rearrangement[16] is especially attractive. This reaction, comprising rearrangement of carbohydrate-derived enopyranoside **3** to ketone **4**, proceeds smoothly and allows a variety of different functionalities appended to the pyran core in **2**. Compound **3** is in turn prepared from the corresponding 6'-OH pyranose **2**, and different stereoisomeric parent sugars (glucose, galactose, mannose) can be employed in the sequence. Ferrier product **4** in turn features a β-hydroxy ketone entity that should ensure installation of the requisite carboxylate and amine at either of the two sides of the cyclohexane core, depending on the synthetic sequence employed.

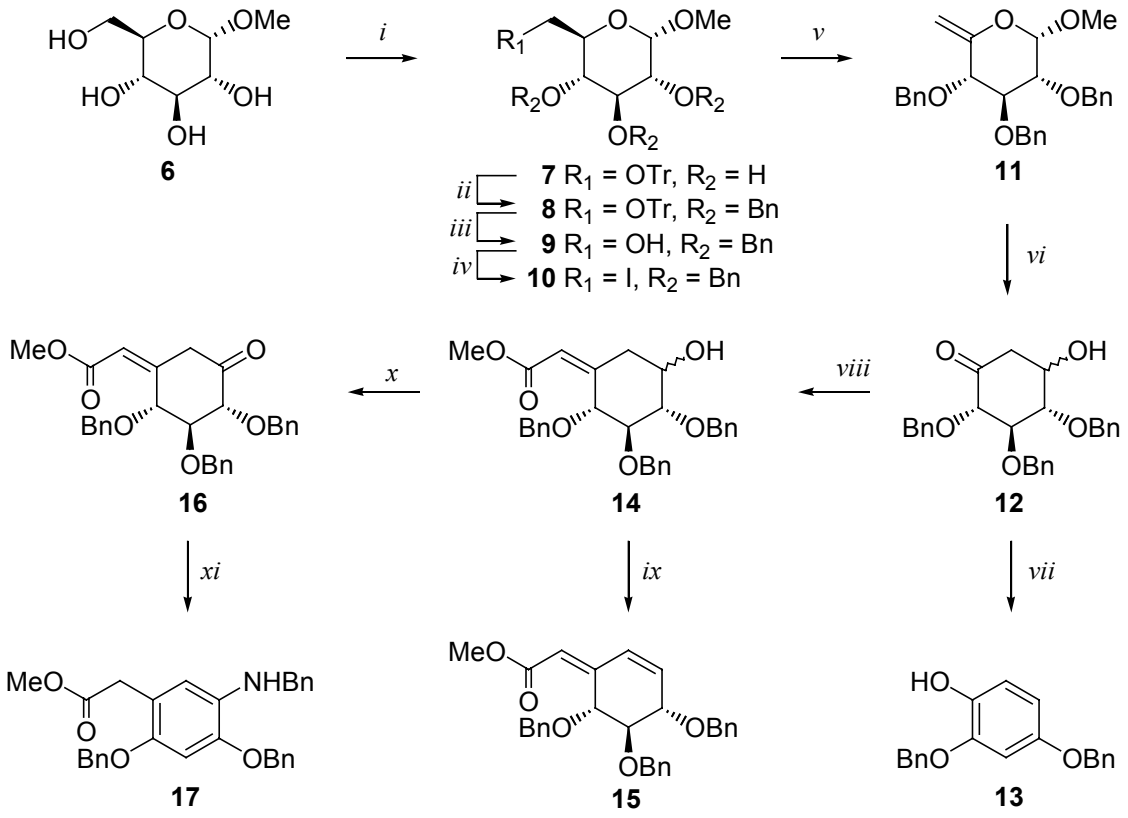
This chapter describes the elaboration of the strategy outlined above. Several synthetic routes are explored, all starting with Ferrier rearrangement of α-methyl-glucoside, and culminating in the synthesis of CSAA **5**. In addition, the incorporation of **5** as a replacement of the Gly-Gly dipeptide in Leu-enkephalin is presented.

Results and discussion

With the aim to investigate the viability of the above concept, Ferrier rearrangement product **12** (Scheme 2) was selected as general intermediate for all ensuing synthetic routes. Commencing the synthesis with commercially available D-glucose **6**, ketone **12** was prepared according to literature procedures,[17] as follows. Protection of the primary hydroxyl in **6** as the trityl ether followed by benzylation of the remaining hydroxyl groups using sodium hydride and benzyl bromide furnished fully protected glucose **8** in 80% yield over the two steps. Liberation of the primary hydroxyl using *p*-TsOH followed by subsequent conversion into the corresponding iodide, using Gareggs conditions,[18] gave access to 6-deoxy-6-iodoglucoside **10**. Base induced elimination afforded **11** which was subjected to mercury(II) chloride mediated Ferrier rearrangement resulting in the formation of β-hydroxyketone **12** as a mixture of diastereoisomers.

At this stage attention was focussed on the installation of a carboxyl moiety at the left hand side of the molecule through derivatisation of the ketone in **12** via a three step Wittig olefination, enol ether tautomerisation and oxidation procedure. However, treatment of ketone **12** with (methoxymethylene)triphenylphosphorane did not afford the expected olefin but furnished phenol **13** (57%) as the sole product. Under these basic

Scheme 2



Reagents and conditions: *i*) TrCl (1.3 equiv.), DMAP (cat.), pyr., rt, 17 h. *ii*) BnBr (3.3 equiv.), NaH (3.3 equiv.), TBAI (cat.), DMF, 0 ^{o}C to rt, 15 h, 80% (2 steps). *iii*) *p*-TsOH (pH<4), MeOH/CH_2Cl_2 (2:1), 15 h, rt, 80%. *iv*) imidazole (2.5 equiv.), Ph_3P (2.5 equiv.), I_2 (2.0 equiv.), toluene, rt, 2.5 h, 99%. *v*) NaH (5.0 equiv), DMF, 0 ^{o}C to rt, 16 h, 97%. *vi*) $HgCl_2$ (1.1 equiv.), acetone/H_2O (2:1), reflux, 2 h, 80%. *vii*) $MeOCH_2PPh_3Cl$ (2.5 equiv.), *n*-BuLi (2.5 equiv.), THF, -50 ^{o}C to rt, 30 min, then ketone **12**, -50 ^{o}C to rt, 17 h, 57%. *viii*) $Ph_3P{=}CHCO_2Me$ (1.5 equiv.), toluene, 70 ^{o}C, 17 h, 97%. *ix*) (*S*-isomer), dppa (1.2 equiv.), DBU (1.2 equiv.), toluene, 0 ^{o}C to rt, 24 h, quant. *x*) Dess-Martin periodinane (1.5 equiv.), CH_2Cl_2, rt, 20 h, 67%. *xi*) $BnNH_2$ (1.1 equiv.), HOAc (1.0 equiv.), $Na(OAc)_3BH$ (1.5 equiv.), 1,2-DCE, rt, 24 h, 71%.

conditions, β-elimination of benzyl alcohol occurred followed by dehydration to give aromatic derivative **13**.[19] Introduction of the carboxylate under neutral conditions should circumvent this cascade of eliminations. Indeed, Wittig olefination of ketone **12** using methyl (triphenylphosphoranylidene)acetate proved succesful, resulting in unsaturated ester **14** as a mixture of free hydroxyls in an overall yield of 97%. At this stage, installation of an amine equivalent was examined.

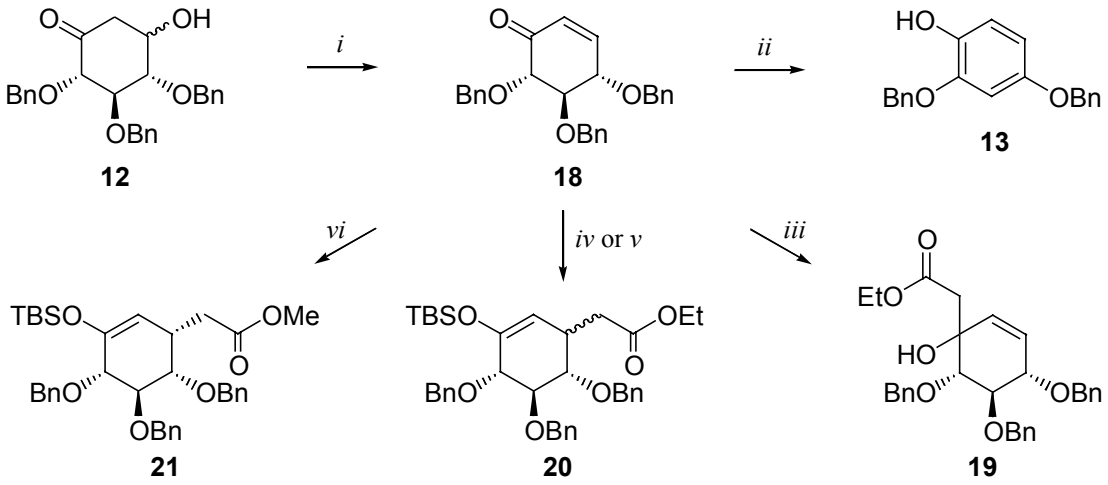
Thompson and co-workers[20] have reported a new procedure for the conversion of alcohols into azides with concomitant inversion of configuration. In this procedure the alcohol is treated with diphenylphosphoryl azide (dppa) and DBU which should lead to the formation of the azide from the transiently formed phosphate. Reaction of the *S*-isomer of **14** under the above conditions, however, did not result in the formation of the desired azide. Rather, diene **15** was formed in quantitative yield, presumably through β-elimination of the phosphate intermediate under the basic conditions applied.

Next, incorporation of the amine at the right hand side, by a two-step oxidation/reductive amination, was investigated. Oxidation of the hydroxyl moiety, employing the Dess-Martin periodinane, resulted in the formation of ketone **16**. Reaction of **16** with benzylamine under reductive amination conditions (acetic acid, sodium triacetoxyborohydride in 1,2-DCE) however, did not yield the expected secondary amine. Instead, a less polar product proved to be formed exclusively, which, after work up and spectroscopic analysis, was found to be phenylamine derivative **17**.

Therefore, in an alternative approach, intermediate **12** was transformed into enone **18** (MsCl, base, Scheme 3) which was applied in several studies aimed at the introduction of added functionalities by means of 1,4-addition.

In a first attempt, Michael reaction of **18** with diethylmalonate anion, generated under the agency of sodium hydride or sodium methoxide, did not result in expected 1,4-addition. Instead, elimination of benzyl alcohol followed by tautomerisation, led to the quantitative formation of phenol derivative **13**. At this stage attention was focussed on several Lewis acid mediated Mukaiyama-Michael additions with 1-(*tert*-butyldimethylsilyloxy)-1-ethoxyethene[21] to bring about the desired 1,4-addition on **18**.

Scheme 3



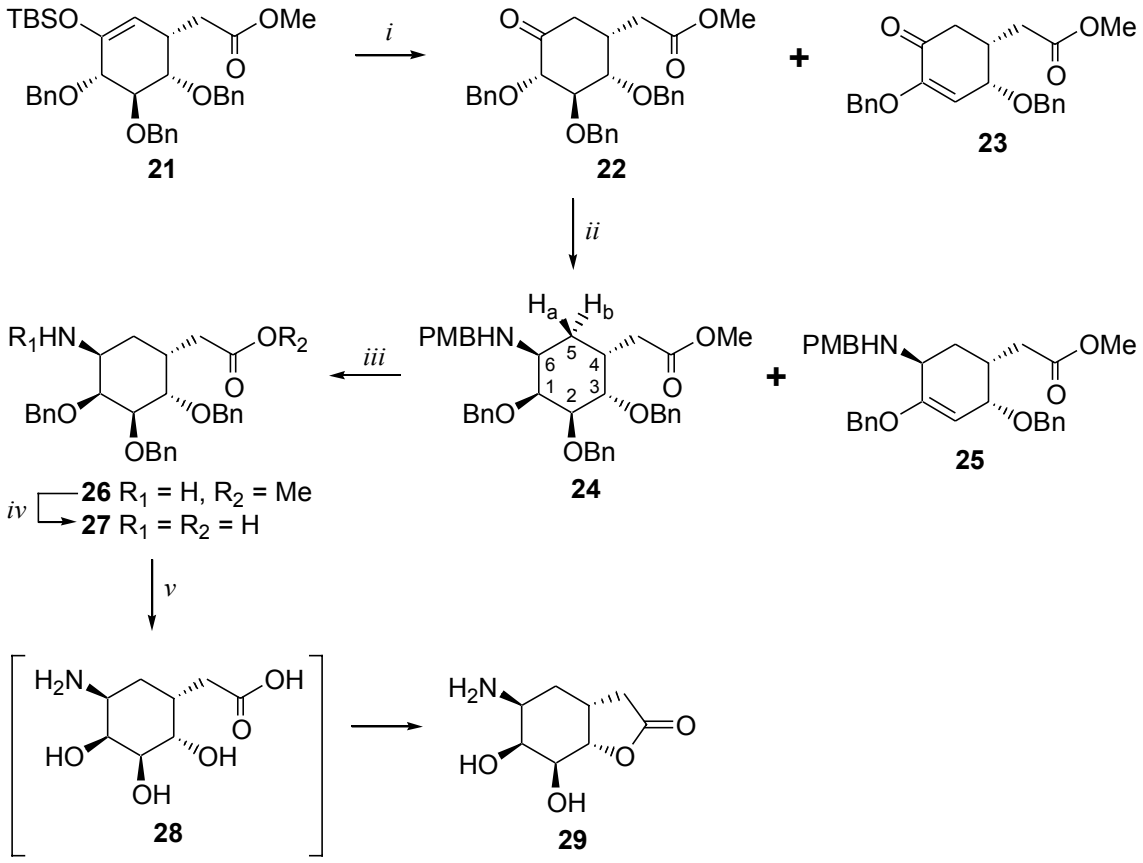
Reagents and conditions: *i*) MsCl (2.7 equiv.), DMAP (cat.), pyr., rt, 2 h, 87%. *ii*) diethylmalonate (1.5 equiv.), NaH or NaOEt (1.5 equiv.), THF, rt, 45 min, 99%. *iii*) TBSOC(OEt)=CH_2 (1.5 equiv.), $TiCl_4$ (1.5 equiv.), CH_2Cl_2, -78 ^oC, 30 min, 78%. *iv*) TBSOC(OEt)=CH_2 (1.5 equiv.), $SnCl_4$ (1.5 equiv.), CH_2Cl_2, -78 ^oC, 20 min, 55%. *v*) TBSOC(OEt)=CH_2 (1.5 equiv.), $LiClO_4$ (5.0 equiv.), Et_2O, rt, 48 h, 73%. *vi*) TBSOC(OMe)=CH_2 (3.0 equiv.), $LiClO_4$ (10.0 equiv.), Et_2O, rt, 30 min, 98%.

The use of titanium(IV) chloride led to 1,2-addition giving allyllic alcohol **19** as a single diastereoisomer in 78% yield. Upon application of tin(IV) chloride as Lewis acid in DCM, 1,4-addition was achieved resulting in the formation of ester **20** in 55% as an inseparable mixture of isomers. Switching to lithium perchlorate in Et_2O, afforded, after 48 hours reaction time, ester **20** in 73% yield. Upon changing the alkylating species to (*tert*-butyldimethylsilyloxy)-1-methoxyethene, a spectacular change in the outcome of the reaction was observed. Now enone **18** was consumed in only 30 minutes resulting in Michael adduct **21** as single diastereoisomer in 98% yield.

In continuation of the synthetic studies, silyl enol ether **21** was transformed into ketone **22** amenable for ensuing reductive amination (Scheme 4). At the first instance several desilylating conditions were explored such as TBAF in THF or 80% aqueous acetic acid at 50 ^oC or a combination of thereof. In all cases β-elimination proved to occur resulting in the formation of compound **23** as the only product in yields varying from 71% to 80%. Fortunately, it was found that β-elimination could be suppressed

completely by switching to HF·pyridine as the desilylating agent. Under these conditions, ketone **22** was isolated as the sole product in 99% yield. Importantly, the reaction with HF·pyridine was complete within 30 minutes. Prolonged reaction times led to the formation of enone **23** through β-elimination of benzyl alcohol. It was found that this transformation also occurs, over time, upon storage of **22**, dictating the necessity to proceed with the next step directly. Thus, after hydrolysis and work up, immediate reductive amination employing 4-methoxybenzylamine, acetic acid and sodium

Scheme 4



Reagents and conditions: *i*) HF·pyr., THF/pyr. (4:1), rt, 30 min, 99%. *ii*) *p*-MeOBnNH$_2$ (2.0 equiv.), Na(OAc)$_3$BH (1.5 equiv.), HOAc (1.0 equiv), 1,2-DCE, rt, 1 h, **24**: 51%, **25**: 15% (2 steps). *iii*) CAN (2.5 equiv.), H$_2$O/MeCN (1:2), rt, 24 h, 56%. *iv*) LiOH, H$_2$O/dioxane (1:4), rt, 3 h, quant. *v*) H$_2$, 10% Pd/C (cat.), HOAc (1.0 equiv.), *t*-BuOH/H$_2$O (1:1), rt, 17 h, quant.

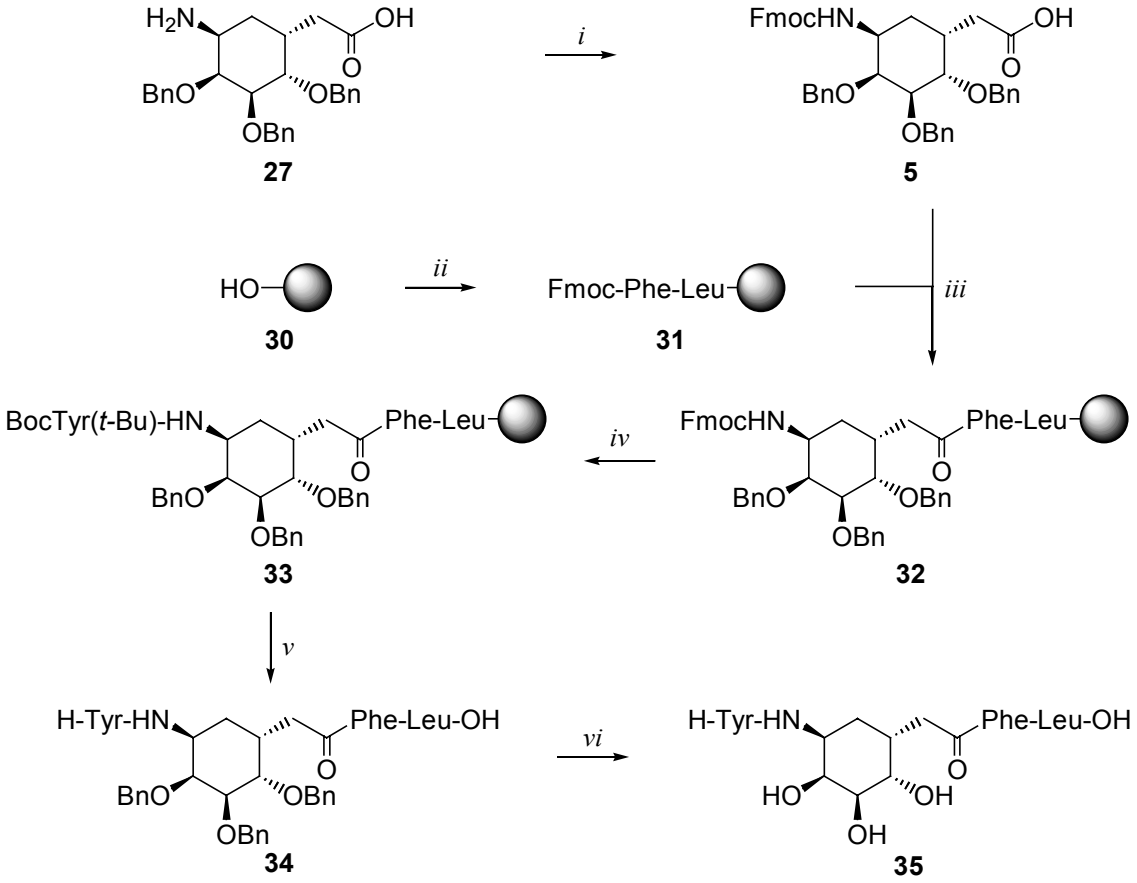
triacetoxyborohydride afforded CSAA **24** in 51% over two steps. Rather surprisingly, epimerisation at C1 occurred under the basic conditions applied. Most likely this is the result of tautomerisation of either ketone **22** or of the intermediate imine, resulting in the formation of amine **24** as the more stable isomer. The absolute configuration of **24** was firmly established by NOE difference experiments, with key NOE's between H5b-H1 on the one hand, and H5a-H3 on the other. In addition, the *trans*-disposition of the newly introduced amine- and carboxymethyl substituent was assigned. In a competing process, benzyl alcohol proved to be prone to elimination again, leading to the formation of enol ether **25** as major side product, in a yield of 15% over the last two steps.

At this stage an attempt was undertaken to generate fully unprotected CSAA **28**. Removal of the *N*-4-methoxybenzyl group of **24**, using ceric ammonium nitrate (CAN), liberated the free amine to give compound **26**. Saponification of the methyl ester under the agency of LiOH furnished amino acid **27**. At this stage it was found that cyclisation to lactone **29** could not be avoided after removal of the benzyl ethers. As a consequence, partially protected **27** was applied as amino acid building block in the preparation of a novel Leu-enkephalin analogue as follows. Protection of the amine function of **27** was accomplished using Fmoc-OSu in saturated aqueous $NaHCO_3$/dioxane (Scheme 5), resulting in CSAA **5** in a yield of 92%. Application of standard Fmoc-based solid phase peptide synthesis protocols gave Fmoc-Phe-Leu-Wang resin **31** starting from **30**. Condensation of acid **5** with **31** proceeded smoothly to give immobilised tripeptide **32**. Further elongation with a Boc-protected tyrosine and acidic cleavage from the resin, along with removal of the *tert*-Bu-moiety, gave protected peptide **34**. Hydrogenolysis of the benzyl ethers followed by reverse phase HPLC purification afforded Leu-enkephalin analogue **35**.

Conclusion

In summary, a synthetic route to novel CSAA **5** was developed having a high yielding and stereoselective lithium perchlorate assisted Mukaiyama-Michael 1,4-addition on enone **18** as key step. In addition, dipeptide isoster **5** was succesfully applied in a solid phase protocol towards Leu-enkephalin analogue **35**.

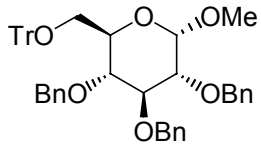
Scheme 5



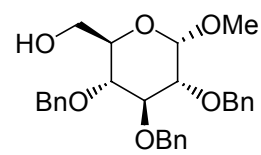
Reagents and conditions: *i*) FmocOSu, sat. aq. $NaHCO_3$/dioxane (4:1), 17h, 92%. *ii*) a) DIC, DMAP, Fmoc-Leu-OH, CH_2Cl_2; b) 20% piperidine in DMF, 3× 10 min; c) Fmoc-Phe-OH, HCTU, DiPEA, DMF, 3× 1h. *iii*) a) 20% piperidine in DMF, 3× 10 min; b) **5** (1.0 equiv.), HATU (0.95 equiv.), DiPEA, DMF (2.5 equiv.), 2× 10 min. *iv*) a) 20% piperidine in DMF, 3× 10 min; b) Boc-Tyr(*t*-Bu)-OH, HCTU, DiPEA, DMF, 2 h. *v*) TFA/TIS/H_2O (95:2.5:2.5), 15 min; *vi*) H_2, 10% Pd/C (cat.), HOAc (1.0 equiv.), *t*-BuOH/H_2O (1:1), 17 h, rt, quant.

Experimental section

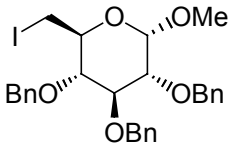
For general methods and materials see Chapter 2.



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside (8): To a solution of methyl α-D-glucopyranoside (19.42 g, 100.0 mmol) in pyridine (200 mL) was added trityl chloride (35.00 g, 125.6 mmol, 1.26 equiv.) and DMAP (1.5 g). After 17 h the reaction mixture was cocnentrated and the residue was crystallised from EtOH (200 mL) and the crystals were dissolved in DMF (400 mL). After addition of BnBr (39.3 mL, 330.0 mmol, 3.3 equiv.) the mixture was cooled to 0 °C. NaH (13.2 g 60% dispersion in mineral oil, 3.3 equiv.) was added in portions and the mixture was allowed to reach rt overnight. The reaction was quenched by addition of MeOH (150 mL) and the solvents were evaporated. The residue was dissolved in Et_2O and washed with water, the aqueous phase was separated and washed with Et_2O. All organic layers were combined, dried ($MgSO_4$) and purified by column chromatography (EtOAc/PE 1:2) to yield **8** (56.8 g, 80.4 mmol) in 80%. ^{13}C-NMR (50 MHz, $CDCl_3$): δ 143.8 (3× C_q Ph Tr), 138.7, 138.3, 137.9 (3× C_q Ph Bn), 128.7-126.9 (CH_{arom}), 97.8 (C-1), 86.2 (C_q Tr), 82.2, 80.2, 78.1 (C-2, C-3, C-4), 75.9, 74.9, 73.3 (3× CH_2 Bn), 70.2 (C-5), 62.6 (C-6), 54.8 (CH_3 OMe).

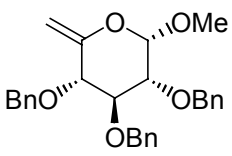


Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (9): Compound **8** (56.8 g, 80.4 mmol) was dissolved in MeOH/DCM (2:1, 500 mL) and *p*-TsOH was added (pH<4). After stirring for 17 h the reaction was neutralised with Et_3N and the mixture was concentrated and purified by silica gel column chromatography (EtOAc/PE 1:4). Recrystallisation from EtOAc/PE afforded **9** (29.8 g, 64.1 mmol, 80%) as crystalline needles. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.37-7.25 (m, 15H, CH_{arom}), 5.01-4.55 (m, 7H, H-1, 3× CH_2 Bn), 4.00 (m, 1-H, H-3), 3.77-3.46 (m, 5H, H-2, H-4, H-5, H-6), 3.36 (s, 3H, CH_3 OMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.8, 138.3, 138.2 (3× C_q Bn), 128.0-127.6 (CH_{arom}), 98.0 (C-1), 81.9, 80.0, 78.1 (C-2, C-3, C-4), 75.6, 74.9, 73.2 (3× CH_2 Bn), 70.9 (C-5), 61.5 (C-6), 55.1 (CH_3 OMe).

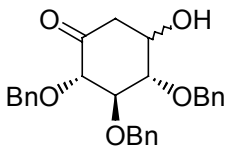


Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (10): To a solution of alcohol **9** (18.58 g, 40.0 mmol) in toluene (350 mL) was added imidazole (6.81 g, 100.0 mmol, 2.5 equiv.), triphenylphosphine (26.23 g, 100.0 mmol, 2.5 equiv.) and iodine (20.30 g, 80.0 mmol, 2.0 equiv.). After stirring for 2.5 h the mixture was quenched with 1.0 M aq. $Na_2S_2O_3$ and extracted with Et_2O (3×). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. The residue was taken up in Et_2O, PE was added and the resulting precipitate was filtered off. The solution was concentrated and the residue was purified by silica gel column chromatography (Et_2O/PE 1:9 to 3:7) to give iodide **10** (22.9 g, 39.9 mmol, 99%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.33-7.24 (m, 15H,

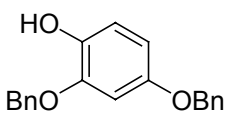
CH_{arom}), 5.01-4.60 (m, 7H, H-1, 3× CH_2 Bn), 4.01 (t, 1H, J = 9.1 Hz, H-3), 3.57-3.24 (m, 5H, H-2, H-4, H-5, H-6), 3.42 (s, 3H, OMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 138.4, 137.9 (3× C_q Bn), 128.4-127.6 (CH_{arom}), 97.9 (C-1), 81.4, 81.3, 79.9 (C-2, C-3, C-4), 75.6 75.2, 73.3 (3× CH_2 Bn), 69.1 (C-5), 55.4 (CH_3 OMe), 7.6 (C-6).



Methyl 2,3,4-tri-*O*-benzyl-α-D-*xylo*-hex-5-enopyranoside (11): NaH (7.0 g, 175.0 mmol 60% dispersion in mineral oil, 5.0 equiv.) was added in portions to an ice-cooled solution of iodide **10** (20.11 g, 35.0 mmol) in DMF (150 mL) and this mixture was allowed to reach rt. After 16h the reaction was quenched by slow addition of MeOH and the resulting mixture was concentrated. The residue was dissolved in Et_2O and washed with water, sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (EtOAc/PE 1:9) afford alkene **11** (15.23 g, 34.1 mmol, 97%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.32-7.26 (m, 15H, CH_{arom}), 4.94-4.70 (m, 8H, 3× CH_2 Bn, H-6), 4.61 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.01-3.88 (m, 2H, H-3, H-4), 3.59 (dd, 1H, J = 3.6 Hz, J = 9.5 Hz, H-2), 3.42 (s, 3H, OMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 153.4 (C-5), 138.5, 137.9, 137.8 (3× C_q Bn), 128.2, 128.0, 127.6, 127.4 (CH_{arom}), 98.8 (C-1), 96.6 (C-6), 80.9, 79.3, 79.1 (C-2, C-3, C-4), 75.5, 74.2, 73.3 (3× CH_2 Bn), 55.2 (CH_3 OMe).



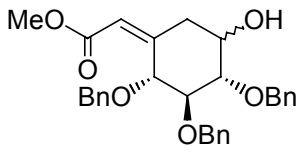
(2*S*, 3*R*, 4*S*, 5*R*/*S*)-2,3,4-Tris-benzyloxy-5-hydroxy-cyclohexanone (12): Compound **11** (5.96 g, 13.36 mmol) was dissolved in a mixture of acetone/water (2:1). $HgCl_2$ (3.99 g, 14.69 mmol, 1.1 equiv.) was added and the mixture was heated till reflux. After 2 h the mixture was cooled to rt and concentrated. The resulting white solid was dissolved in DCM, washed with water (2×) and brine (2×). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. Purification by silica gel column chromatography (EtOAc/PE 1:3 to 2:3) gave **12** as a mixture of hydroxyketones in a combined overall yield (4.64 g, 10.73 mmol) of 80%. Major isomer (**5*S***): ^{13}C-NMR (50 MHz, $CDCl_3$): δ 204.0 (C-1), 138.3, 137.6 (3× C_q Bn), 128.6, 128.4, 128.2, 127.9, 127.8, 127.6, 127.5, 127.1 (CH_{arom}), 85.2, 81.6, 81.4 (C-2, C-3, C-4), 75.7, 73.3, 72.9 (3× CH_2 Bn), 66.3 (C-5), 42.6 (C-6). Minor isomer (**5*R***): ^{13}C-NMR (50 MHz, $CDCl_3$): δ 203.2 (C-1), 138.0, 137.9, 137.4 (3× C_q Bn), 128.6, 128.4, 128.1, 128.0, 127.9 (CH_{arom}), 85.9, 84.6, 81.9 (C-2, C-3, C-4), 75.6, 75.3, 73.5 (3× CH_2 Bn), 67.9 (C-5), 44.1 (C-6).



2,4-Bis-benzyloxy-phenol (13): *Wittig olefination*: A solution of the phosphonium ylide was prepared by dropwise addition of *n*-BuLi (0.234 mL, 1.6M in hexanes) to a suspension of (methoxymethyl)triphenylphosphonium chloride (129 mg, 0.375 mmol, 2.5 equiv.) in anhydrous THF (1.0 mL) at –50 °C. This solution was allowed to warm to rt. After stirring for 30 min. the solution turned orange and was subsequently cooled again to –50 °C. Ketone **12** (65 mg, 0.150 mmol) in THF (1.0 mL) was added dropwise. The reaction was allowed to reach rt and stirred

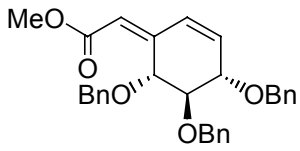
overnight. TLC analysis (EtOAc/PE 1:4) revealed a higher running spot and the reaction was quenched by addition of sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated. Purification by column chromatography (EtOAc/PE 1:19) gave phenol **13** (26 mg, 0.0849 mmol, 57%).

Michael additions: To a mixture of NaH (6 mg, 0.15 mmol 60% dispersion in mineral oil, 1.5 equiv.) or NaOEt (0.15 mL 1.0 M, prepared from 103 mg Na in 45.0 mL EtOH, 1.5 equiv.) in freshly distilled THF (2.5 mL) was added diethylmalonate (23 µL, 0.15 mmol, 1.5 equiv.) at 0 °C. After 15 min of stirring a solution of unsaturated ketone **18** (42 mg, 0.10 mmol) in THF (0.5 mL) was added dropwise and the mixture was allowed to reach rt. After 45 min TLC analysis (EtOAc/PE 1:4) revealed complete consumption of enone **18** and the reaction was quenched by addition of water and diluted with EtOAc. The aqueous layer was separated and extracted once more with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography as described above gave phenol derivative **13** (30 mg, 0.10 mmol) in a quantitative yield. Analytical data of compound **13**: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.42-7.31 (m, 10H, CH_{arom} Bn), 6.84 (d, 1H, $J_{6,5}$ = 8.8 Hz, H-6), 6.63 (d, 1H, $J_{3,5}$ = 2.9 Hz, H-3), 6.48 (dd, 1H, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, H-5), 5.28 (s, 1H, OH), 5.04 (s, 2H, CH_2 Bn), 4.97 (s, 2H, CH_2 Bn). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 146.2, 140.2, 140.2, 137.1, 136.1 (5× C_q), 128.6, 128.5, 128.3, 127.8, 127.5, 126.9 (CH Bn), 114.3, 106,1, 101.7 (C-3, C-5, C-6), 71.0, 70.7 (2× CH_2 Bn). MS (ESI): *m/z* = 307.1 $[M+H]^+$, 329.2 $[M+Na]^+$, 635.4 $[2M+Na]^+$.

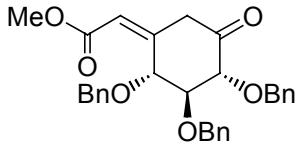


(2*R*, 3*S*, 4*S*, 5*R*/*S*)-2,3,4-Tris-benzyloxy-5-hydroxy-1-(methyloxycarbonylmethylene)-cyclohexane (14): Hydroxy-ketone **12** (***R*/*S***) (3.39 g, 7.85 mmol) was dissolved in toluene (80 mL). Methyl (triphenylphosphoranylidene)acetate (3.94 g, 11.77 mmol, 1.5 equiv.) was added and the mixture was heated to 70 °C. After stirring for 17 h, TLC analysis (EtOAc/PE 1:3) revealed no starting material was present and the mixture was concentrated. Purification by silica gel column chromatography (EtOAc/PE 1:3) afforded unsaturated ester **14** (3.70 g, 7.58 mmol) in a combined yield of 97% as a epimeric mixture of alcohols. Major isomer (**5*S***): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 15H, CH_{arom}), 6.30 (t, 1H, $J_{CH,2}$ = $J_{CH,6a}$ = 1.7 Hz, C*H*CO), 4.88 (d, 1H, *J* = 10.8 Hz, CH Bn), 4.79 (d, 1H, *J* = 10.8 Hz, CH Bn), 4.73 (d, 1H, *J* = 11.7 Hz, CH Bn), 4.72 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.69 (d, 1H, *J* = 11.7 Hz, CH Bn), 4.66 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.15 (m, 1H, H-7), 4.10 (dd, 1H, $J_{6a,5}$ = 4.1 Hz, $J_{6a,6b}$ = 14.3 Hz, H-6a), 3.90 (dd, 1H, $J_{2,CH}$ = 1.8 Hz, $J_{2,3}$ = 9.1 Hz, H-2), 3.80 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 8.9 Hz, H-3), 3.70 (s, 3H, OMe), 3.55 (dd, 1H, $J_{4,3}$ = 8.7 Hz, $J_{4,5}$ = 3.0 Hz, H-4), 2.49 (bs, 1H, OH), 1.93 (dt, 1H, $J_{6b,CH}$ = 2.0 Hz, $J_{6b,5}$ = 14.3 Hz, H-6b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.1 (C=O), 152.8 (C-1), 138.5, 137.9 137.8 (3× C_q Bn), 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5 (CH_{arom}), 115.8 (*C*HCO), 83.3 (C-2, C-3), 75.7, 73.6, 72.6 (3× CH_2 Bn), 66.9 (C-7), 51.1 (CH_3 OMe), 30.4 (C-6). MS (ESI): *m/z* = 489.2 $[M+H]^+$, 511.3 $[M+Na]^+$. Minor isomer (**5*R***): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.40-7.30 (m, 15H, CH_{arom}), 6.20 (s, 1H, C*H*CO), 5.00-4.92 (m, 2H, CH_2 Bn), 4.79-4.61 (m, 4H, 2× CH_2 Bn), 4.09-3.98 (m, 2H, H-5, H-6a), 3.73 (s, 3H, OMe), 3.60-3.34 (m, 3H, H-2, H-3, H-4), 2.34 (bs, 1H, OH), 1.94 (t, 1H, *J* = 11.7 Hz, H-

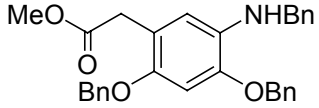
6b). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 166.3 (C=O), 151.6 (C-1), 138.1, 137.4 (3× C_q Bn), 128.1-127.3 (CH_{arom}), 114.4 (*C*HCO), 85.4, 84.2, 83.4 (C-2, C-3, C-4), 75.4, 75.2, 74.8 (3× CH_2 Bn), 70.8 (C-5), 50.8 (CH_3 OMe), 32.2 (C-6). MS (ESI): *m/z* = 489.2 $[M+H]^+$, 511.3 $[M+Na]^+$.



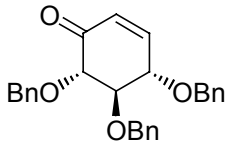
(4*S*, 5*R*, 6*R*)-4,5,6-Tris-benzyloxy-1-(methyloxycarbonyl-methylene)-cyclohex-2-ene (15): Compound **14** (***S***-isomer, 0.484 g, 0.991 mmol) was dissolved in anhydrous toluene (2.5 mL) and cooled to 0 °C. Diphenylphosphoryl azide (0.256 mL, 1.19 mmol, 1.2 equiv.) was added followed by addition of DBU (0.179 mL, 1.19 mmol, 1.2 equiv.) and the mixture was allowed to reach rt. After stirring for 24 h TLC-analysis (EtOAc/PE 1:3) showed all starting material was converted into a higher running spot. The mixture was washed with water and 5% aq. HCl. The organic layer was dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (EtOAc/PE 1:9) gave conjugate derivative **15** (0.465 g, 0.989 mmol) as an oil in quantitative yield. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.58 (dd, 1H, $J_{2,CH}$ = 2.2 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 7.45-7.25 (m, 15H, CH_{arom}), 6.23 (s, 1H, C*H*CO), 6.10 (dd, 1H, $J_{3,CH}$ = 2.2 Hz, $J_{3,2}$ = 10.2 Hz, H-3), 5.01-4.67 (m, 6H, 3× CH_2 Bn), 4.37 (dt, 1H, $J_{4,5}$ = 7.3 Hz, $J_{4,3}$ = 2.2 Hz, H-4), 4.21 (dd, 1H, $J_{6,CH}$ = 2.2 Hz, $J_{6,5}$ = 10.2 Hz, H-6), 3.88 (dd, 1H, *J* = 7.3 Hz, *J* = 8.0 Hz, H-5), 3.73 (s, 3H, CH_3 OMe). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 166.4 (C=O), 150.7 (C-1), 138.2, 138.0, 137.6 (3× C_q Bn), 129.8-127.5 (CH_{arom}), 125.3, 124.2 (C-2, *C*HCO), 112.9 (C-3), 84.7, 80.0, 79.7 (C-4, C-5, C-6), 75.0, 74.6, 72.0 (3× CH_2 Bn), 50.9 (CH_3 OMe). MS (ESI): *m/z* = 493.3 $[M+Na]^+$.



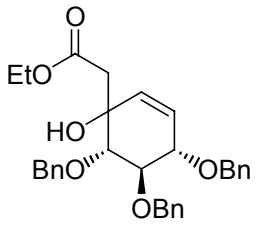
(2*R*, 3*S*, 4*R*)-2,3,4-Tris-benzyloxy-5-(methyloxycarbonyl-methylene)-cyclohexanone (16): Compound **14** (a mixture of alcohols) (1.75 gr, 3.58 mmol) was dissolved in DCM and Dess-Martin periodinane (2.34 g, 5.37 mmol, 1.5 equiv.) was added. After 20 h, TLC analysis (1:2 EtOAc/PE) showed complete conversion of starting material into a higher running spot. Sat. aq. $NaHCO_3$ and 1.0 M aq. $Na_2S_2O_3$ (20 mL each) and EtOAc (50 mL) were added and the mixture was vigorously stirred for 30 min, after which the organic layer was separated. After extraction of the aqueous phase wtih EtOAc, the organic layers were combined, dried ($MgSO_4$) and concentrated. Column chromatography (EtOAc/PE 1:9 to 1:5) yielded ketone **16** (1.17 g, 2.40 mmol, 67%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.46-7.23 (m, 15H, CH_{arom}), 5.97 (s, 1H, CHCO), 5.11 (d, 1H, *J* = 11.8 Hz, CH Bn), 5.02 (d, 1H, *J* = 11.0 Hz, CH Bn), 5.01 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.76 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.70 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.59 (d, 1H, *J* = 11.7 Hz, CH Bn), 4.55 (d, 1H, $J_{2,3}$ = 8.0 Hz, H-2), 4.14 (d, 1H, $J_{4,3}$ = 11.0 Hz, H-4), 4.00 (dd, 1H, $J_{3,2}$ = 8.0 Hz, $J_{3,4}$ = 11.0 Hz, H-3), 3.62 (s, 3H, CH_3 OMe), 3.61 (d, 1H, $J_{6a,6b}$ = 16.8 Hz, H-6a), 3.18 (d, 1H, $J_{6b,6a}$ = 16.8 Hz, H-6b). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 196.3 (C-1), 169.6 (CO CO_2Me), 137.8, 137.5, 137.5 (3× C_q Bn), 84.9, 83.9, 79.3 (C-2, C-3, C-4), 75.6, 75.3, 74.2 (3× CH_2 Bn), 51.8 (CH_3 OMe), 38.2 (C-6). MS (ESI): *m/z* = 487.1 $[M+H]^+$, 509.4 $[M+Na]^+$, 973.3 $[2M+H]^+$, 995.8 $[2M+Na]^+$.



5-Benzylamino-2,4-bis-benzyloxy-phenylacetic acid metyl ester (17): Ketone **16** (0.100 g, 0.21 mmol) was dissolved in anhydrous 1,2-DCE (2.0 mL) and 4Å molecular sieves were added. Benzylamine (24.7 µL, 0.23 mmol, 1.1 equiv.), acetic acid (11.8 µL, 0.21 mmol, 1.0 equiv.) and $Na(OAc)_3BH$ (65 mg, 0.31 mmol, 1.5 equiv.) were added. After 24 h the mixture was filtered, diluted with DCM and washed against sat. aq. $NaHCO_3$. The organic layer was collected, washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel clomun chromatography (EtOAc/PE 1:19) gave phenylamine **17** (68 mg, 0.15 mmol, 71%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.34-7.21 (m, 15H, CH_{arom}), 6.56, 6.47 (2× s, 2H, H-3, H-6), 5.00, 4.92 (2× s, 4H, 2× CH_2 Bn), 4.29 (s, 2H, CH_2 BnNH), 3.57 (s, 3H, OMe), 3.54 (s, 2H, CH_2 CH_2CO). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 148.0, 145.6 (C-2, C-4), 139.7 (C_q BnN), 137.5, 136.8 (2× C_q Bn), 132.9 (C-5), 128.5, 128.4, 128.2, 128.0, 127.6, 127.5, 127.4, 127.2 (CH_{arom}), 116.1 (C-1), 113.0, 100.4 (C-3, C-6), 71.8, 70.8 (2× CH_2 Bn), 52.8 (CH_2 BnN), 51.7 (CH_3 OMe), 35.4 (CH_2 CH_2CO). MS (ESI): *m/z* = 468.3 $[M+H]^+$, 935.5 $[2M+H]^+$.

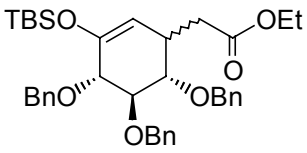


(4*S*, 5*R*, 6*S*)-4,5,6-Tris-benzyloxy-cyclohex-2-enone (18): To a mixture of alcohol **12** (0.432 g, 1.00 mmol) and mesylchloride (0.209 mL, 2.7 mmol, 2.7 equiv) dissolved in pyridine (10 mL) was added a catalytic ammount of DMAP. After 2 h the reaction was complete according to TLC-analysis (EtOAc/PE 1:1). Ice was added and the mixture was extracted with Et_2O. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated. After purification by column chromatography, unsaturated keton **18** was obtained (0.361 g, 0.87 mmol) in a yield of 87%. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.46-7.26 (m, 15H, CH_{arom}), 6.81 (dd, 1H, $J_{3,2}$ = 10.2 Hz, $J_{3,4}$ = 2.2 Hz, H-3), 6.39 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{2,4}$ = 2.2 Hz, H-2), 5.11-4.70 (m, 6H, 3× CH_2 Bn), 4.35 (dt, 1H, $J_{4,2} = J_{4,3}$ = 2.2 Hz, $J_{4,5}$ = 7.3 Hz, H-4), 4.04 (d, 1H, $J_{6,5}$ = 10.2 Hz, H-6), 3.97 (dd, 1H, $J_{5,4}$ = 7.3 HZ, $J_{5,6}$ = 10.2 Hz, H-5). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 197.3 (C-1), 148.0 (C-3), 138.1, 137.7, 137.5 (3× C_q Bn), 128.5 (C-2), 128.3-127.7 (CH_{arom}), 84.6, 83.7, 78.9 (C-4, C-5, C-6), 75.6, 74.4, 73.5 (3× CH_2).



(4*S*, 5*R*, 6*S*)-4,5,6-Tris-benzyloxy-1-ethoxycarbonylmethyl-cyclohex-2-en-1-ol (19): α,β-Unsatured ketone **18** (0.124 g, 0.30 mmol) was dissolved in freshly distilled DCM (2.5 mL) under an argon atmosphere. 1-(*tert*-Butyldimethylsilyloxy)-1-ethoxyethene[20] (91.0 mg, 0.45 mmol, 1.5 equiv.) was added and the mixture was cooled to –78 °C. After dropwise addition of $TiCl_4$ (49.6 µL, 0.45 mmol, 1.5 equiv.) the mixture turned dark red. After 30 min TLC-analysis (EtOAc/PE 1:3) showed complete disappearance of starting material along with the formation of a lower running spot. The reaction was quenched by addition of water (1.0 mL) and warmed to rt after which the red color disppeared. The mixture was diluted with Et_2O and the separated organic layer was collected,

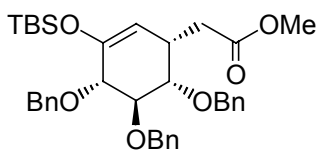
washed with brine, dried ($MgSO_4$) and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/PE 1:19 to 1:9) gave 1,2-adduct **19** (0.117 g, 0.23 mmol, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 15H, CH_{arom}), 5.80 (2× dd, 2H, J = 1.8 Hz, J = 10.2 Hz, H-2, H-3), 5.09 (d, 1H, J = 11.2 Hz, CH Bn), 4.91 (d, 1H, J = 11.0 Hz, CH Bn), 4.85 (d, 1H, J = 11.0 Hz, CH Bn), 4.69 (s, 2H, CH_2 Bn), 4.69 (d, 1H, J = 11.2 Hz, CH Bn), 4.16 (dt, 1H, J = 1.8 Hz, $J_{4,5}$ = 7.8 Hz, H-4), 4.09 (dd, 1H, $J_{5,4}$ = 7.8 Hz, $J_{5,6}$ = 9.8 Hz, H-5), 4.01 (q, 2H, J = 7.1 Hz, CH_2 Et), 3.66 (d, 1H, $J_{6,5}$ = 9.8 Hz, H-6), 3.36 (s, 1H, OH), 2.57 (dd, 2H, J = 14.3 Hz, CH_2CO), 1.18 (t, 3H, J = 7.1 Hz, CH_3 Et). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5 (C=O), 138.6, 138.4, 138.1 (3× C_q Bn), 129.8, 129.7 (C-2, C-3), 128.3-127.5 (CH_{arom}), 81.3 (C-5), 80.4 (C-6), 80.1 (C-4), 75.5, 75.2 (2× CH_2 Bn), 72.2 (C-1), 71.8 (CH_2 Bn), 60.6 (CH_2 Et), 43.4 (*C*H_2CO), 14.1 (CH_3 Et). IR (thin film): 3030, 1728, 1497, 1454, 1367, 1302, 1209, 1177, 1067, 1026, 734, 696 cm^{-1}. MS (ESI): *m/z* = 503.4 $[M+H]^+$, 520.3 $[M+NH_4]^+$, 1005.7 $[2M+H]^+$, 1022.7 $[2M+NH_4]^+$.



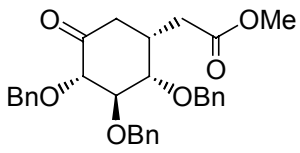
(3*R*/*S*, 4*S*, 5*R*, 6*S*)-4,5,6-Tris-benzyloxy-1-(*tert*-butyldimethyl-silyloxy)-3-ethoxycarbonylmethyl-cyclohex-1-ene (20): *$SnCl_4$ mediated Mukaiyama-Michael addition:* To a solution of unsaturated ketone **18** (57 mg, 0.14 mmol) in freshly distilled DCM (1.0 mL) was added a solution of silylketen acetal[21] (50 mg, 0.25 mmol, 1.8 equiv.) in DCM (1.0 mL) under an argon atmosphere. The mixture was cooled to – 78 °C and 2 drops of $SnCl_4$ were added. After 20 min TLC-analysis (EtOAc/PE 1:4) revealed complete consumption of starting material, water (0.5 mL) was added and the mixture was warmed to rt. The mixture was diluted with Et_2O and the organic layer was separated. After extraction of the aqueous layer with Et_2O, all organic layers were combined, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:19) gave ester **20** as a colorless oil as a mixture of diastereoisomers (47 mg, 0.076 mmol, 55%).

$LiClO_4$ mediated Mukaiyama-Michael addition: To a solution of unsaturated ketone **18** (83 mg, 0.20 mmol) in freshly distilled Et_2O (2.0 mL) was added a solution of silylketene acetal[21] (61 mg, 0.30 mmol, 1.5 equiv.) in Et_2O (0.3 mL) at rt. Next, a 1.0 M solution of $LiClO_4$ in Et_2O (1.0 mL, 0.106 gr, 5.0 equiv.) was added. After 48 h, TLC analysis (EtOAc/PE 1:4) showed all starting material was converted into a higher running spot. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. Purification of the residue as described above, resulted in 1,4-addition product **20** (90 mg, 0.15 mmol, 73%) as an inseparable mixture of diatsereoisomers.

Analytical data of compound **20**: ^{13}C-NMR (200 MHz, $CDCl_3$): δ 173.0, 172.2 (C=O), 149.6, 149.2 (C-1), 128.2, 127.9, 127.8, 127.6, 127.4 (CH_{arom}), 106.3, 106.1 (C-2), 84.7, 82.0, 81.2, 81.0, 80.0, 78.2 (C-4, C-5, C-6), 75.0, 74.8, 74.6, 74.0, 73.7, 72.1 (CH_2 Bn), 60.3 (CH_2 Et), 37.4, 36.1 (*C*H_2C=O), 37.0, 33.0 (C-1), 25.8 (C-3), 18.2, 16.2 (C_q TBS), 14.2 (CH_3 Et). MS (ESI): *m/z* = 617.5 $[M+H]^+$, 639.4 $[M+Na]^+$.

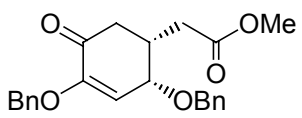


(3*S*, 4*S*, 5*R*, 6*S*)-4,5,6-Tris-benzyloxy-1-(*tert*-butyldimethyl-silyloxy)-3-(methoxycarbonylmethyl)-cyclohex-1-ene (21): To a 1.0 M solution of $LiClO_4$ in Et_2O (110 mL) was added compound **18** (4.575 g, 11.04 mmol) at rt. This mixture was stirred until the ketone dissolved completely, followed by the addition of (*tert*-butyldimethylsilyloxy)-1-methoxyethene (7.23 mL, 33.11 mmol, 3.0 equiv.). Stirring was continued for 30 min after which TLC analysis (EtOAc/toluene 1:19) indicated complete disappearance of starting material together with the formation of a higher running spot. After quenching the reaction, by addition of sat. aq. $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted once more with Et_2O. All ether layers were combined, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/toluene 1:49) gave methylester **21** (6.53 g, 10.83 mmol, 98%) as single stereoisomer. $[\alpha]_D^{20}$ –18.9 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.21 (m, 15H, CH_{arom}), 4.94 (d, 1H, $J_{2,3}$ = 5.8 Hz, H-2), 4.85 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.82 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.71 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.70 (d, 1H, *J* = 11.0 Hz, CH Bn), 4.63 (s, 2H, CH_2 Bn), 4.00 (d, 1H, $J_{6,5}$ = 6.2 Hz, H-6), 3.83 (dd, 1H, $J_{5,4}$ = 9.8 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.72 (dd, 1H, $J_{4,3}$ = 5.6 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 3.59 (s, 3H, CH_3 OMe), 3.10 (ddt, 1H, $J_{3,CH}$H = $J_{3,4}$ = 5.6 Hz, $J_{3,CH}$*H* = 8.9 Hz, $J_{3,2}$ = 5.8 Hz, H-3), 2.79 (dd, 1H, J_{CH}H,CH*H* = 15.8 Hz, J_{CH}H,3 = 5.6 Hz, C*H*H), 2.26 (dd, 1H, $J_{CHH,CH}$H = 15.8 Hz, $J_{CHH,3}$ = 8.9 Hz, CH*H*), 0.92 (s, 9H, 3× CH_3 *t*-Bu), 0.16 (s, 3H, CH_3 TBS), 0.15 (s, 3H, CH_3 TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.6 (C=O), 149.3 (C-1), 138.4, 138.1 (3× C_q Bn), 128.6, 128.2, 128.1, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0 (CH_{arom}), 106.0 (C-2), 80.6 (C-6), 79.4 (C-5), 77.8 (C-4), 74.0, 73.5, 71.1 (3× CH_2 Bn), 50.8 (CH_3 OMe), 35.5 (*C*H_2CO), 32.7 (C-3), 25.4 (CH_3 *t*-BuSi), 17.8 (C_q *t*-BuSi), -4.7, -4.9 (2× CH_3 SiMe). IR (thin film): 3032, 2928, 2858, 2359, 1734, 1661, 1454, 1205, 1094, 839, 696 cm^{-1}. MS (ESI): *m/z* = 603.4 $[M+H]^+$, 625.4 $[M+Na]^+$. HRMS (ESI): calcd for $[C_{36}H_{46}O_6Si+NH_4]^+$ 620.3407. Found 620.3439.

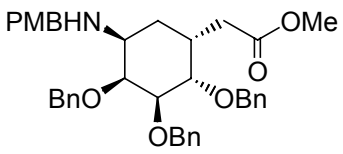


(2*S*, 3*R*, 4*S*, 5*R*)-2,3,4-Tris-benzyloxy-5-(methoxycarbonyl-methyl)-cyclohexanone (22): To a solution enol ether **21** (0.301 g, 0.50 mmol) dissolved in THF (2.0 mL) and pyridine (0.5 mL), was added HF·pyridine (70/30 v/v, 0.25 mL). After 30 min water and Et_2O were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted once more with Et_2O. All organic layers were combined, dried ($MgSO_4$), filtered and concnetrated. Purification of the residue by column chromatography (EtOAc/PE 1:9 to 1:4) gave ketone **22** (0.242 g, 0.495 mmol) in a yield of 99%. $[\alpha]_D^{20}$ –60.6 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.7.22 (m, 15H, CH_{arom}), 4.86 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.75 (d, 1H, *J* = 11.1 Hz, CH Bn), 4.71 (d, 1H, *J* = 11.1 Hz, CH Bn), 4.60 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.50 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.49 (d, 1H, *J* = 11.4 Hz, CH Bn), 4.09 (d, 1H, *J* = 6.9 Hz, H-2), 3.80-3.75 (m, 2H, H-3, H-4), 3.59 (s, 3H, CH_3 OMe), 2.95-2.87 (m, 1H, H-5), 2.55 (dd, 1H, *J* = 5.5 Hz, *J* = 16.2 Hz, C*H*H), 2.46 (dd, 1H, *J* = 6.0 Hz, *J* = 15.4 Hz, H-6a), 2.40 (dd, 1H, *J* = 6.7 Hz, *J* = 15.4 Hz, H-6b), 2.15 (dd, 1H, *J* = 8.9 Hz, *J* = 16.2 Hz, CH*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 205.7 (C-1),

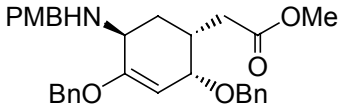
172.3 (C=O CO_2Me), 137.9, 137.6, 137.5 (3× C_q Bn), 128.2-127.6 (CH_{arom}), 85.0, 81.6, 79.0 (C-2, C-3, C-4), 74.1, 73.0, 71.8 (3× CH_2 Bn), 51.6 (CH_3 OMe), 40.2 (C-6), 33.7 (*C*H_2CO), 32.0 (C-5). IR (thin film): 1730, 1497, 1454, 1437, 1352, 1205, 1092, 1074, 1051, 1026, 908, 731, 696, 611 cm^{-1}. MS (ESI): *m/z* = 489.2 $[M+H]^+$, 511.5 $[M+Na]^+$. HRMS (ESI): calcd for $[C_{30}H_{32}O_6+NH_4]^+$ 506.2543. Found 506.2543.



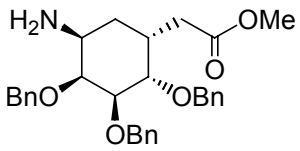
(4*S*, 5*R*)-2,4-Bis-benzyloxy-5-(methoxycarbonylmethyl)-cyclohex-2-en-1-one (23): Upon storage, ketone **22** degraded into unsaturated ketone **23**: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.38-7.22 (m, 15H, CH_{arom}), 5.86 (d, 1H, $J_{3,4}$ = 5.1 Hz, H-3), 4.89 (d, 1H, *J* = 13.2 Hz, CH Bn), 4.82 (d, 1H, *J* = 13.2 Hz, CH Bn), 4.48 (d, 1H, *J* = 11.7 Hz, CH Bn), 4.41 (d, 1H, *J* = 11.7 Hz, CH Bn), 4.24 (dd, 1H, $J_{4,5}$ = 2.9 Hz, $J_{4,3}$ = 5.1 Hz, H-4), 3.65 (s, 3H, CH_3 OMe), 2.81-2.29 (m, 5H, H-5, H-6a, H-6b, C*H*H, CH*H*). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 192.4 (C-1), 172.1 (C=O CO_2Me), 150.3 (C-2), 137.6, 135.3 (2× C_q Bn), 128.2, 127.9, 127.8, 127.6, 127.3, 126.8, 126.4 (CH_{arom}), 115.1 (C-3), 71.5 (C-4), 70.3, 69.1 (2× CH_2 Bn), 51.2 (CH_3 OMe), 39.3 (C-6), 35.2 (C-5), 34.3 (*C*H_2CO_2Me). IR (thin film): 2363, 2343, 1734, 1697, 1624, 1497, 1456, 1261, 1204, 1140, 1067, 1028, 999, 739, 698, 623 cm^{-1}. MS (ESI): *m/z* = 403.1 $[M+Na]^+$.



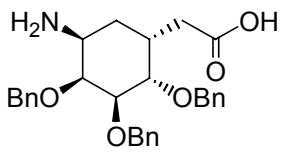
(1*S*, 2*R*, 3*S*, 4*R*, 6*S*)-1,2,3-Tris-benzyloxy-6-(*para*-methoxy-benzylamino)-4-(methoxycarbonylmethyl)-cyclohexane (24): Enol ether **21** (0.602 g, 1.00 mmol) was cleaved using HF·pyridine, following the procedure described above for the preparation of **22**. After work up, without further purifications, intermediate **22** was dissolved in 1,2-DCE (10 mL), followed by addition of $Na(OAc)_3BH$ (0.318 g, 1.50 mmol, 1.5 equiv.). Next *p*-$MeOBnNH_2$ (0.261 mL, 2.0 mmol, 2.0 equiv.) and acetic acid (57.7 µL, 1.0 mmol, 1.0 equiv.) were added. The reaction was stirred for 1 h at rt after which TLC analysis (EtOAc/PE 3:7) indicated the complete disappearance of starting material along with the formation of three lower running spots. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and diluted with DCM. The organic phase was collected, dried ($MgSO_4$), concentrated and purified by column chromatography (MeOH/DCM 1:99) resulting in protected CSAA **24** (0.311 g, 0.51 mmol) in a yield of 51% over two steps. $[\alpha]_D^{20}$ +17.0 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, MeOD, T = 333K): δ 7.36-7.23 (m, 15H, CH_{arom} Bn), 7.20-7.15 (m, 2H, CH_{arom} PMB), 6.84-6.80 (m, 2H, CH_{arom} PMB), 4.68 (s, 2H, CH_2 Bn), 4.66 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.55 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.47 (s, 2H, CH_2 Bn), 3.89-3.86 (m, 1H, H-1), 3.85-3.82 (m, 1H, H-3), 3.78-3.75 (m, 1H, H-2), 3.75 (s, 3H, CH_3 OMe PMB), 3.61 (s, 3H, CH_3 OMe), 3.02-2.96 (m, 1H, H-6), 2.69-2.60 (m, 1H, H-4), 2.53 (dd, 1H, *J* = 7.2 Hz, $J_{CHH,CHH}$ = 15.4 Hz, *CH*H), 2.20 (dd, 1H, *J* =7.4 Hz, $J_{CHH,CHH}$ = CH*H*), 1.72 (ddd, 1H, *J* = 4.1 Hz, *J* = 6.8 Hz, $J_{5a,5b}$ = 13.5 Hz, H-5a), 1.58 (ddd, 1H, *J* = 3.8 Hz, *J* = 9.0 Hz, $J_{5b,5a}$ = 13.5 Hz, H-5b). IR (thin film): 2872, 1732, 1611, 1510, 1454, 1246, 1099, 737, 698 cm^{-1}. MS (ESI): *m/z* = 610.4 $[M+H]^+$, 1220.0 $[2M+H]^+$. HRMS (ESI): calcd for $[C_{38}H_{43}NO_6+H]^+$ 610.3169. Found 610.3213.



(3*S*, 4*R*, 6*S*)-1,3-Bis-benzyloxy-6-(*para*-methoxybenzyl-amino)-4-(methoxycarbonylmethyl)-cyclohex-1-ene (25): Enamine **25** (73.0 mg, 0.15 mmol, 15% over two steps), was formed as a minor product in the procedure described above, going from compound **21** to amine **24**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.37-7.22 (m, 10H, CH_{arom} Bn), 7.20-7.16 (m, 2H, CH_{arom} PMB), 6.84-6.78 (m, 2H, CH_{arom} PMB), 5.09 (d, 1H, $J_{2,3}$ = 5.4 Hz, H-2), 4.75 (s, 2H, CH_2 Bn), 4.61 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.40 (d, 1H, *J* = 11.8 Hz, CH Bn), 3.97 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{3,2}$ = 5.4 Hz, H-3), 3.77-3.67 (m, 2H, CH_2 PMB), 3.76 (s, 3H, CH_3 OMe PMB), 3.64 (s, 3H, CH_3 OMe), 3.47 (dd, 1H, *J* = 6.4 Hz, *J* = 10.1 Hz, H-6), 2.65 (dd, 1H, *J* = 7.4 Hz, $J_{CHH,CHH}$ = 16.0 Hz, *CH*H), 2.49 (dd, 1H, *J* = 7.0 Hz, $J_{CHH,CHH}$ = 16.0 Hz, CH*H*), 2.24-2.15 (m, 1H, H-4), 2.00-1.88 (m, 1H, H-5a), 1.86-1.79 (m, 1H, H-5b). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.5 (C=O), 158.8 (C_q OMe PMB), 158.4 (C-1), 139.1, 136.6 (2× C_q Bn), 132.3 (C_q PMB), 129.3 (CH_{arom} PMB), 128.4. 128.1. 127.9, 127.5, 127.2 (CH_{arom} Bn), 113.6 (CH_{arom} PMB), 96.6 (C-3), 72.0 (C-4), 69.8, 69.1 (2× CH_2 Bn), 55.1 (CH_3 OMe PMB), 54.9 (C-6), 51.3 (CH_3 OMe), 49.3 (CH_2 PMB), 36.4 (CH_2CO_2), 34.9 (C-4), 29.5 (C-5). MS (ESI): *m/z* = 502.3 $[M+H]^+$, 1003.6 $[2M+H]^+$.

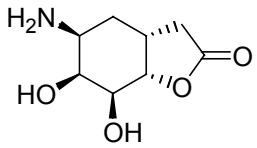


(1*S*, 2*R*, 3*S*, 4*R*, 6*S*)-6-Amino-1,2,3-tris-benzyloxy-4-(methoxycarbonylmethyl)-cyclohexane (26): To a solution of compound **24** (0.476 g, 0.781 mmol) in a mixture of acetonitrile (6 mL) and water (3 mL) was added CAN (1.07 g, 1.95 mmol, 2.5 equiv.). This orange two phase system was vigourously stirred for 24 h. After addition of sat. aq. $NaHCO_3$ followed by dilution with EtOAc, the aqueous phase was separated and washed twice with EtOAc. All organic layers were combined, dried ($MgSO_4$) and concentrated. Purification of the residue by silica gel chromatography (MeOH/DCM 1:19) gave title compound **26** as a yellow oil (0.214 g, 0.437 mmol, 56%). ^{1}H-NMR (400 MHz, MeOD): δ 7.39-7.22 (m, 15H, CH_{arom}), 4.67 (d, 1H, *J* = 12.3 Hz, CH Bn), 4.62 (d, 1H, *J* = 12.3 Hz, CH Bn), 4.59 (s, 2H, CH_2 Bn), 4.54 (d, 1H, *J* = 12.1 Hz, CH Bn), 4.48 (d, 1H, *J* = 12.1 Hz, CH Bn), 3.88 (ddd, 1H, *J* = 1.2 Hz, *J* = 3.1 Hz, $J_{2,1}$ = 4.3 Hz, H-2), 3.78 (dd, 1H, $J_{1,2}$ = 3.1 Hz, *J* = 4.4 Hz, H-1), 3.71 (m, 1H, H-3), 3.65-3.55 (m, 1H, H-6), 3.63 (s, 3H, CH_3 OMe), 2.52 (m, 1H, H-4), 2.45 (dd, $J_{CHH,4}$ = 7.7 Hz, $J_{CHH,CHH}$ = 15.8 Hz, C*H*H), 2.27 (dd, 1H, $J_{CHH,4}$ = 6.5 Hz, $J_{CHH,CHH}$ = 15.8 Hz, CH*H*), 1.80 (m, 2H, H-5a, H-5b). MS (ESI): *m/z* = 490.3 $[M+H]^+$, 979.7 $[2M+H]^+$.

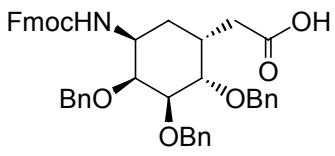


(1*S*, 2*R*, 3*S*, 4*R*, 6*S*)-6-Amino-1,2,3-tris-benzyloxy-4-carboxymethyl-cyclohexane (27): To a solution of ester **26** (95 mg, 0.194 mmol) in 1,4-dioxane (2.0 mL), was added an aq. solution of LiOH (0.5 mL, 1.0 M). After 3 h, TLC analysis (MeOH/DCM 15:85) showed complete conversion of starting material into a lower running spot. The mixture was neutralised with 1.0 M aq. HCl to pH 7 and extracted thoroughly with EtOAc (3 times). The combined organic phases were dried ($MgSO_4$) and concentrated to give amino acid **27** (92 mg, 0.194 mmol) in quantitative yield as a white solid. ^{1}H-NMR (400 MHz,

MeOD): δ 7.33-7.26 (m, 15H, CH_{arom}), 4.63 (d, 1H, *J* =12.0 Hz, CH Bn), 4.57 (d, 1H, *J* = 12.0 Hz, CH Bn), 4.53 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.43 (d, 1H, *J* = 11.9 Hz, CH Bn), 4.40 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.27 (d, 1H, *J* = 11.8 Hz, CH Bn), 3.85-3.82 (ddd, 1H, *J* = 1.3 Hz, *J* = 2.9 Hz, $J_{2,1}$ = 4.3 Hz, H-2), 3.76 (dd, 1H, *J* = 3.1 Hz, $J_{1,2}$ = 4.3 Hz, H-1), 3.76 (m, 1H, H-3), 3.70 (dd, 1H, *J* = 3.6 Hz, *J* = 7.3 Hz, H-6), 2.51 (m, 1H, H-4), 2.42 (dd, 1H, $J_{CH\mathit{H},4}$ = 7.2 Hz, $J_{CH\mathit{H},CH\mathit{H}}$ = 16.0 Hz, *CH*H), 2.29 (1H, dd, $J_{CHH,4}$ = 6.6 Hz, $J_{CHH,CH\mathit{H}}$ = 16.0 Hz, CH*H*), 1.99-1.92 (dddd, 1H, *J* = 1.2 Hz, *J* = 3.1 Hz, *J* = 4.1 Hz, $J_{5a,5b}$ = 14.8 Hz, H-5a), 1.86-1.77 (dd, 1H, *J* = 3.8 Hz, $J_{5b,5a}$ = 14.8 Hz, H-5b). MS (ESI): *m/z* = 476.2 $[M+H]^+$.

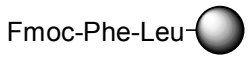


(1*S*, 2*S*, 3*S*, 4*S*, 6*R*)-4-Amino-2,3-dihydroxy-9-oxa-bicyclo-[4,3,0]-nonane-8-one (29): Amino acid **27** (41 mg, 0.0842 mmol) was dissolved in a mixture of water/*t*-BuOH (1:1, 4.0 mL) and aq. acetic acid (85 µL, 1.0 M) was added. This solution was degassed, a catalytic ammount of Pd/C was added and the solution was degassed again. The reaction was stirred under a H_2 atmosphere for 17 h after which TLC analysis (*n*-BuOH/water/EtOAc/HOAc 1:1:1:1) showed complete conversion of starting material into a more polar product. The mixture was filtered over Glass Fiber (GF/2A Whatman) and concentrated. The residue was filtered over a short plug of silica and the filtrate was concentrated to afford lactone **29** in a quantitative yield (16 mg, 0.084 mmol). $[\alpha]_D^{20}$ +5.2 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, MeOD): δ 4.58 (t, 1H, $J_{1,2}$ = $J_{1,6}$ = 7.4 Hz, H-1), 3.97 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 2.6 Hz, H-3), 3.75 (dd, 1H, $J_{2,1}$ = 7.6 Hz, $J_{2,3}$ = 2.6 Hz, H-2), 3.55 (ddd, 1H, $J_{4,3}$ = 2.6 Hz, $J_{4,5a}$ = 10.5 Hz, $J_{4,5b}$ = 4.7 Hz), 2.97 (ddddd, 1H, $J_{6,1}$ = 7.2 Hz, $J_{6,5a}$ = 6.4 Hz, $J_{6,5b}$ = 4.2 Hz, $J_{6,7a}$ = 10.5 Hz, $J_{6,7b}$ = 8.6 Hz, H-6), 2.56 (dd, 1H, $J_{7a,6}$ = 8.6 Hz, $J_{7a,7b}$ = 17.4 Hz, H-7a), 2.51 (dd, 1H, $J_{7b,6}$ = 10.5 Hz, $J_{7b,7a}$ = 17.4 Hz, H-7b), 2.12 (ddd, 1H, $J_{5a,4}$ = 10.5 Hz, $J_{5a,5b}$ = 14.2 Hz, $J_{5a,6}$ = 6.3 Hz, H-5a), 1.87 (ddd, 1H, $J_{5b,4}$ = 4.7 Hz, $J_{5b,5a}$ = 14.2 Hz, $J_{5b,6}$ = 4.4 Hz, H-5b). IR (thin film): 3358, 2930, 1668, 1520, 1186, 1136, 1107, 1059, 1016, 843, 800, 723, 638, 606 cm^{-1}. HRMS (ESI): calcd for $[C_8H_{13}NO_4+H]^+$ 188.0923. Found 188.0920.



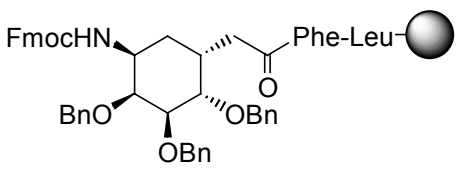
(1*S*, 2*R*, 3*S*, 4*R*, 6*S*)-*N*-(9-Fluorenylmethoxycarbonyl)-6-amino-1,2,3-tris-benzyloxy-4-carboxymethyl-cyclohexane (5): To a suspension of amino acid **27** (0.194 mmol) in dioxane (0.5 mL) and sat. aq. $NaHCO_3$ (2.0 mL) was added Fmoc-OSu (85 mg, 0.252 mmol, 1.3 equiv). After stirring for 17 h, TLC analysis (MeOH/DCM 1:19) revealed complete consumption of starting material into a higher running spot. Water and dioxane were added to the suspension and the resulting solution was acidified with 1.0 M aq. HCl to pH 5. The mixture was diluted with EtOAc, the organic layer was separated and the aqueous layer extracted twice with EtOAc. All organic layers were combined, dried ($MgSO_4$), filtered and concentrated. After purification by silica gel column chromatography (EtOAc/PE 1:1 + 1.0 % HOAc) carbamate **5** was obtained (0.124 g, 0.178 mmol, 92%). $[\alpha]_D^{20}$ +25.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (600 MHz, C_6D_6): δ 7.56-7.54 (m, 4H, CH_{arom} Fmoc), 7.37-7.30 (m, 4H, CH_{arom} Fmoc), 7.22-7.06 (m, 15H, CH_{arom} Bn), 6.79 (bs, 1H, NH), 4.64 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.60 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.58

(m, 1H, H-6), 4.54 (d, 1H, *J* = 11.8 Hz, CH Bn), 4.50 (dd, 1H, *J* = 10.6 Hz, *J* = 7.3 Hz, C*H*H, CH_2Fmoc), 4.27 (dd, 1H, *J* = 10.6 Hz, *J* = 7.3 Hz, CH*H* CH_2Fmoc), 4.22 (m, 1H, CH Bn), 4.16 (m, 3H, CH_2 Bn, CH Fmoc), 3.84 (m, 1H, H-2), 3.74 (m, 1H, H-3), 3.71 (m, 1H, H-1), 2.69 (m, 1H, H-4), 2.40 (m, 1H, C*H*H CH_2CO_2H), 2.11 (m, 1H, CH*H* CH_2CO_2H), 1.92 (m, 1H, H-5a), 1.60 (m, 1H, H-5b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.6 (C=O CO_2H), 156.5 (C=O Fmoc), 144.1, 141.2 (2× C_q Fmoc), 138.3, 137.9, 137.8 (3× C_q Bn), 129.0, 128.5, 128.4, 128.4, 127.9, 127.8, 127.6, 127.5, 127.0 (CH_{arom} Bn), 125.3, 119.8 (CH_{arom} Fmoc), 77.3 77.0, 76.7 (C-1, C-2, C-3), 73.8, 72.6, 70.4 (3× CH_2 Bn), 66.8 (CH_2 Fmoc), 47.8 (C-6), 47.2 (CH Fmoc), 30.7 (*C*H_2CO_2), 29.7 (C-4), 28.2 (C-5). IR (thin film): 3032, 2924, 2870, 2363, 2341, 1705, 1514, 1452, 1248, 1055, 739, 698 cm^{-1}. MS (ESI): *m/z* = 698.5 $[M+H]^+$, 1395.6 $[2M+H]^+$. HRMS (ESI): calcd for $[C_{44}H_{43}NO_7+NH_4]^+$ 715.3383. Found 715.3370.

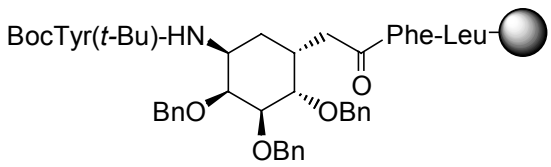


Fmoc-Phe-Leu-Wang resin (31): *Loading of resin*. Commercially available Wang resin **30** (0.96 mmol/g, 1.79 g) was allowed to swell in DCM (40 mL). A solution was prepared of DIC (1.07 mL, 0.87 g, 6.88 mmol, 4.0 equiv.), Fmoc-Leu-OH (2.43 g, 6.88 mmol, 4.0 equiv.) and DMAP (cat.) in DCM. The mixture was left overnight with occasional shaking. The resin was filtered, washed subsequently with DMF and DCM and dried (air). The loading was determined by treatment of the dried resin (2.3 mg) with a solution of 20% piperidine/DMF (1.0 mL). After stirring for 10 min followed by dilution to 10.00 mL with EtOH the absorption of the solution was measured at 300 nm. The loading was calculated to be 0.49 mmol/g, using the formula: Loading (mmol/g) = $[A_{300}]$*10/[7.8*m].

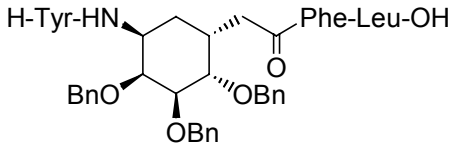
Peptide coupling: Fmoc-Leu-Wang-resin 1.00 g (0.49 mmol) was used and treated with 10 mL 20% piperidine/DMF (3× 10 min) to effect Fmoc cleavage. The resin was filtered, washed (DMF and DCM) and swollen in DMF. The resin was treated with a solution of Fmoc-Phe-OH (0.75 g, 1.94 mmol, 4.0 equiv.), HCTU (0.80 g, 1.94 mmol, 4.0 equiv.) and DiPEA (0.64 mL, 3.88 mmol, 8.0 equiv.) in DMF (5.0 mL). After shaking the mixture for 1h, the resin was filtered, rinsed with DMF. This procedure was repeated twice to ensure complete coupling indicated by a negative Kaiser test. Any unreacted amines were capped using a solution of 0.5 M Ac_2O and 0.125 M DiPEA in DMF (50 mL, 5 min). After filtration and washing with DMF and DCM, the resin was filtered and dried by an air flow.



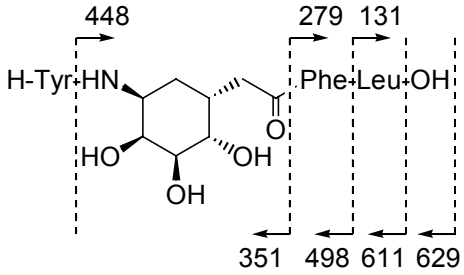
Fmoc-CSAA-$(OBn)_3$-Phe-Leu-Wang resin (32): Resin **31** (70.0 mg, 34.0 μmol) was swollen in DMF and a solution of 20 % piperidine/DMF (3× 10 min) was used for Fmoc deprotection. A solution of CSAA **5** (47.9 mg, 68.7 μmol, 2.0 equiv.) in DMF (700 μL) was prepared. Next, the carboxylate in this solution (350 μL) was preactivated for 30 sec. with HATU (12.0 mg, 32.3 μmol, 0.95 equiv.) and DiPEA (15.0 μL, 84.9 μmol, 2.5 equiv) and the mixture was subsequently added to the resin and shaken for 10 min. After filtration of the resin followed by rinsing with DMF, this coupling procedure was repeated once more. After a negative Kaiser test revealed complete consumption of free amines, the resin was washed with DMF, DCM and dried (air flow).



Boc-Tyr(*t*-Bu)-CSAA-(OBn)$_3$-Phe-Leu-Wang resin (33): Resin **32** was swollen in DMF followed by Fmoc cleavage using a 20% piperidine/DMF (3× 10 min), washed with DMF, DCM, filtered and dried (air). Boc-Tyr(*t*-OBu)-OH (50.6 mg, 0.15 mmol, 4.4 equiv.) was coupled using HCTU (62.1 mg, 0.15 mmol, 4.4 equiv.) and DiPEA (49.6 µL, 0.300 mmol, 8.8 equiv.) in DMF and shaken for 2 h. A negative Kaiser test indicated a complete coupling of the free amines. The resin was filtered, washed with DMF and DCM and air dried.



H-Tyr-CSAA-(OBn)$_3$-Phe-Leu-OH (34): Cleavage of the peptide from the resin along with the removal of the *t*-Bu and Boc group was effected transferring immobilised peptide **33** into a glass tube followed by the addition of a mixture of TFA/TIS/water (95:2.5:2.5, 1.0 mL). After shaking for 15 min, the mixture was filtered, washed DMF, DCM and dried. Purification by silica gel chromatography (MeOH/DCM 1:9) gave title compound **34** (29.4 mg) as a white solid. LC/MS (50-90% acetonitrile/water), R_t 10.02 min. MS (ESI): *m/z* = 899.9 $[M+H]^+$, 1799.4 $[2M+H]^+$.



H-Tyr-CSAA-Phe-Leu-OH (35): Compound **34** (16.2 mg) was dissolved in *t*-BuOH (1.0 mL) and water (1.0 mL). and the resulting solution was degassed. A catalytic ammount of Pd/C was added and after degassing the solution for a second time the reaction was stirred under a hydrogen atmosphere. After 15 h, TLC analysis (MeOH/DCM 15:85) indicated complete conversion of starting material into a lower running spot. The reaction mixture was filtered over Celite and the filtrate was concentrated to give Leu-enkephalin analogue **35** in a quantitative yield. After HPLC purification (18-30% acetonitrile/water) an analytical sample was obtained. LC/MS (10-40% acetonitrile/water), R_t 14.02 min. MS (ESI): *m/z* = 629.5 $[M+H]^+$, 651.4 $[M+Na]^+$, 1257.8 $[2M+H]^+$. ^{1}H NMR (600 MHz, DMSO d_6, T = 313K): δ 9.25 (s, 1H), 8.09 (d, 1H, *J* = 7.2 Hz), 7.99 (bs, 1H), 7.84 (d, 1H, *J* = 7.2 Hz), 7.32-6.91 (m, 9H), 6.71-6.68 (m, 2H), 4.62 (m, 1H), 4.48 (m, 1H), 4.20 (m, 1H), 4.04-3.93 (m, 2H), 3.69 (m, 1H), 3.59 (m, 1H), 3.35-3.21 (m, 2H), 3.08-3.00 (m, 2H), 2.81 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 2.31 (m, 1H), 2.23 (m, 1H), 1.95 (m, 1H), 1.77-1.74 (m, 2H), 1.75 (m, 1H), 1.71-1.66 (m, 2H), 0.89 (m, 6H). IR (thin film): 3275, 2963, 2361, 2341, 1678, 1015 cm^{-1}. HRMS (ESI): calcd for $[C_{32}H_{44}N_4O_9+H]^+$ 629.3181. Found 629.3178. Additional proof of the amino acid sequence in penatpeptide **35** was obtained by use of ESI (HRMS-MS) mass spectrometry.

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Chapter 5

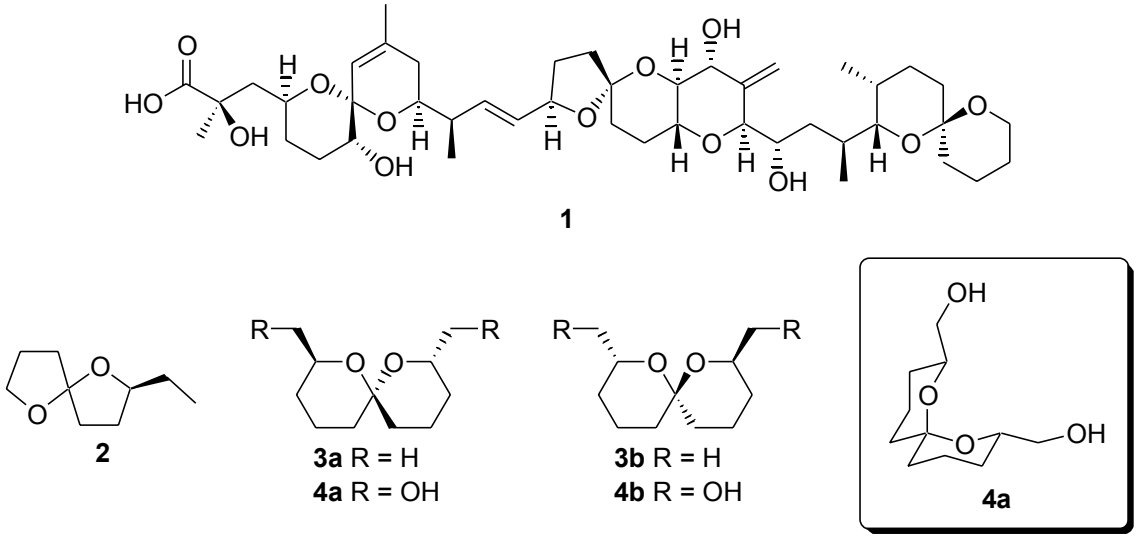
Claisen Self-Condensation/Decarboxylation as the Key Steps in the Synthesis of C_2-Symmetrical 1,7-Dioxaspiro[5.5]undecanes[1]

Introduction

Spiroketals are found as structural entities in many biologically active compounds isolated from a variety of natural sources, including insects, microbes, fungi, plants and marine organisms.[2] The vast majority of the spiroketal frameworks found in natural products are composed of spiro[5.5], spiro[4.5] and spiro[4.4] ring systems (see for representative examples Figure 1). The cytotoxic polyether okadaic acid (**1**) was isolated in 1981 from two marine sponges,[3] and is associated with diarrhetic shellfish poisoning.[4] It acts as an inhibitor of protein phosphatases.[5] The first total synthesis of okadaic acid, which contains two 1,7-dioxaspiro[5.5]undecane ring systems and one 1,6-dioxaspiro[4.5]decane fragment, was accomplished in 1986 by Isobe *et al*.[6] The first spiroketal identified from insects is chalcogran (2-ethyl-1,6-dioxaspiro[4.4]nonane, **2**). It was isolated as a mixture of isomers from the bark beetle *Pityogenes chalcographus* and found to be the principle component of the aggregation pheromone.[7] One of the most widespread spiroketal compounds found in nature is 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**3a,b**), present in several species of fruit flies, bees, wasps, ants

and beetles.[8] Several reports appeared in literature describing the synthesis of 2,8-dihydroxymethyl-1,7-dioxaspiro[5.5]undecanes (**4a,b**), versatile intermediates for the construction of 6,6-spiroketals as prevalent structural element in many natural products, but also as starting point for the development of natural product derived compound libraries.[9] For example, spiroketal **4b** has been evaluated on its biological activity such as inhibition of microtubule assembly and induction of apoptosis in human breast cancer cells.[10]

Figure 1



The conformational preference of substituted 1,7-dioxaspiro[5.5]undecane ring systems is influenced by stereoelectronic effects, steric interactions and, to a lesser extend, internal hydrogen bonding.[11] The thermodynamically most stable spiroketal will adopt a configuration in which substituents reside in equatorial positions and result in a ketal function with maximum stability (double anomeric effect). When both these stabilising factors are present a confident prediction of the molecular conformation can be made (e.g. **4a**), however there are numerous examples in which steric factors outweigh the anomeric effect and vise versa, resulting in mixtures of diastereomers at the spiro carbons. These stabilising factors are less consistent and predictable in the formation of dioxaspiro[4.4] (e.g. **2**) and dioxaspiro[4.5] ring systems.

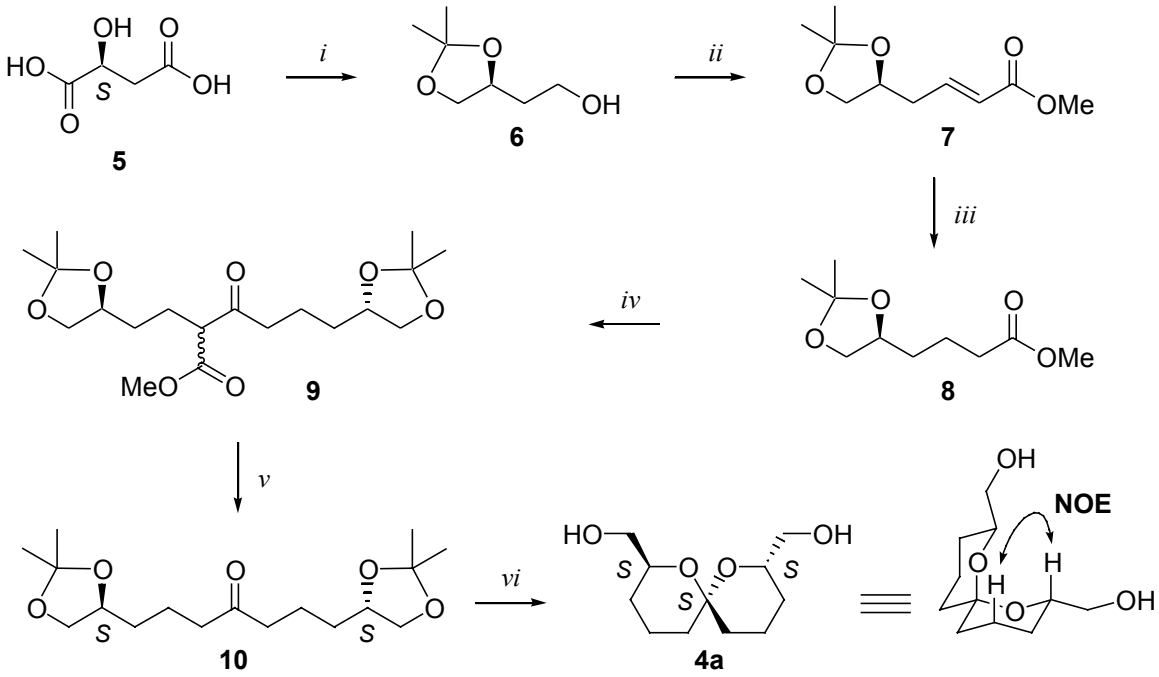
The vast majority of synthetic efforts in the preparation of spiroketal entities is focussed on the general ring systems depicted in Figure 1. Strategies towards spiroketal synthesis are based on two general approaches. The most common route is the intramolecular acid-catalysed ketalisation of dihydroxyketones or equivalents thereof. The second approach makes use of a preformed ring, followed by the addition of a carbon chain containing the necessary oxygen function to effect cyclisation. Main focus in all strategies concerns the installation of the spiro center from a ketone. Several representative examples to obtain the requisite carbonyl source, destined to be the spiro carbon, involve the use of nucleophilic additions to lactones,[12] 1,3-dithianes,[13] dimethylhydrazones,[14] nitroalkanes,[15] aldol condensation products[16] and hetero Diels-Alder reactions.[17] Claisen self-condensation of appropriately functionalised hydroxy esters, followed by decarboxylation and spiroketal formation, presents an efficient alternative for the preparation of C_2-symmetrical spiroketals, including **4a**. Rather surprisingly, this strategy has not been fully exploited to date.[18]

In this chapter the synthesis of a set of chiral C_2-symmetrical 1,7-dioxaspiro[5.5]undecane ring systems is reported. Key to this strategy is the realisation that suitable dihydroxyketone precursors amenable to acid-catalysed spiroketalisation are readily available via Claisen self-condensation of chiral, protected hydroxy-esters, followed by decarboxylation.

Results and discussion

As a first example, the synthesis of spiroketal **4a** commences with reduction of the carboxylate functions of (*S*)-malic acid (**5**) with borane-methyl sulfide complex followed by protection of the vicinal diol as the isopropylidene acetal, providing protected (*S*)-butanetriol derivative **6** in 83% over two steps (Scheme 1).[19] The requisite ester function was installed by a sequential Swern oxidation/Wittig olefination procedure. Treatment of **6** with oxalylchloride, dimethyl sulfoxide and diisopropylethylamine in dichloromethane followed by chain elongation of the crude aldehyde using methyl (triphenylphosphoranylidene)acetate in dichloromethane, resulted in the formation of *E*-

Scheme 1

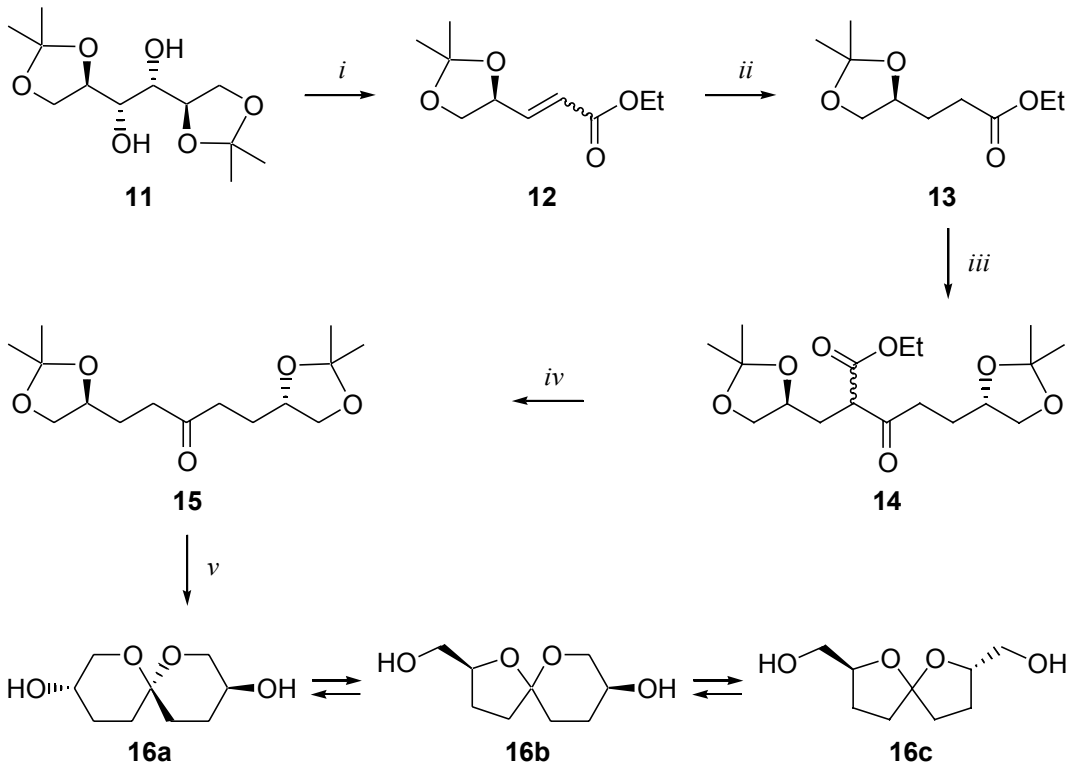


Reagents and conditions: *i*) a) $BH_3 \cdot Me_2S$, THF, 0 °C to rt, 15 h; b) acetone, *p*-TsOH, 17 h, rt, 83% (2 steps). *ii*) a) $(COCl)_2$, DMSO, DiPEA, CH_2Cl_2, -78 °C, 2 h; b) $Ph_3P{=}CHCO_2Me$ (1.4 equiv.), 0 °C to rt, 15 h, 81% (2 steps). *iii*) H_2, 10% Pd/C (cat.), EtOH, 24 h, rt, 88%. *iv*) LHMDS (1.0 M in hexanes, 2.5 equiv.), TMEDA (5.0 equiv.), THF, 0 °C, 2 h, 84%. *v*) LiCl (3.8 equiv.), DMSO, H_2O, reflux, 10 min, 94%. *vi*) HOAc/H_2O (3:2), rt, 90 min, quant.

alkene **7** in 81% yield. Hydrogenation of **7** over palladium on carbon afforded saturated ester **8** in 88%. Claisen self-condensation of **8** was effected by slow addition of excess lithium hexamethyldisilazane (LHMDS) and tetramethylethylenediamine (TMEDA) over a period of 2 hours at 0 °C, providing β-ketoester **9** in 84%.[18c] Decarboxylation of methyl ester **9** proceeded smoothly under the agency of lithium chloride and water in dimethyl sulfoxide[20] to give C_2-symmetrical ketone **10** in 94% yield. Unmasking of the diol functionalities by treatment with acid followed by intramolecular cyclisation led to the formation of spiroketal **4a** as the single isomer in quantitative yield. The conformation of **4a** was assigned based on NMR analysis through a NOE observed between the axial protons H2 and H4a.

Next, the use of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**11**) was investigated in the synthesis towards hydroxy substituted spiroketals **16** (Scheme 2). Periodate-assisted diol cleavage of **11**, immediately followed by Horner Wadsworth Emmons olefination, gave α,β-unsaturated ester **12** in 96% yield over two steps.[21] At this stage, in analogy with conditions described in Scheme 1, saturation of the double bond in **12** was achieved through palladium-catalysed hydrogenation (94%). Claisen self-condensation of the resulting ester **13** produced β-ketoester **14** in 58%. Decarboxylation of **14** with the LiCl/water/DMSO system furnished ketone **15** in a yield of 92%. Acid

Scheme 2

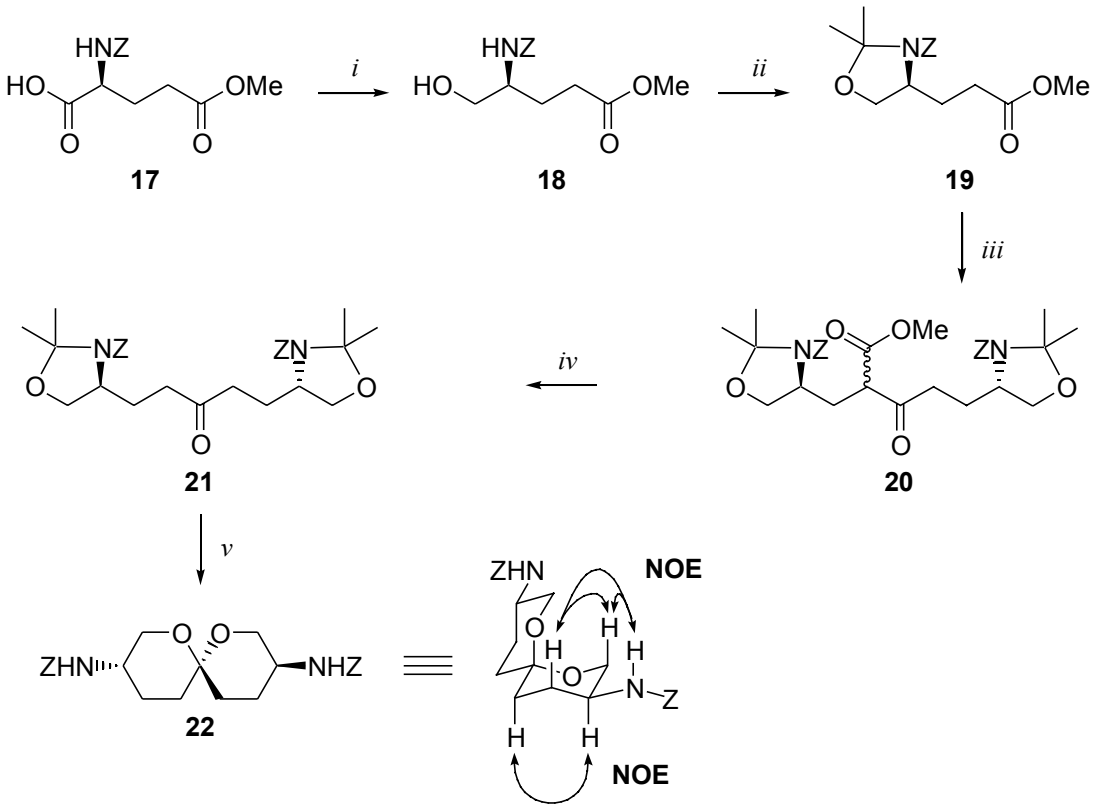


Reagents and conditions: *i*) a) $NaIO_4$ (1.2 equiv.), 5% aq. $NaHCO_3$, rt, 1 h; b) $(EtO)_2POCH_2COEt_2$ (4.2 equiv.), 6*M* aq. K_2CO_3, 0 °C to rt, 17 h, 96% (2 steps). *ii*) H_2, 10% Pd/C (cat.), EtOH, 45 min, 94%. *iii*) LHMDS (2.0 equiv.), TMEDA (4.0 equiv.), THF, 0 °C, 2.5 h, 58%. *iv*) LiCl (3.8 equiv.), DMSO, H_2O, reflux, 5 min, 92%. *v*) HOAc/H_2O (3:2), rt, 90 min, 76%.

mediated tandem deprotection/cyclisation resulted in the formation of a thermodynamic mixture of spiroketals (**16a-c**) in an overall yield of 76% (prolonged exposure to TFA did not result in a shift towards one of the individual spiroketals).

It was reasoned that replacement of the secondary hydroxyl groups in **15** with an amine functionality, as in **21**, would lead to 6,6-spiroketal **22** as the single product. In a two-step procedure the carboxylic acid moiety in glutamic acid derivative **17** was selectively reduced in the presence of the methyl ester (Scheme 3).[22] Treatment of **17**

Scheme 3



Reagents and conditions: *i*) a) NMM, $ClCO_2Et$, THF, -10 °C, 10 min; b) $NaBH_4$ (3.0 equiv.), 0 °C, 30 min, 83% (2 steps). *ii*) dimethoxypropane, acetone, *p*-TsOH, rt, 17 h, 94%. *iii*) LHMDS (1.0 M in hexanes, 2.5 equiv.), TMEDA (5.0 equiv.), THF, 0 °C, 3 h, 72%. *iv*) KOH (2.5 equiv.), MeOH/H_2O (1:1), reflux, 1 h, 79%. *v*) HOAc/H_2O (1:1), reflux, 3 h, 90%.

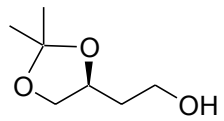
with *N*-methylmorpholine (NMM) and ethyl chloroformate yielded the corresponding mixed anhydride which was subsequently reduced with sodium borohydride furnishing alcohol **18** in 83%. Installation of the isopropylidene gave oxazolidine **19** (94%), of which Claisen self-condensation under the conditions previously described afforded β-ketoester **20** in a yield of 72%. Saponification of **20** at elevated temperature gave the corresponding β-ketoacid which immediately underwent decarboxylation yielding ketone **21** in 79% yield. Acidic removal of the isopropylidene protecting groups and concomitant cyclisation provided amine protected spiroketal **22** in a yield of 90%. The structure of compound **22** was established by NMR spectroscopy through observed NOEs indicated in Scheme 3.

Conclusion

In conclusion, a new route for the stereoselective synthesis of functionalised 1,7-dioxaspiro[5.5]undecane ring systems was developed. The C_2-symmetrical spiroketals were efficiently obtained via acid-catalysed cyclisation of different dihydroxyketones which are readily available from Claisen self-condensation of suitably substituted hydroxy esters.

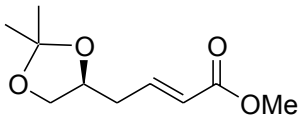
Experimental section

For general methods and materials see Chapter 2.

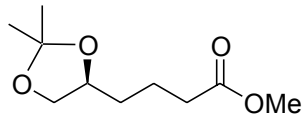


1,2-*O*-Isopropylidene-(*S*)-butane-1,2,4-triol (6): A solution of BH_3·DMS complex (58.6 mL, 0.610 mol, 3.05 equiv.) in freshly distilled THF (250 mL) was cooled to 0 °C. A solution of (*S*)-malic acid (26.82 g, 0.200 mol) in THF (150 mL) was added dropwise over 75 min to the borane mixture. After the addition was complete the cooling bath was removed and the reaction was stirred at rt for 15 h after which TLC analysis (MeOH/EtOAc 1:9) revealed complete consumption of starting material. Methanol (250 mL) was carefully added dropwise over 75 min and the solution was concentrated. The crude product was purified by flash chromatography (MeOH/EtOAc 1:9) to yield (*S*)-1,2,4-butanetriol (21.1 g, 0.199 mol). $[\alpha]_D^{20}$ –25.0 (*c* 1.0 MeOH). ^{13}C-NMR (50.0 MHz, MeOD): δ 70.4 (C-2), 67.3 (C-1), 59.7 (C-4), 36.8 (C-3). To a part of this triol (2.60 g, 24.50 mmol), dissolved in acetone (125 mL) was added *p*-TsOH (220 mg) and the solution was stirred overnight at rt. The mixture

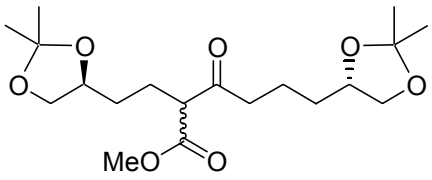
was neutralised with Et_3N and followed by concentration of the mixture. Purification by column chromatography (EtOAc/PE 1:3) gave **6** (2.96 g, 20.3 mmol, 83%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.27 (m, 1H, H-2), 4.09 (dd, 1H, $J_{1a,2}$ = 6.2 Hz, $J_{1a,1b}$ = 7.7 Hz, H-1a), 3.87 (t, 1H, $J_{4,3}$ = 5.8 Hz, H-4), 3.59 (t, 1H, $J_{1b,1a}$ = 7.7 Hz, H-1b), 2.65 (bs, 1H, OH), 1.81 (m, 1H, H-3), 1.42 (s, 3H, Me), 1.37 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 108.1 (C_q *i*Pr), 73.9 (C-2), 69.1 (C-1), 59.2 (C-4), 35.6 (C-3), 26.5, 25.3 (2× CH_3, *i*Pr).



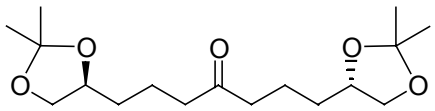
Methyl-(*S*)-(*E*)-5,6-isopropylidenedioxyhex-2-enoate (7): To a cold solution (-78 ºC) of oxalyl chloride (1.82 mL, 2.70 g, 21.2 mmol, 1.1 equiv.) in DCM (50 mL) was added dropwise a solution of DMSO (2.81 mL, 3.09 g, 39.6 mmol, 2.1 equiv.) in DCM (10 mL). After stirring for 10 min, a solution of **6** (2.82 g, 19.3 mmol) in DCM (15 mL) was added dropwise over 30 min. After stirring the resulting slurry for 40 min at –78 ºC, DiPEA (16.0 mL, 12.5 g, 96.6 mmol, 5.0 equiv.) was added slowely. The cooling bath was removed and the reaction mixture was stirred for 1 h. The yellow mixture was cooled to 0 ºC and treated with methyl (triphenylphosphoranylidene)acetate (9.03 g, 27.0 mmol, 1.4 equiv.). After stirring for 1 h the reaction mixture was allowed to reach rt overnight. The mixture was diluted with Et_2O and washed with water (three times). The organic phase was separated, washed with brine dried ($MgSO_4$) and concentrated. Purification by column chromatography (EtOAc/PE 1:6 to 1:3) gave alkene **7** (3.13 g, 15.6 mmol, 81% over two steps). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.78 (dt, 1H, $J_{3,4}$ = 7.3 Hz, $J_{3,2}$ = 15.3 Hz, H-3), 5.76 (dd, 1H, $J_{2,4}$ = 1.5 Hz, $J_{2,3}$ = 15.3 Hz, H-2), 4.06 (quintet, 1H, $J_{5,4} = J_{5,6a} = J_{5,6b}$ = 6.6 Hz, H-5), 3.90 (dd, 1H, $J_{6a,5}$ = 6.6 Hz, $J_{6a,6b}$ = 8.0 Hz, H-6a), 3.56 (s, 3H, CH_3 OMe), 3.42 (dd, 1H, $J_{6b,5}$ = 6.6 Hz, $J_{6b,6a}$ = 8.0 Hz, H-6b), 2.32 (m, 2H, H-4), 1.25 (s, 3H, CH_3 *i*Pr), 1.18 (s, 3H, CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 166.0 (C-1), 143.8 (C-3), 123.0 (C-2), 108.8 (C_q *i*Pr), 73.8 (C-5), 68.4 (C-6), 51.0 (CH_3 OMe), 36.1 (C-4), 26.4, 25.1 (2× CH_3 *i*Pr).



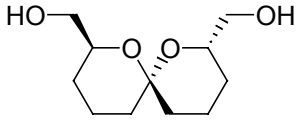
Methyl-(*S*)-5,6-isopropylidenedioxyhexanoate (8): A solution of alkene **7** (2.06 g, 10.3 mmol) dissolved in EtOAc (50 mL) was degassed. A catalytic ammount of Pd/C was added and after degassing the solution for a second time the reaction was stirred under a hydrogen atmosphere. After 24 h, TLC analysis (acetone/PE 1:9) showed complete conversion of starting material into a higher running spot. The mixture was filtered over Glass Fiber (GF/2A Whatman) and concentrated. The residue was filtered over a short plug of silica (acetone/PE 1:9) and the filtrate was concentrated to afford ester **8** (1.84 g, 9.11 mmol, 88%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.07 (m, 2H, H-6), 3.67 (s, 3H, CH_3 OMe), 3.52 (m, 1H, H-5), 2.37 (t, 1H, $J_{2,3}$ = 7.0 Hz, H-2), 1.66 (m, 4H, H-3, H-4), 1.41 (s, 3H, CH_3 *i*Pr), 1.35 (s, 3H, CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.0 (C-1), 108.1 (C_q *i*Pr), 75.1 (C-5), 68.8 (C-6), 50.8 (CH_3 OMe), 33.1, 32.5 (C-2, C-4), 26.4, 25.1 (2× CH_3 *i*Pr), 20.7 (C-3).



(2*S*, 5*R/S*, 10*S*)-1,2;10,11-Bis(isopropylidenedioxy)-5-methoxycarbonylundecan-6-one (9): Ester **8** (0.45 g, 2.23 mmol) was dissolved in THF (10 mL) and cooled to 0 °C under an argon atmosphere. A solution was prepared of LHMDS (5.57 mL, 5.57 mmol, 1.0 M in hexanes, 2.5 equiv.) and TMEDA (1.68 mL, 1.29 g, 11.1 mmol, 5.0 equiv) in THF (10 mL) and added dropwise to the cooled ester solution. After 2 h no starting material was present according to TLC analysis (EtOAc/PE 1:3). The reaction mixture was diluted with Et_2O and neutralised by addition of 1.0 M HCl. The layers were separated, the aqueous layer was washed with Et_2O. All organic layers were combined, washed against sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:3) afforded an isomeric mixture of β-ketoester **9** (0.348 g, 0.935 mmol, 84%). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 204.0, 203.9 (C-6), 169.7, 169.6 (C=O CO_2Me), 108.4, 108.3 (C_q *i*Pr), 75.3 (C-2, C-10), 68.8 (C-1, C-11), 58.0, 57.7 (C-5), 51.9 (CH_3 OMe), 41.4, 41.0 (C-7), 32.3, 31.0, 30.7 (C-3, C-9), 26.5, 25.2 (CH_3 *i*Pr), 24.1 (C-4), 19.3 (C-8). IR (thin film): 1742, 1715 cm^{-1}. MS (ESI): *m/z* = 395.1 $[M+Na]^+$.

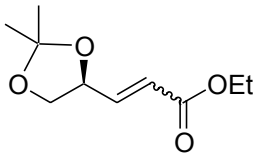


(2*S*, 10*S*)-1,2;10,11-Bis(isopropylidenedioxy)undecan-6-one (10): To a solution of β-ketoester **9** (0.215 g, 0.578 mmol) in DMSO (2.5 mL) were added two drops of water and LiCl (91.8 mg, 2.17 mmol, 3.75 equiv.). After 10 min heating under reflux, TLC analysis (acetone/PE 1:3) revealed complete consumption of starting material. The mixture was diluted with water followed by the addition of EtOAc and brine. The aqueous layer was separated and washed twice with EtOAc. All organic layers were combined, dried ($MgSO_4$), filtered and concentrated. Purification by silicagel column chromatography afforded ketone **10** (170 mg, 0.541 mmol, 94%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.07 (m, 4H, H-1, H-11), 3.48 (m, 2H, H-2, H-10), 2.46 (m, 4H, H-5, H-7), 1.72-1.43 (m, 8H, H-3, H-4, H-8, H-9), 1.40 (s, 6H, 2× CH_3 *i*Pr), 1.35 (s, 6H, 2× CH_3 *i*Pr).^{13}C-NMR (50 MHz, $CDCl_3$): δ 209.7 (C-6), 108.4 (C_q *i*Pr), 75.5 (C-2, C-10), 69.0 (C-1, C-11), 42.1 (C-3, C-9), 32.7 (C-5, C-7), 26.7, 25.4 (CH_3 *i*Pr), 19.7 (C-4, C-8). IR (thin film): 3327, 2937, 2872, 2359, 2343, 1717, 1456, 1437, 1223, 1204, 1082, 1047, 1016, 980 cm^{-1}. MS (ESI): *m/z* = 337.2 $[M+Na]^+$.

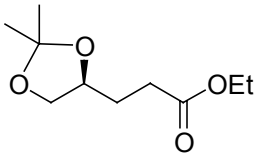


(2*S*, 6*S*, 8*S*) 2,8-Bishydroxymethyl-1,7-dioxaspiro[5.5]undecane (4a): Ketone **10** (0.163 g, 0.519 mmol) was dissolved in a 3:2 mixture of HOAc/water (3 mL) and stirred at rt for 90 min after which TLC analysis (1:1 EtOAc/PE) indicated complete consumption of starting material into a lower running spot. The reaction mixture was concentrated and traces of acid were coevaporated three times with toluene. The residue was purified by column chromatography (EtOAc/PE 1:3 to 1:1) to afford spiroketal **4a** (0.112 g, 0.518 mmol,

quantitative yield). $[\alpha]_D^{20}$ +59.0 (*c* = 0.8, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.75 (m, 2H, H-2, H-8), 3.60 (dd, 2H, *J* = 3.4 Hz, *J* = 11.4 Hz, 2× C*H*H CH_2OH), 3.51 (dd, 2H, *J* = 6.9 Hz, *J* = 11.4 Hz, 2× CH*H* CH_2OH), 2.54 (s, 2H, 2× OH), 1.99-1.82 (dddd, 2H, *J* = 4.2 Hz, *J* = 13.2 Hz, *J* = 26.4 Hz, H-4a, H-10a), 1.67-1.58 (m, 4H, H-4b, H-5a, H-10b, H-11a), 1.51 (m, 2H, H-3a, H-9a), 1.41 (m, 2H, H-5b, H-11b), 1.28 (ddd, 2H, *J* = 3.8 Hz, *J* = 12.8 Hz, *J* = 25.0 Hz, H-3b, H-9b). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 96.0 (C-6), 72.0 (C-2, C-8), 66.1 (2× CH_2OH), 35.1 (C-5, C-11), 26.4 (C-3, C-9), 18.2 (C-4, C-10). IR (thin film): 3377, 2937, 1225, 1082, 1045, 1014, 982 cm^{-1}. HRMS (ESI): calcd for $[C_{11}H_{20}O_4+H]^+$: 217.1434. Found: 217.1437.

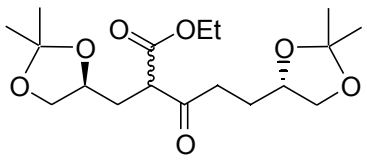


Ethyl-(*S*)-(*E/Z*)-4,5-isopropylidenedioxypent-2-enoate (12): A 5% aqueous $NaHCO_3$ solution (50 mL) was added to 1,2:5,6 diisopropylidenemannitol **11** (6.30 g, 24.02 mmol) and the resulting suspension was cooled to 0 °C. A solution of $NaIO_4$ (6.3 g, 29.45 mmol, 1.2 equiv.) dissolved in water (50 mL) was added to the cooled mannitol suspension, stirred for 90 min at rt and cooled again at 0 °C. To this slurry was added triethylphosphonoacetate (19.84 mL, 22.4 g, 100 mmol, 4.2 equiv.). A solution of K_2CO_3 (150 mL, 6M) was added slowly (CAUTION! Exothermic reaction) and the reaction was stirred overnight at rt. The mixture was diluted with DCM and extracted three times with DCM and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Column chromatography (EtOAc/PE 1:9) of the residue afforded **12** as an E/Z mixture of alkenes in a combined yield (9.21 g, 46.0 mmol, 96%). *E*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.88 (dd, 1H, $J_{3,4}$ = 5.8 Hz, $J_{3,2}$ = 15.3 Hz, H-3), 6.09 (dd, $J_{2,4}$ = 1.5 Hz, $J_{2,3}$ = 15.3 Hz, H-2), 4.65 (m, 1H, H-4), 4.20 (q, 2H, *J* = 7.3 Hz, CH_2 Et), 4.14 (m, 1H, H-5a), 3.67 (dd, 1H, *J* = 7.3 Hz, *J* = 8.0 Hz, H-5b), 1.44 (s, 3H, CH_3 *i*Pr), 1.40 (s, 3H, CH_3 *i*Pr), 1.29 (t, 3H, *J* = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 165.5 (C-1), 144.4 (C-3), 122.0 (C-2), 109.7 (C_q *i*Pr), 74.6 (C-4), 68.4 (C-5), 60.1 (CH_2 Et), 26.1, 25.4 (2× CH_3 *i*Pr), 13.8 (CH_3 Et). *Z*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.37 (dd, 1H, $J_{3,4}$ = 6.6 Hz, $J_{3,2}$ = 11.7 Hz, H-3), 5.85 (dd, 1H, $J_{2,4}$ = 2.2 Hz, $J_{2,3}$ = 11.7 Hz, H-2), 5.49 (m, 1H, H-4), 4.38 (dd, 1H, *J* = 6.9 Hz, *J* = 8.4 Hz, H-5a), 4.18 (q, 2H, *J* = 7.3 Hz, CH_2 Et), 3.63 (dd, 1H, *J* = 6.9 Hz, *J* = 8.4 Hz, H-5b), 1.46 (s, 3H, CH_3 *i*Pr), 1.40 (s, 3H, CH_3 *i*Pr), 1.30 (t, 3H, *J* = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 164.9 (C-1), 149.1 (C-3), 120.1 (C-2), 109.0 (C_q *i*Pr), 73.1 (C-4), 68.8 (C-5), 59.7 (CH_2 Et), 26.0, 24.8 (2× CH_3 *i*Pr), 13.6 (CH_3 Et).

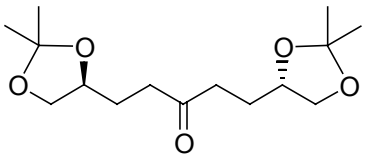


Ethyl-(*S*)-4,5-isopropylidenedioxypentanoate (13): A mixture of *E/Z* alkenes **12** (0.218 g, 1.09 mmol) dissolved in EtOH (8 mL) was degassed. A catalytic ammount of Pd/C was added and after degassing the solution for a second time the reaction was stirred under a hydrogen atmosphere. After 45 min TLC analysis (EtOAc/PE 1:3) showed complete conversion of starting material into a lower running spot. The mixture was filtered over Glass Fiber (GF/2A Whatman) and concentrated. The residue was filtered over a short plug of silica (EtOAc/PE 1:3) and the filtrate was concentrated to afford ester **13** (0.208 g, 1.03 mmol,

94%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.13 (q, 2H, *J* = 7.3 Hz, CH_2 Et), 4.08 (m, 2H, H-4, H-5a), 3.54 (m, 1H, H-5b), 2.42 (m, 2H, H-2), 1.85 (m, 2H, H-3), 1.40 (s, 3H, CH_3 *i*Pr), 1.33 (s, 3H, CH_3 *i*Pr), 1.26 (t, 3H, *J* = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 172.8 (C-1), 108.6 (C_q *i*Pr), 74.7 (C-4), 68.8 (C-5), 60.0 (CH_2 Et), 30.1, 28.5 (C-2, C-3), 26.6, 25.3 (2× CH_3 *i*Pr), 13.9 (CH_3 Et).

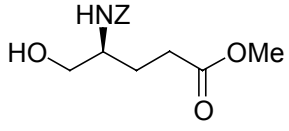


(2*S*, 4*R/S*, 8*S*)-1,2;8,9-Bis(isopropylidenedioxy)-4-ethoxycarbonylnonan-5-one (14): A solution of ester **13** (0.404 g, 1.998 mmol) in freshly distilled THF (10 mL) was cooled to 0 °C. A solution of LHMDS (0.668 g, 4.00 mmol, 2.0 equiv.) in freshly distilled THF (5 mL) and TMEDA (1.21 mL, 0.929 g, 7.99 mmol, 4.0 equiv.) was added to the chilled ester solution. After 2.5 h of stirring at 0 °C TLC analysis (EtOAc/PE 1:3) indicated complete consumption of starting material. The reaction mixture was neutralised by addition of HCl (25 mL, 1.0 M) and diluted with Et_2O. The aqueous phase was separated and extracted twice with Et_2O. All organic layers were combined, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:9) afforded β-ketoester **14** (0.208 g, 0.581 mmol, 58%) as an isomeric mixture. ^{13}C-NMR (50 MHz, $CDCl_3$): δ 203.8 (C-5), 169.0, 168.8 (C=O CO_2Et), 108.7, 108.4 (C_q *i*Pr), 74.5, 74.4, 73.4, 72.9 (C-2, C-8), 68.8 (C-1, C-9), 61.0 (CH_2 Et), 55.3, 54.6 (C-4), 38.5, 37.7 (C-6), 31.8, 31.4 (C-3), 26.9 (C-7), 26.5, 25.2 (4× CH_3 *i*Pr), 13.6 (CH_3 Et). MS (ESI): *m/z* = 381.1 $[M+Na]^+$, 739.6 $[2M+Na]^+$.



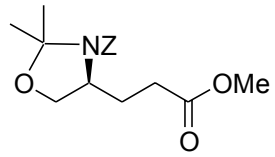
(2*S*, 8*S*)-1,2;8,9-Bis(isopropylidenedioxy)nonan-5-one (15): Decarboxylation of **14** (0.117 g, 0.327 mmol) using the procedure described going from **9** to **10**, gave after refluxing for 5 min, ketone **15** (86 mg, 0.301 mmol, 92%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.99 (m, 4H, H-1, H-9), 3.44 (m, 2H, H-2, H-8), 2.47 (m, 4H, H-4, H-6), 1.74 (m, 4H, H-3, H-7), 1.32 (s, 6H, 2× CH_3 *i*Pr), 1.25 (s, 6H, 2× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 209.2 (C-5), 108.7 (C_q *i*Pr), 74.8 (C-2, C-8), 69.0 (C-1, C-9), 38.5 (C-4, C-6), 27.2 (C-3, C-7), 26.7, 25.4 (4× CH_3 *i*Pr). MS (ESI): *m/z* = 309.1 $[M+Na]^+$.

Spiroketals (16 a-c): According to the procedure described going from **10** to **4**, ketone **15** (60.0 mg, 0.210 mmol) was dissolved in a mixture of (1.5 mL HOAc/water 3:2). After stirring for 90 min at rt, TLC analysis (MeOH/EtOAc 1:19) revealed complete consumption of starting material also indicating the formation of three lower running spots. Work up as described for **4a** resulted in the formation of compounds **16a**, **16b**, **16c** (30 mg, 0.159 mmol, 76%).

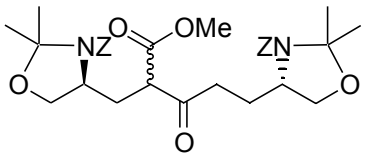


Methyl-(*S*)-4-[(benzyloxycarbonyl)amino]-5-hydroxypentanoate (18): Z-Glu(OMe)-OH, **17**, (1.48 g, 5.00 mmol) was dissolved in THF (25 mL) and cooled to –10 °C. To this solution were added NMM (0.550 mL, 0.506 g, 5.00

mmol) and ethyl chloroformate (0.478 mL, 0.543 g, 5.00 mmol). After stirring this mixture for 10 min at –10 °C, $NaBH_4$ (0.567 g, 15.0 mmol, 3.0 equiv.) was added in one portion, followed by slow addition of MeOH (50 mL). The reaction mixture was stirred and allowed to reach 0 °C. After 30 min, the reaction was quenched by the addition of 1.0 M HCl (11 mL, pH 5). After addition of water, brine and EtOAc, the organic phase was separated, dried ($MgSO_4$) and concentrated. Purification by column chromatography (EtOAc/PE 2:1 to 3:1) gave title compound **18** (1.17 g, 4.15 mmol, 83%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.36 (m, 5H, CH_{arom}), 5.10 (s, 2H, CH_2 Z), 3.65 (m, 6H, H-4, H-5, CH_3 Me), 2.43 (m, 2H, H-2), 1.88 (m, 2H, H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.7 (C=O CO_2Me), 156.3 (C=O Z), 136.0 (C_q Z), 127.9, 127.5 (CH_{arom}), 66.1, 63.9 (C-5, CH_2 Z), 52.0, 51.1 (C-4, CH_3 OMe), 30.0, 25.9 (C-2, C-3).). IR (thin film): 3315, 1693, 1529, 1439, 1242, 1172, 1059, 1028 cm^{-1}. MS (ESI): *m/z* = 282.3 $[M+H]^+$, 304.0 $[M+Na]^+$, 585.2 $[2M+Na]^+$.

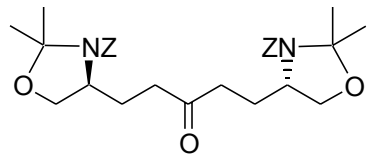


Methyl 3-[(4*S*)-3-(benzyloxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]-propanoate (19): Alcohol **18** (0.640 g, 2.28 mmol) was dissolved in dry acetone (20 mL). Dimethoxypropane (3.0 mL, 24.2 mmol) and a catalytic ammount of *p*-TsOH (65 mg) were added and the mixture was stirred overnight at rt. After 18 h, TLC analysis revealed complete consumption of starting material. Pyridine (0.1 mL) was added and the organic solvents were removed under reduced pressure. The residue was dissolved in EtOAc, washed against sat. aq. $NaHCO_3$, water and brine. The separated organic layer was dried ($MgSO_4$) and purified by column chromatography (EtOAc/PE 1:6 to 1:3) to give oxazolidine **19** (0.689 g, 2.15 mmol, 94%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.36 (m, 5H, CH_{arom}), 5.13 (m, 2H, CH_2 Z), 4.03 (m, 2H, H-5), 3.70 (m, 4H, H-4, CH_3 Me), 2.31 (m, 2H, H-2), 1.98 (m, 2H, H-3), 1.55 (m, 6H, 2× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 172.3 (C=O CO_2Me), 151.5 (C=O Z), 136.0 (C_q Z), 127.7, 127.2 (CH_{arom}), 93.4, 92.9 (C_q *i*Pr), 66.4, 65.7 (C-5, CH_2 Z), 56.6, 55.6, 50.6 (C-4, CH_3 OMe), 29.7, 28.2, 27.7 (C-2, C-3), 26.8, 25.8, 23.7, 22.2 (CH_3 *i*Pr). IR (thin film): 2951, 1736, 1697, 1404, 1348, 1252, 1070 cm^{-1}. MS (ESI): *m/z* = 344.2 $[M+Na]^+$, 360.0 $[M+K]^+$, 665.3 $[2M+Na]^+$.

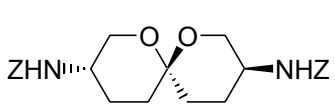


(2*R/S*)-1,5-Bis((4S)-3-(benzyloxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl)-2-methoxycarbonyl-pentan-3-one (20): Condensation of ester **19** (0.304 g, 0.95 mmol), as described for the synthesis of **9**, gave after 3 h and purification by column chromatography (EtOAc/PE 1:3 to 1:1), β-ketoester **20** (0.208 g, 0.341 mmol, 72%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 10H, CH_{arom}), 5.11 (m, 4H, 2× CH_2 Z), 3.92 (m, 4H, H-1, H-9), 3.64 (m, 6H, H-2, H-4, H-8, CH_3 OMe), 2.59 (m, 2H, H-6), 2.14 (m, 2H, H-3), 1.87 (m, 2H, H-7), 1.62-1.43 (m, 12H, 4× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 203.0 (C-5), 169.5 (C=O CO_2Me), 152.0 (C=O Z), 136.1 (C_q Z), 128.2, 127.7 (CH_{arom}), 93.9 (C_q *i*Pr), 67.4, 66.9, 66.3, 65.5 (C-1, C-9, 2× CH_2 Z), 56.0, 55.4 (C-2, C-4, C-8), 52.1 (CH_3 OMe), 37.7 (C-6), 32.6 (C-3),

27.0 (C-7), 27.6, 26.3, 24.1, 22.7 (CH_3 *i*Pr). IR (thin film): 1744, 1697, 1404, 1350, 1251, 1207, 1072 cm^{-1}. MS (ESI): *m/z* = 611.4 $[M+H]^+$, 633.4 $[M+Na]^+$, 1221.9 $[2M+H]^+$, 1243.6 $2M+Na]^+$.



1,5-Bis((4S)-3-(benzyloxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl)-pentan-3-one (21): To a solution of β-ketoester **20** (73.0 mg, 0.120 mmol), dissolved in MeOH/water (1:1, 3.0 mL), was added KOH (16.8 mg, 0.299 mmol, 2.5 equiv.). The reaction mixture was heated till reflux and after 1 h TLC analysis (EtOAc/toluene 1:3) indicated complete disappearance of starting material. The mixture was concentrated and the residue dissolved in Et_2O and washed against water and brine. The organic phase was dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/toluene 1:3) to yield ketone **21** (52.0 mg, 0.094 mmol) in 79%. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 10H, CH_{arom}), 5.12 (s, 4H, 2× CH_2 Z), 3.94 (m, 4H, H-1, H-9), 3.70 (m, 2H, H-2, H-8), 2.36 (m, 4H, H-4, H-60, 1.87 (m, H-3, H-7), 1.63-1.43 (m, 12H, 4× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 208.7 (C-5), 152.3 (C=O Z), 136.5 (C_q Z), 128.5, 128.0, 127.9 (CH_{arom}), 94.2, 93.7 (C_q *i*Pr), 67.2, 66.5 (C-1, C-9, 2× CH_2 Z), 57.1, 56.3 (C-2, C-8), 38.7 (C-2, C-6), 27.4 (C-3, C-7), 26.5, 24.5, 23.0 (CH_3 *i*Pr). IR (thin film): 1699, 1406, 1352, 1074 cm^{-1}. MS (ESI): *m/z* = 553.5 $[M+H]^+$, 575.6 $[M+Na]^+$, 591.2 $[M+K]^+$.



(3*S*, 6*S*, 9*S*)-3,9-Bis((benzyloxycarbonyl)amino)-1,7-dioxaspiro[5.5] undecane (22): Ketone **21** (38 mg, 0.069 mmol) was dissolved in HOAc/water (3mL 1:1) and heated till reflux. After 3 h, TLC analysis (EtOAc/toluene 1:1) showed complete conversion of starting material into a lower running spot. The mixture was concentarted under reduced pressure and purified over a small plug of silica (EtOAc/toluene 1:1) to give spiroketal **22** (29 mg, 0.064 mmol, 90%). $[\alpha]_D^{20}$ +12.0 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (400 MHz, DMSO-d_6, 333K): δ 7.40-7.27 (m, 10H, CH_{arom}), 7.05 (2H, 2× NH), 5.01 (m, 4H, 2× CH_2 Z), 3.51 (dd, 2H, *J* = 4.6 Hz, *J* = 9.8 Hz, H-2a, H-8a), 3.44 (m, 2H, H-3, H-9), 3.18 (m, 2H, H-2b, H-8b), 1.64 (m, 6H, H-4a, H-4b, H-5a, H-10a, H-10b, H-11a), 1.50 (dd, 2H, *J* = 4.6 Hz, *J* = 13.0 Hz, H-5b, H-11b). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.5 (C=O Z), 137.0 (C_q Z), 128.3, 127.8 (CH_{arom}), 93.2 (C-6), 65.3 (CH_2 Z), 62.1 (C-2, C-8), 46.3 (C-3, C-9), 33.7 (C-5, C-11), 24.7 (C-4, C-10). IR (thin film): 3300, 2953, 1684, 1545, 1439, 1312, 1292, 1084, 1024, 964 cm^{-1}. HRMS (ESI): calcd for $[C_{25}H_{30}N_2O_6+H]^+$: 455.2177. Found: 455.2175.

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Chapter 6

Summary and Future Prospects

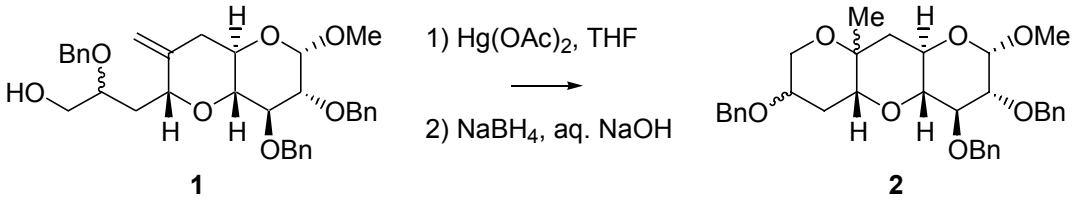
The focus of the research described in this Thesis entails the conversion of monosaccharides into polycyclic ethers, novel sugar amino acids and spiroketals. A common theme in this research, besides protective group manipulations and functional group transformations, comprises the cyclisation methods employed throughout the syntheses. These include radical cyclisations, selenocyclisations, Ferrier rearrangements and spiroketalisations. **Chapter 1** gives a selective overview concerning the use of carbohydrates as starting material in the construction of natural products and biologically relevant compounds. Examples discussed involve the synthesis of oligosaccharides, fused polycyclic ethers, alkaloids, sugar amino acids and spiroketals.

The synthesis of *trans*-fused tricyclic ethers containing a methyl group located at a bridgehead position was investigated in **Chapter 2**. Radical cyclisation of carbohydrate-derived ene-yne intermediates proceeded smoothly to furnish two pyrano-pyran ring systems. In the next ring-closing event, it was anticipated to take full advantage of the exocyclic vinylstannane moiety thereby simultaneously installing the methyl group. Attempts to obtain a tricyclic ether composed of three pyran rings were

inefficacious, but the synthesis of an analogous 8,6,6-tricyclic ether was accomplished successfully.

In a pilot experiment to assemble a 6,6,6-tricyclic ether, cyclisation and concomitant release of the methyl group could be effected (Scheme 1). By means of an oxymercuration,[1] ring-closure of compound **1** proceeded to give **2**, but the absolute stereochemistry could not be determined at this stage.

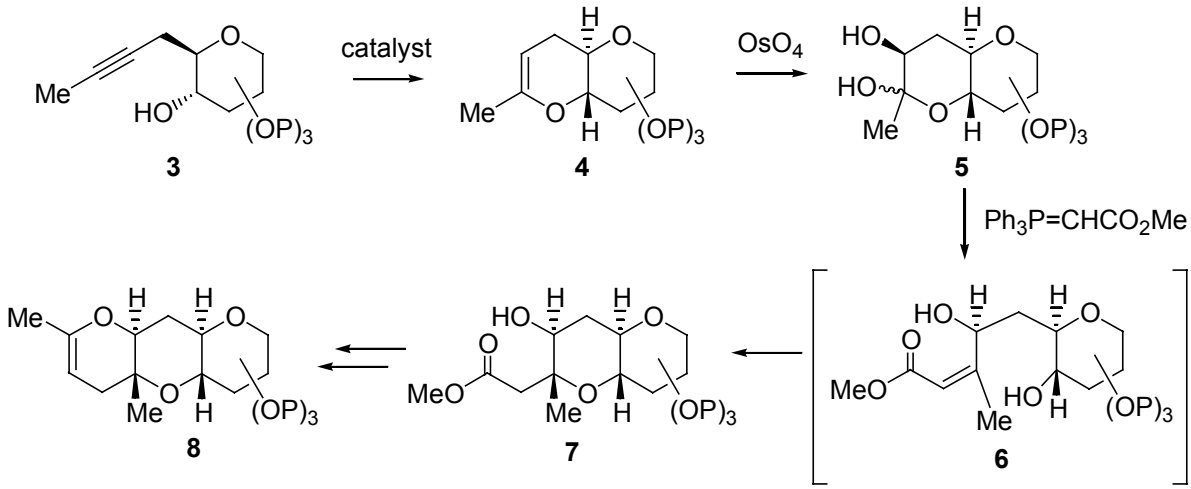
Scheme 1



1 **2**

Tungsten- or ruthenium-catalysed cyclisomerisation of terminal alkyne alcohols have been found to form 5-, 6- and 7-membered cyclic enol ethers.[2] However, application of 2-alkynes as substrates for this transformation, such as **3** (Scheme 2), have not been reported. *Endo*-cyclisation of 2-alkynes can be effected under the agency of mercury or palladium catalysts.[3] Based on these findings, carbohydrate-derived alkynol **3** could in

Scheme 2



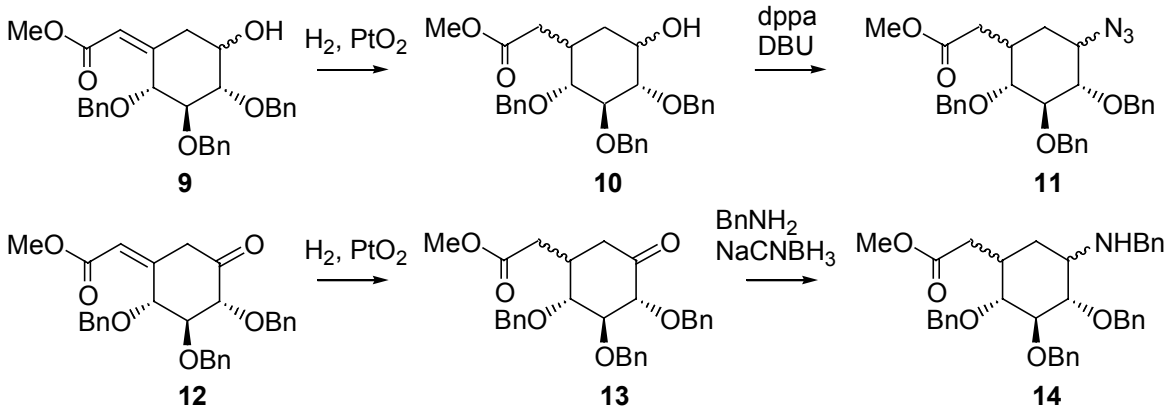
3 **4** **5** **6** **7** **8**

potential be used in an iterative procedure, as follows. Cyclisation of **3** under the influence of one of the above catalytic systems should give enol ether **4**. Further elaboration of **4**, with the angular methyl already installed, to construct a third pyran ring would proceed as follows: 1) dihydroxylation of the double bond (**4** to **5**), 2) Wittig olefination of the resulting ketal functionality (**5** to **6**), 3) ring-closure through Michael addition (**6** to **7**) followed by 4) transformation of the methylester into an alkyne. After transformation of the methylester into a 2-alkyne, the same sequence of events may provide tricyclic system **8**.

Chapter 3 describes the application of the radical cyclisation strategy towards the synthesis of conformationally constrained γ-sugar amino acids. Obtaining the requisite alkynol proved to be the crucial step throughout the course of operations. For instance, nucleophilic opening of a cyclic sulfate was accompanied by side-reactions. Instead, opening of an oxetane in the presence of a Lewis acid, served as a suitable alternative to furnish an appropriate Michael acceptor.

In **Chapter 4**, the synthesis of a novel carbasugar amino acid (CSAA) is presented. Methodologies to assemble this class of hybrid molecules remain relatively unexplored to date. The carbocyclic core was readily accessible by converting a carbohydrate-derived enol acetate into a cyclitol via a Ferrier rearrangement. Installation of the carboxylate and amine functionalities was shown to be rather cumbersome, often due to the occurrence of β-eliminations and subsequent aromatisations. After exploring several conditions, introduction of the carboxylate functionality was achieved using a Lewis acid mediated Mukaiyama-Michael addition. Ensuing reductive amination afforded a novel conformationally restricted CSAA which can be regarded as a dipeptide isoster. In view of the β-eliminations during the syntheses, saturation of the double bonds in either **9** or **12** (Scheme 3) should prevent eliminations to occur. Thus, selective hydrogenation of **9** and **12** should allow installation of amine functionalities under basic conditions at the right hand side of the cyclohexane core in **10** and **13**.

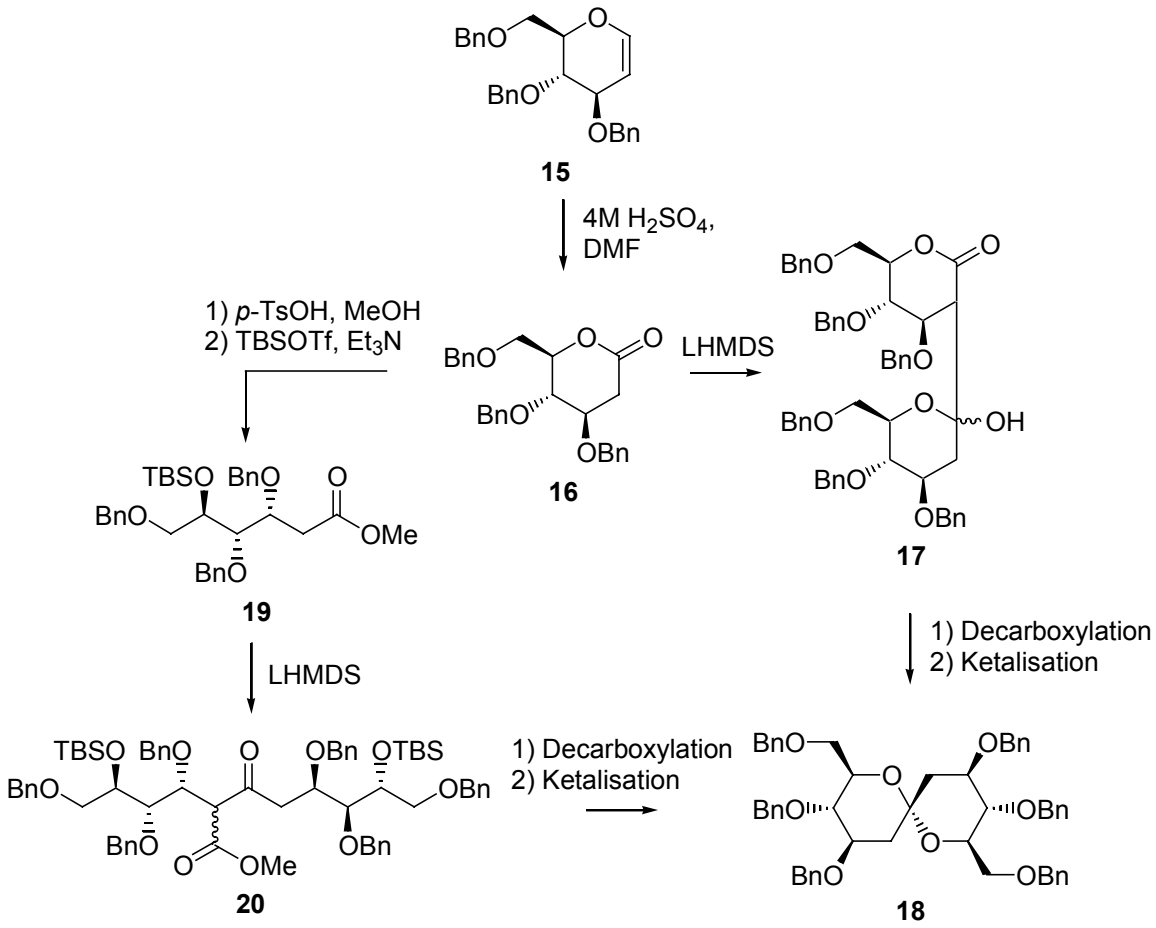
Scheme 3



A general and efficient strategy to construct functionalised 1,7-dioxaspiro[5.5]undecane ring systems is presented in **Chapter 5**. This procedure is based on an acid catalysed spiroketalisation of C_2-symmetrical dihydroxyketones. Accordingly, Claisen self-condensation of suitably protected hydroxyesters afforded the corresponding β-keto esters. Hydrolysis of the ester functions followed by decarboxylation of the resulting β-keto acids smoothly furnished the requisite dihydroxyketones. Acidic removal of the protective groups and subsequent ring-closure effectively transformed the hydroxyketones into the spiroketals. The absolute stereochemistry and conformational preference of the spiroketals entirely hinges on the chirality present in the starting material. This chirality induces a double anomeric effect of the ketal center and forces substituents to adopt equatorial positions resulting in the formation of the thermodynamically most favorable isomer.

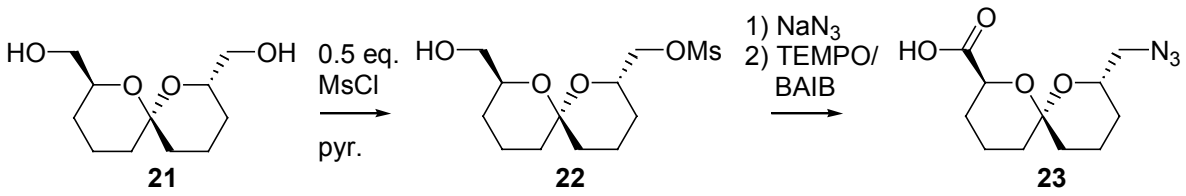
It would be of interest to establish the viability of the Claisen condensation/decarboxylation procedure in the synthesis of more densely functionalised spiroketals, starting from more complex precursors. For instance, starting from 2-deoxy gluconolactone **16**, easily accessible from D-glucal **15** (Scheme 4) and application of the two-step condensation/decarboxylation procedure, the synthesis of polyhydroxylated spiroketal **18** may be feasible. In case Claisen self-condensation of lactone **16** proves to be troublesome, transformation of **16** into protected hydroxyester **19** and ensuing Claisen self-condensation/decarboxylation provides an alternative entry to assemble spiroketal **18**.

Scheme 4



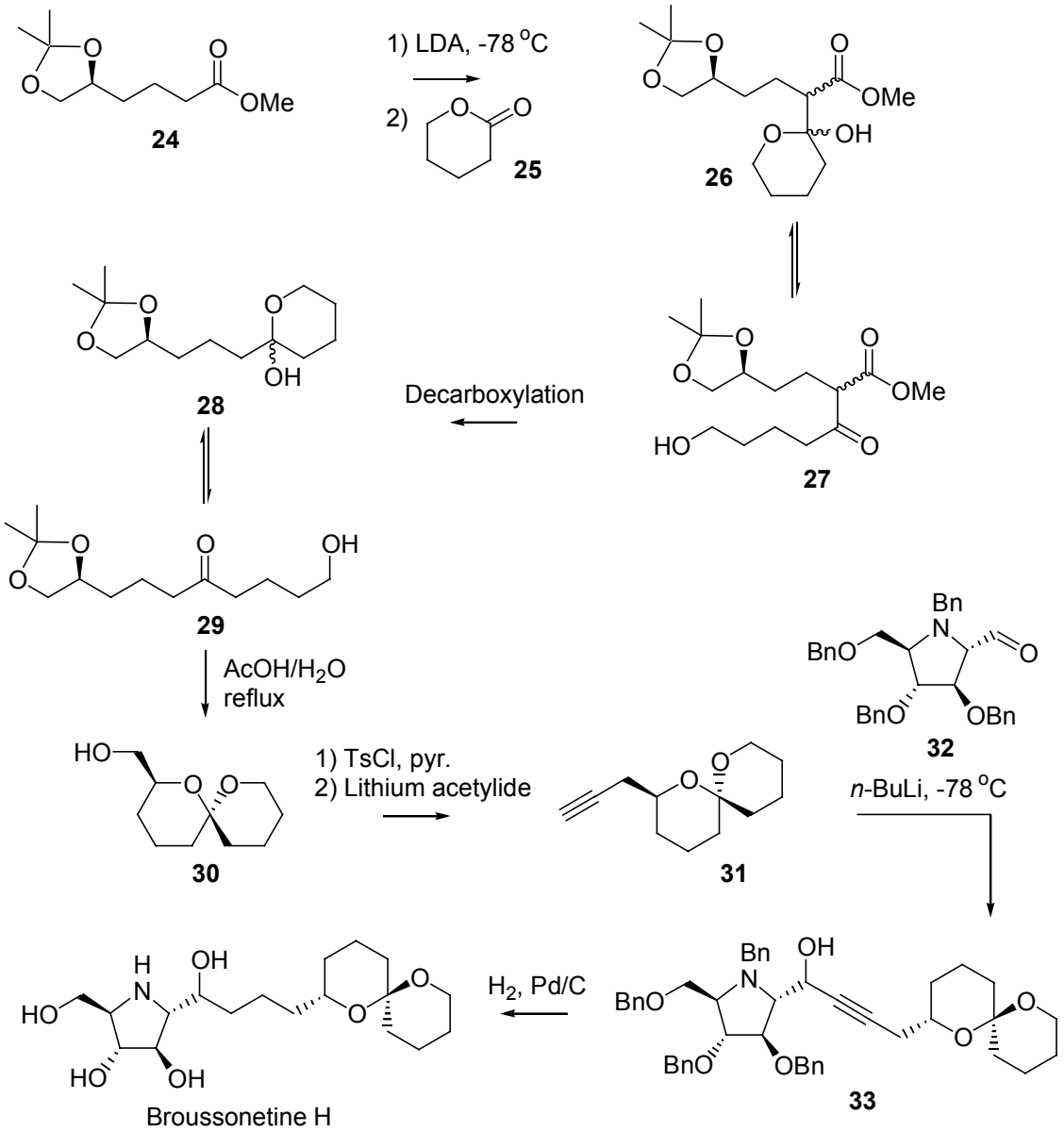
A second interesting follow-up of the research described in **Chapter 5** is to investigate whether dihydroxy spiroketal **21** can be transformed into a novel conformationally restricted amino acid **23** (Scheme 5). Installation of a mesylate function (**22**), subsequently followed by nucleophilic displacement with an azide and oxidation of the primary alcohol may furnish spiroketal **23**.

Scheme 5



A variety of natural products, such as broussonetine H[4] (Scheme 6), contain spiroketal entities. The construction of the spiroketal can in potential be achieved starting from protected hydroxy ester **24** and δ-valerolactone (**25**). Enolate formation of **24** under the agency of LDA[5] followed by addition of **25** would result in either β-substituted ester **26** or **27**. Decarboxylation and acidic ketalisation then furnishes spiroketal **30**.

Scheme 6



Installation of an acetylene would facilitate coupling of **31** with pyrrolidine **32**.[6] Removal of the protective groups along with saturation of the triple bond in **33** completes the synthesis of broussonetine H.

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Samenvatting

Koolhydraten zijn een klasse van natuurlijk voorkomende verbindingen die gekenmerkt wordt door een grote structurele diversiteit. Zo komen koolhydraten niet alleen voor als mono-, oligo-, of polysacchariden maar vormen zij ook een onderdeel van conjugaten zoals glycoproteïnen en glycolipiden. Koolhydraten fungeren als structuurelement en energiebron en vervullen een rol in tal van essentiële biologische processen zoals celgroei, afweermechanismen en cel-cel herkenning. Om meer inzicht te verkrijgen in deze processen wordt er veel onderzoek verricht naar de synthese van natuurlijk voorkomende koolhydraatstructuren en analoga daarvan.

Een tak van onderzoek waarbij koolhydraten ook een belangrijke rol spelen is de synthese van complexe chirale natuurstoffen. Immers, de monosacchariden waaruit koolhydraten zijn opgebouwd, zijn gemakkelijk toegankelijk, goedkoop en vormen een klasse van veelzijdige chirale uitgangsstoffen.

Het onderzoek dat in dit proefschrift wordt beschreven, is gericht op het gebruik van monosachariden voor de synthese van polycyclische ethers, spiroketalen en nieuw ontworpen suikeraminozuren. In het onderzoek wordt behalve aan beschermgroep

manipulaties en functionele groep omzettingen ook speciale aandacht besteed aan verschillende cyclisatiemethoden, zoals radicaal- en selenocyclisaties en spiroketaliseringen.

In **Hoofdstuk 1** wordt een beknopt overzicht gegeven omtrent het gebruik van monosacchariden als veelzijdige uitgangsstoffen voor de bereiding van biologisch relevante natuurprodukten en analoga daarvan. Er wordt ondermeer aandacht besteed aan de vervaardiging van oligosacchariden, gefuseerde polycyclische ethers, alkaloïden, suikeraminozuren en spiroketalen.

Hoofdstuk 2 behandelt het onderzoek naar de synthese van *trans*-gefuseerde tricyclische ethers die voorzien zijn van een methylgroep op een bruggenhoofdpositie. Dit moeilijk toegankelijke structuurelement vormt een onderdeel van enkele toxische polycyclische ethers, die door verschillende zeeorganismen worden geproduceerd. Uitgaande van glucose werd een "een-yne" intermediair gesynthetiseerd, dat door middel van een radicaalcyclisatie kon worden omgezet in een pyrano-pyran ringsysteem, voorzien van een *exo*-cyclische vinyltingroep. Op voorhand was bedacht dat deze dubbele binding aangewend kon worden voor het sluiten van de derde etherring en de gelijktijdige vorming van de methylgroep op het bruggenhoofd. Verschillende selenocyclisaties leidden niet tot de vorming van 6,6,6-tricyclische ethers. Een 8,6,6-tricyclische ether kon wel met succes gevormd worden, zij het met een *cis*-verknoopte ring.

Hoofdstuk 3 beschrijft de synthese van een nieuw conformationeel vastgelegd suikeraminozuur. In de syntheseroute werd de radicaalreactie uit het voorgaande hoofdstuk gebruikt om zowel ringsluiting te bewerkstelligen als een carboxylaat functie te introduceren. Bovendien werd met behulp van een Lewis zuur gekatalyseerde opening van een oxetaan, een efficiënte procedure ontwikkeld om het benodigde beschermde alkynol intermediair in handen te krijgen. Michael-additie van dit intermediair met ethylpropiolaat gevolgd door radicaalcyclisatie leverde het beschermde suikeraminozuur op. Aandacht werd besteed aan de vaststelling van de configuratie van het nieuw geïntroduceerde chirale centrum in het verkregen suikeraminozuur.

In **Hoofdstuk 4** wordt de synthese gepresenteerd van een nieuw carbasuikeraminozuur dat beschouwd kan worden als een dipeptideisosteer. Dit type

suikeraminozuur verschilt met die uit het vorige hoofdstuk door de aanwezigheid van een methyleengroep op de positie van het zuurstofatoom in de cyclische ether. Door een enol acetaat afgeleid van glucose te onderwerpen aan een Ferrier omlegging, werd het benodigde cyclitol derivaat verkregen. De daaropvolgende invoering van een amine en carbonzuur functie bleek gepaard te gaan met nevenreacties. Regelmatig traden er onder de gebruikte condities β-eliminaties op, die soms leidden tot aromatische verbindingen. Uiteindelijk kon de carbonzuur functie worden ingevoerd door middel van een Lewis zuur gekatalyseerde Mukaiyama-Michael additie. Een reductieve aminering leverde vervolgens een conformationeel vastgelegd carbasuikeraminozuur op.

Een algemene en efficiënte methode om gefunctionaliseerde 1,7-dioxa-spiro[5.5]undecanen te synthetiseren wordt beschreven in **Hoofdstuk 5**. Deze methode wordt gekenmerkt door een zuur gekatalyseerde condensatie van C_2-symmetrische dihydroxyketonen tot spiroketalen. Er werden drie verschillende dihydroxyketonen bereid, die elk voorzien waren van zuur labiele beschermgroepen. De gewenste ketonen werden verkregen door beschermde hydroxyesters, via een Claisen zelf-condensatie, om te zetten in de overeenkomstige β-keto esters. Hydrolyse van de ester functie, gevolgd door decarboxylatie, leidde tot de beschermde dihydroxyketonen. De beschermgroepen van de hydroxyl functies werden verwijderd door behandeling met zuur, waarna cyclisatie tot spiroketalen plaatsvond. Omdat deze cyclisaties evenwichtsreacties zijn, kunnen meerdere isomere spiroketalen gevormd worden. Bij twee van de cyclisaties werd één spiroketaal geïsoleerd. De stabiliteit van de gevormde produkten wordt in belangrijke mate bepaald door de equatoriale posities van de substituenten en de aanwezigheid van een dubbel anomeer effect van het ketaal centrum.

List of Publications

"A Stereoselective and Efficient Route to (3S,4R,5S)-(+)-4,5-Dihydroxycyclopent-1-en-3-ylamine: The Side Chain of the Hypermodified Nucleoside Q", Ovaa, H.; Codée, J. D. C.; Lastdrager, B.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 7987-7990.

"A Versatile Approach to the Synthesis of Highly Functionalised Carbocycles", Ovaa, H.; Codée, J. D. C.; Lastdrager, B.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *Tetrahedron Lett.* **1999**, *40*, 5063-5066.

"A Flexible Synthesis of Cyclopentitol Derivatives Based on Ring-Closing Metathesis of Carbohydrate-Derived 1,6-Dienes", Ovaa, H.; Lastdrager, B.; Codée, J. D. C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Chem. Soc. Perkin Trans. 1* **2002**, *21*, 2370-2377.

"Claisen Self-Condensation/Decarboxylation as the Key Steps in the Synthesis of C_2-Symmetrical 1,7-dioxaspiro[5.5]undecanes", Lastdrager, B.; Timmer, M. S. M.; van der Marel, G. A.; Overkleeft, H. S. *Tetrahedron Lett.* **2005**, *46*, 6195-6198.

Curriculum Vitae

Bastiaan Lastdrager werd op 6 augustus 1974 geboren te Heemskerk. Na het behalen van het VWO-diploma in 1993 aan de Louise de Coligny Scholengemeenschap te Leiden werd in datzelfde jaar begonnen met de studie scheikunde aan de Universiteit van Leiden. Van februari 1998 tot januari 1999 werd in het kader van de hoofdvakstage onderzoek verricht in de vakgroep Bio-organische synthese onder leiding van prof. dr. J. H. van Boom naar de synthese van carbacyclische verbindingen met behulp van de metathese reactie. In de periode van november 1999 tot mei 2000 werd een buitenlandstage verricht aan het Massachusetts Institute of Technology (MIT, Cambridge USA) in de werkgroep van prof. dr. P. H. Seeberger. Er werd gewerkt aan de synthese van tri-sacchariden via één-pots glycosylerings reacties van fosfaat donoren alsmede aan de ontwikkeling van halobenzyl ethers als nieuwe beschermgroepen. Het doctoraal-diploma werd behaald in juli 2000.

Van augustus 2000 tot december 2005 werd als assistent-in-opleiding het in dit proefschrift beschreven onderzoek uitgevoerd in de vakgroep Bio-organische synthese onder supervisie van prof. dr. J. H. van Boom en prof. dr. H. S. Overkleeft, onder de dagelijkse begeleiding van prof. dr. G. A. van der Marel en dr. ing. M. Overhand. Onderdelen van dit proefschrift werden gepresenteerd op een bijeenkomst van de sectie organische chemie (maart 2004, Leiden, Nederland) en op het 22nd International Carbohydrate Symposium (juli 2004, Glasgow, UK).

Nawoord

Veel mensen zijn direkt en indirekt betrokken geweest bij de totstandkoming van dit proefschrift. Een aantal van hen wil ik op deze plaats noemen. Allereerst wil ik mijn ouders bedanken voor de mogelijkheid die ze mij geboden hebben om een academische opleiding te volgen en de onvoorwaardelijke steun die ze mij tijdens mijn studie en promotie hebben gegeven. De belangstelling van vrienden en familie voor mijn onderzoekswerkzaamheden heb ik zeer gewaardeerd. In het bijzonder wil hierbij Annouk noemen, als ook de leden van mijn volleybalteam van DVO die voor de nodige ontspanning en relativering hebben gezorgd.

In het kader van hun hoofd- en bijvakstage hebben Varsha Kapoerchan en Joris Berding een wezenlijke bijdrage geleverd aan het onderzoek naar de synthese van polycyclische ethers en conformationeel vastgelegde suikeraminozuren. Ik bewaar zeer goede herinneringen aan de prettige sfeer binnen de vakgroep bio-organische synthese en aan de vele gezamenlijke activiteiten buiten het laboratorium. De dagelijkse samenwerking met de leden van de vakgroep heb ik als zeer stimulerend ervaren. In dit verband wil ik Richard van den Berg, Kimberly Bonger, Leendert van den Bos, Silvia Cavalli, Dima Filippov, Martijn de Koning, Michiel Leeuwenburgh, Rian van den Nieuwendijk, Micha Slegt, Karen Sliedregt-Bol, Paul van Swieten, Erwin Tuin, Martijn Verdoes, Peter de Visser en Tom Wennekes in het bijzonder vermelden. Voorts wil ik enkele “oud-collega’s” noemen die het lab reeds verlaten hebben, te weten: Begoña Aguilera, Jeroen Codée, Clara Comuzzi, Farid El Oualid, Gijs Grotenbreg, Remy Litjens, Huib Ovaa, Jasper Plaisier, Marike van Roon, Mattie Timmer, John Turner, Steven Verhelst en Renate van Well. Hans van den Elst en Nico Meeuwenoord waren altijd zeer behulpzaam bij het opnemen van massaspectra, het uitvoeren van zuiveringen en bij de synthese op vaste drager. Voor het opnemen van NMR-spectra heb ik altijd kunnen rekenen op de hulp van Fons Lefeber en Kees Erkelens. De ama’s Arnold, Henny en Marco dank ik voor hun hulp bij het oplossen van technische mankementen op het lab. De secretariële hulp van Caroline de Bruin dient zeker vermeld te worden.