Inhibitors and probes targeting mannanases

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Design and synthesis of inhibitors and probes for α-*N*-acetylgalactosaminidase and α-*N*-acetylglucosaminidase

4.1 Introduction

Lysosomes are membrane-enclosed acidic organelles that contain more than 50 hydrolases which together process a large variety of macromolecules. Deficiency in a specific lysosomal enzyme can lead to accumulation of its substrate with cellular dysfunction and eventually cell death as the potential result.[1,2] Diseases that are related to the dysfunction of a specific lysosomal enzyme are termed lysosomal storage diseases (LSDs).[3] LSDs comprise a group of more than 50 inherited diseases that are caused by mutations in the genes encoding for lysosomal enzymes. LSDs can be further divided and classified based on the biochemical type of accumulated material. In the context of the research described in this chapter, two subgroups are important: mucopolysaccharidoses, which are characterized by the accumulation of glycosaminoglycans, and glycoproteinosis, which are characterized by accumulation of glycoproteins. In this chapter the design and synthesis of a set of potential covalent probes and inhibitors for both lysosomal α-*N*-acetylgalactosaminidase and α-*N*-acetylglucosaminidase, enzymes involved in several LSDs, is described.

Sanfilippo syndrome

Mucopolysaccharidosis type III, also known as Sanfilippo syndrome, is a lysosomal storage disorder caused by mutations in the protein encoding gene *NAGLU*, resulting in a reduced activity for *N*-acetyl-α-glucosaminidase.[4] Clinical manifestations of this disease include skeleton deformities, behavioural disorders and cognitive decline. The onset of the disease is between the age of 2 and 6 and the life expectancy for patients is 20 to 30 years.[5]

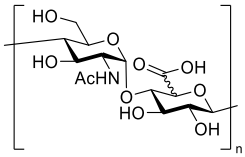


Figure 1 Heparan sulfate consists of a *N*-acetyl-glucosamine-α-1,4-glucuronic/iduronic acid backbone, which is sulfated on a variety of positions (not shown here). *N*-Acetyl-α-glucosaminidase is an exoglycosidase that cleaves GlcNAc from the non-reducing end.

N-Acetyl-α-glucosaminidase (NAGLU) is a retaining glycosidase and one of the four enzymes responsible for the degradation of heparan sulfate (Figure 1). There are more than 100 different mutations known for *NAGLU* that can lead to NAGLU deficiency.[6–8] Most of these mutations affect nonactive residues outside of the active site of the enzyme and affect its folding. Misfolded proteins are often inactive even though its catalytic site remains intact. Improperly folded enzymes are tagged for degradation resulting in NAGLU deficiency and build-up of heparan sulfate in lysosomes and even outside the cell.

Schindler disease

Schindler disease is the result of a mutation in the *NAGA* gene which encodes for *N*-acetyl-α-galactosaminidase (NAGA), a retaining lysosomal exo-glycosidase that cleaves α-*N*-acetylgalactosamine from glycolipids and glycopeptides, which accumulate when the enzyme is deficient.[9] Clinical manifestations of Schindler disease are divided into three types based on their phenotype. Type I manifests as a severe infantile neurodegenerative disorder. Type II, also known as Kanzaki disease, manifests in adults and leads to mild cognitive impairments. Type III contains a variety of symptoms, including autistic disorders, seizures and cardiomyopathy.[10,11] Deficiency in NAGA leads to a build-up of glycoconjugates containing a terminal α-*N*-acetylgalactosamine residue.[10] This includes mucins (*O*- and *N*-linked glycopeptides and glycoproteins) and glycosphingolipids (for example, Forssman glycolipid: GalNAc-α-1,3-GalNAc-β-1,3-Gal-α-1,4-Gal-β-1,4-Glc-β-1,1-Cer[12]). Diagnosing Schindler disease is complicated because it is a very rare disease of which patients are often diagnosed in hindsight without an autopsy.[10] Therefore, not all accumulated glycoconjugates have been fully elucidated to this date.

Interestingly, four major types of glycosylated serine/threonine residues have been identified in urine samples from all three disease phenotypes (Figure 2).[10,13–17] As expected, a major compound contained α-*N*-acetylgalactosamine as terminal residue. However, the three other major compounds contained longer chains and, in all cases, α-*N*-acetylgalactosamine was buried underneath other carbohydrate residues. Furthermore, the accumulated sialoglycopeptides were strikingly similar to those found in the urine of patients with sialidosis (α-*N*-acetylneuraminidase

deficiency) and galactosialidosis (combined β-galactosidase and α-*N*-acetylneuraminidase deficiency). Under normal circumstances these glycopeptides are sequentially hydrolysed by a complex of enzymes, however, it appears that mutations in one of these enzymes can alter the function of the entire complex.[10,13–17]

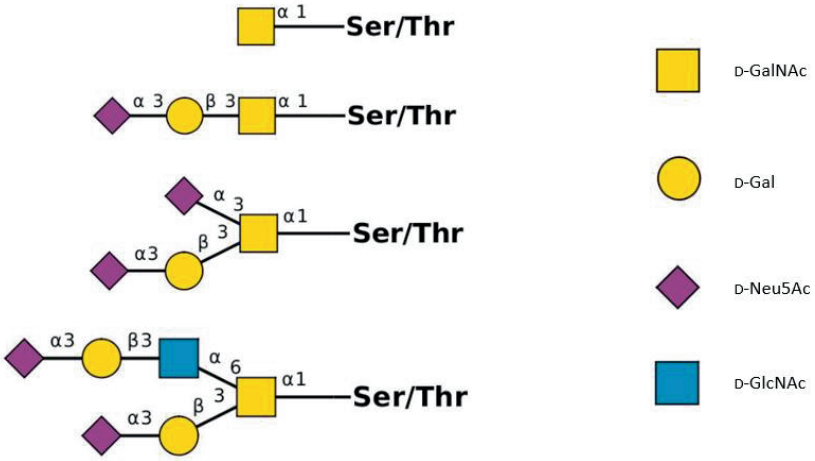


Figure 2 *O*-Linked glycopeptides that were identified in the urine of patients with Schindler disease.

Treatment options for lysosomal storage diseases

Currently only palliative care is available for both Sanfilippo and Schindler disease. However, when considering lysosomal storage disorders in general, three therapeutic therapies are available: enzyme replacement therapy (ERT), substrate reduction therapy (SRT) and pharmacological chaperone therapy (PCT). Both ERT and SRT already have examples available in the clinic. PCT is still in the development phase. In the next subchapters all three therapeutic strategies will be discussed individually.

Enzyme replacement therapy

In enzyme replacement therapy LSD patients are intravenously injected with recombinant enzyme to substitute for diminished or lacking activity of endogenous enzyme.[18] ERT was first approved for type I Gaucher disease, an LSD in which lysosomal glucocerebrosidase (GBA1) is defective and glucocerebroside accumulates in the body (Figure 3, red). ERT with recombinant GBA1 (originally GBA1 isolated from human placentas) proved

to be highly effective in reducing glucocerebroside concentrations in the liver and spleen.[19] However, the effectiveness of ERT is dependent on the penetration of the recombinant enzyme into disease-related tissues. Type II and type III Gaucher disease remain untreatable with ERT because recombinant enzymes in their current form are not capable of passing the blood-brain barrier.[18] Sanfilippo and Schindler disease, which both have a neurological component, are therefore currently not suitable candidates for ERT.

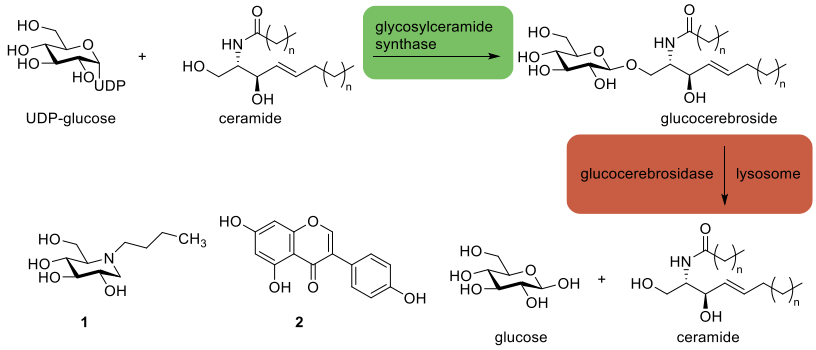


Figure 3 Biosynthesis and metabolism of glucocerebroside.

Substrate reduction therapy

In substrate reduction therapy an enzyme upstream in the biosynthetic pathway of the natural substrate is inhibited with the aim to reduce the rate of biosynthesis of the storage material that is the result of genetic deficiency of the corresponding hydrolase enzyme.[20] Miglustat **1** (Figure 3) is a reversible inhibitor of glycosylceramide synthase (GCS, Figure 3, green) and is used to treat patients with type 1 Gaucher disease. It is used either as supplementary treatment to ERT or for patients who cannot or will not receive ERT.[21,22] Miglustat **1** is a small chemical compound that can pass the blood-brain barrier. It is also used to treat progressive neurological complications in patients with Niemann-Pick disease type C.[23] SRT therapy might prove to be a valuable tool to treat Sanfilippo and Schindler disease. For Sanfilippo disease, supplementation with genistein **2**, known to inhibit glycosaminoglycan synthesis in cultures of fibroblasts, was administered to a group of 19 children for a year. All children had a confirmed diagnosis of Sanfilippo syndrome. The urinary GAG levels and disability of the patients

were evaluated throughout the year but unfortunately the treatment with genistein failed to significantly improve the disease disability.[24,25]

Pharmacological chaperone therapy

A lysosomal storage disease can arise through a wide variety of mutations in the same enzyme. All mutations of a particular enzyme result in the accumulation of the natural substrate, but treatment options may differ based on the type of mutation. The previous two therapies, ERT and SRT, both did not focus on the type of mutation. Where ERT solves these issues by supplementing with active recombinant enzyme, SRT focusses on the reduction of the biosynthesis of the natural substrate. In contrast, pharmacological chaperone therapy focusses on regaining activity of the endogenous, mutant enzyme. In most cases, mutations happen outside of the active site and lead to improper folding or reduced stability of the protein.[26] Pharmacological chaperones (PCs) are small molecular competitive inhibitors that bind specifically to an enzyme and thereby assist in the proper folding of the enzyme within the ER lumen.[27] The properly folded enzyme is then routed to the lysosomes in which the endogenous substrate should theoretically outcompete the competitive inhibitor with an effective regain of function as a result. It is important that PCs are selective for the enzyme of interest to avoid disrupting the quality control system. A straightforward way is to design compounds that resemble the endogenous substrate.[1,2,26–29] Currently only one PC for lysosomal storage disorders is used in the clinic, Migalastat **4** (Figure 4 A), where it is used in combination therapy with ERT. Migalastat helps to stabilize the recombinant enzyme used in the treatment of Fabry disease (deficiency of α-galactosidase).[30,31]

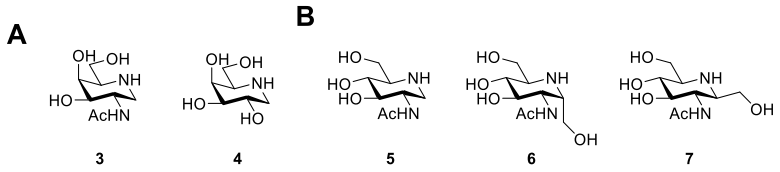


Figure 4 A Competitive inhibitors tested for Schindler disease (α-*N*-acetylgalactosaminidase). **B** A panel of competitive inhibitors tested for Sanfilippo disease (α-*N*-acetylglucosaminidase).

N-Acetyl-α-galactosaminidase has a high sequence similarity with α-galactosidase and even has some reactivity towards terminal α-galactose residues.[32] Therefore Migalastat **4**, as well as its *N*-acetyl analogue **3**, were

tested for their chaperoning ability in cell experiments containing human NAGLU (Figure 4A). As expected, both **3** and **4** proved to be effective at chaperones for NAGLU. However, α-galactosidase and GB1 (β-galactosidase) also were apparent as off-targets, due to the ambiguity of Migalastat **4**, resulting in a decrease of enzyme activity. The presence of the *N*-acetyl moiety in **3** creates a steric clash that prevents binding to either α-or-β-galactosidase.[11,32]
A high-throughput screen in which 1302 compounds were tested for their ability to increase activity of *N*-acetyl-α-glucosaminidase in fibroblasts failed and no hits were found.[33] In a more targeted approach, a panel of iminosugars (scaffolds **5**-**7**, Figure 4B) were tested for their inhibitory potency towards a bacterial homolog of NAGLU from *Clostridium perfringens*. Furthermore, all the compounds were tested for their chaperone capability by measuring an increase in residual activity of NAGLU in cells. These studies revealed that β-C-iminosugar **7** has a lower affinity for NAGLU but higher chaperone capability than α-C-iminosugar **6**.[6,34,35]

In this chapter the design and synthesis of a set of covalent inhibitors and probes for both *N*-acetyl-α-galactosaminidase and *N*-acetyl-α-glucosaminidase is presented. The probes are thought to be valuable tools that may allow quick and easy visualization of active enzymes in native samples. The inhibitors will provide a unique opportunity to study the interactions in the covalent substrate-enzyme complex. This can lead to valuable structural information that can be used to synthesize a next generation of PCs.

Retrosynthesis

The target α-*N*-acetylgalactosamine (α-GalNAc) and α-*N*-acetylglucosamine (α-GlcNAc) mimics consists of two sets of compounds, one bearing an epoxide and one an aziridine, of which the latter is also foreseen as a precursor for a Cy5 probe and a biotin probe by attachment of the reporter to the aziridine (See Figure 5 and 6). The key synthetic transformation in the routes towards all target compounds is the installation of an azide in an equatorial position at C2 (GlcNAc/GalNAc numbering) of an appropriate cyclohexene precursor. A late-stage transformation is desired over an early-stage transformation because of the inherent susceptibility of azides towards

reducing conditions. Late-stage transformations require easy access to carbohydrate-mimetic cyclohexene derivative featuring an axial orthogonally protected 2-OH. For this purpose, a naphthyl group is chosen. From these considerations, talose-configured cyclohexene **14** emerges as the key intermediate for the α-GalNAc-mimetic set of compounds (Figure 5).

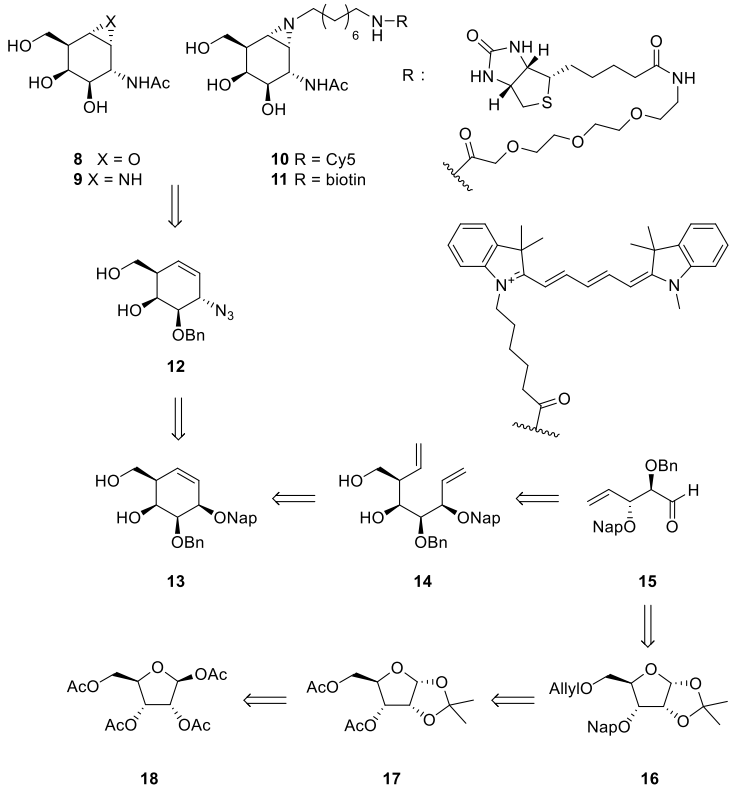


Figure 5 Retrosynthetic analysis of α-GalNAc inhibitors and probes.

It was envisioned that talose-configured cyclohexene **13** could be accessed through a ring closing metathesis of diene **14**. Compound **14** could be synthesized through a chiral auxiliary-controlled aldol reaction using an Evans oxazolidinone on aldehyde **15**.[36] Orthogonally protected aldehyde **15** would be accessible through orthogonally protected acetonide **16**, which in turn would be accessible from commercially available ribofuranose **18**.

For the α-GlcNAc-mimetic set of target compounds, mannose-configured cyclohexene **24** was considered as the key intermediate. Mannose-configured cyclohexene **24** would be accessible through diene **25**, which in

turn was envisioned to be synthesized by a Barbier addition to the common aldehyde intermediate **15**.[37]

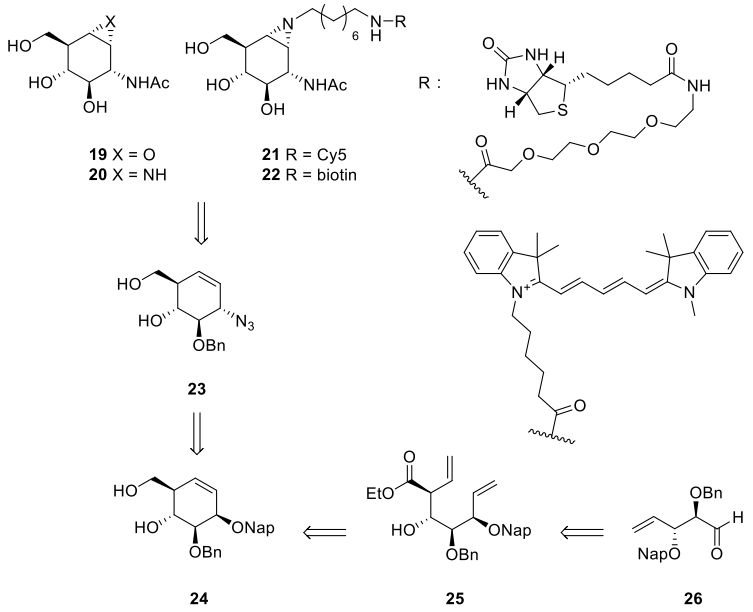


Figure 6 Retrosynthetic analysis of α-GlcNAc inhibitors and probes.

4.2 Results and discussion

Commercially available tetra-*O*-acetyl-ribofuranose **18** was treated with iodine in acetone to obtain acetonide **17** (Figure 7).[38] Deacetylation followed by a selective protection of the primary alcohol in **26** with TBDPS-Cl resulted in compound **27**. Naphthylation followed by removal of the silyl protecting group and subsequent allylation gave ribofuranose **16**. Direct allylation of the primary alcohol of acetonide **26** by leveraging the difference in reactivity between a primary and secondary hydroxyl group was initially attempted. Both Taylor's catalyst (2-aminoethyl diphenyl borinate)[39] and tin ketal chemistry[40] led to low yields (10-30%). Longer reaction times and elevated equivalents of catalysts did not result in a higher yield. Therefore, the longer, but higher yielding reaction sequence, was used to install the allyl protecting group.

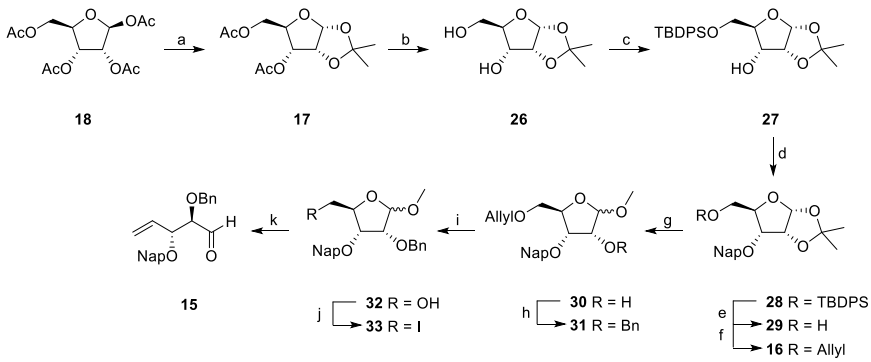


Figure 7 Reagents and conditions: a) I_2, anhydrous acetone, 83%. b) NaOMe, MeOH, crude. c) TBDPS-Cl, imidazole, DMF, 91% over 2 steps. d) Nap-Br, NaH, TBAI, DMF, 90%. e) TBAF, THF, 81%. f) allyl bromide, NaH, TBAI, DMF, 92%. g) CSA, MeOH, 50 °C, 90%. h) BnBr, NaH, TBAI, DMF, 80%. i) $PdCl_2$, MeOH/DCM, 94%. j) I_2, imidazole, PPh_3, THF, 94%, α/β:23/1. k) α: 140 eq. zinc dust, THF/H_2O, 71%. β: 20 eq. zinc dust, THF/H_2O, 75%.

Orthogonally protected acetonide **16** was then treated with camphor sulfonic acid to remove the acetonide to obtain methyl-*O*-ribofuranoside **30** as an α/β mixture which was used in the next steps without separating the anomers. Subsequent benzylation and removal of the allyl group resulted in ribofuranose **32**. Subjection of **32** to Appel-like conditions resulted in iodide **33** which was then converted into aldehyde **15** using a Vasella fragmentation.[37] It is worth mentioning that the anomers of **33** were separated and subjected to Vasella fragmentation conditions separately.

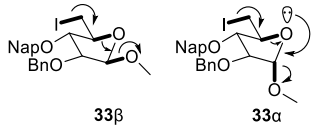


Figure 8 Vasella fragmentation reaction: different anomers have different reactivity.

Vasella *et al.* [41] already noted how different anomers can differ in reactivity in 1984. For the β-anomer all bonds involved in the reaction are antiperiplanar (180° angle), resulting in a concerted fragmentation. For the α-anomer, where the C4-O4 bond and the C1-O1 bond are synclinal to each other (60° angle), the fragmentation requires participation of a lone pair of the ring oxygen (Figure 8). Treatment of **33β** with 20 eq. of zinc showed full conversion in 20 minutes to aldehyde **15**, which was isolated with 71% yield. Treatment of **33α** with 20 eq. of zinc for 20 minutes resulted in no

conversion. Increasing the amount of zinc to 140 eq. and extending the reaction time to 3 hours led to aldehyde **15** in 75%.

The aldol reaction of aldehyde **15** and Evans oxazolidinone **36** then gave compound **34**.[36] Reduction of the cyclic amide followed by ring-closing metathesis resulted in orthogonally protected talose-configured cyclohexene **13** (Figure 8). Aldehyde **15** was also reacted with ethyl-4-bromobut-2-enolate in a Barbier addition[37] resulting in mannose-configured diene **25**. Ring-closing metathesis followed by reduction of the ester resulted in orthogonally protected mannose-configured cyclohexene **24**.

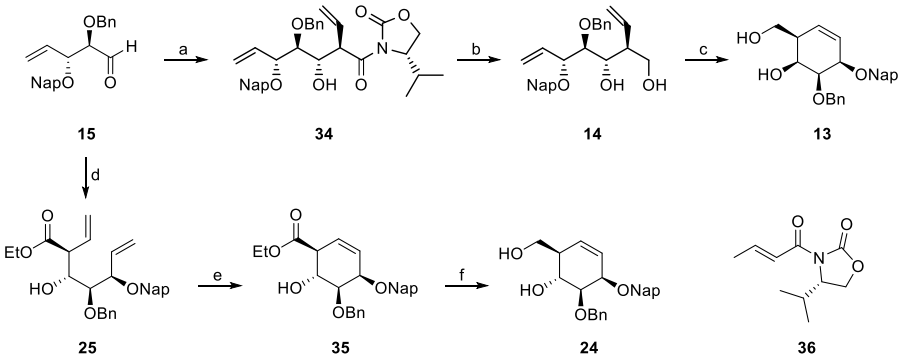


Figure 9 Reagents and conditions: a) Evans oxazolidinone, Bu_2OTf, Et_3N, DCM, 94%. b) $LiBH_4$, THF/H_2O, 91%. c) Grubbs catalyst 2nd gen., DCM, 99%. d) ethyl-4-bromobut-2-enolate, $La(OTf)_3$, In powder, H_2O, 56%. e) Grubbs catalyst 2nd gen., DCM, 99%. f) i) DIBAL-H, THF. ii) $NaBH_4$, H_2O, 94%.

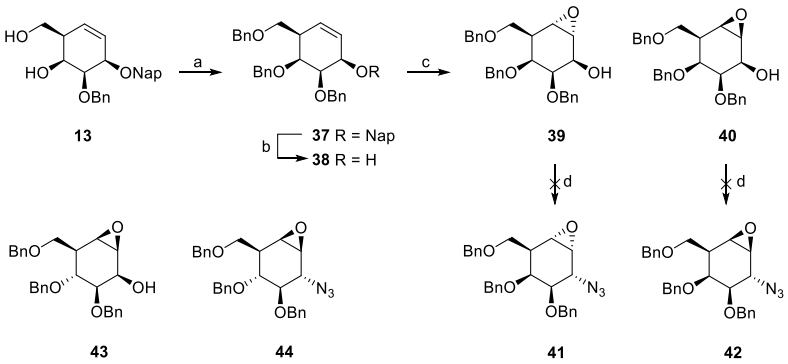


Figure 10 Reagents and conditions: a) BnBr, NaH, TBAI, DMF, 67%. b) DDQ, DCM/H_2O, 82%. c) mCPBA, DCM, 4 °C, 14% **39**, 71% **40**. d) PPh_3, DEAD, DPPA.

Benzylation of **13** under basic conditions, followed by oxidative cleavage of the naphthyl group resulted in cyclohexene **38** (Figure 10). mCPBA-Mediated

epoxidation then gave epoxide **39** as a minor and epoxide **40** as a major product. Ho *et al.*[42] published the synthesis of mannose-configured-epoxide **43** in which standard Mitsunobu conditions (PPh_3, DEAD) and diphenylphosphoryl azide (DPPA) as nitrogen donor are used to substitute the 2-OH for an azide with inversion of configuration to obtain GlcNAc-configured compound **44**.[43–46] Applying these conditions to **40** however did not result in any product formation. Treatment of **40** with an 1,1'-azodicarbonyldipiperidine/PBu_3 mixture, developed by Tsunoda *et al*.[47] as a more reactive Mitsunobu system, did not yield any product. Interestingly, treatment of epoxide **43** with the different Mitsunobu conditions also did not produce any product. Therefore, the Mitsunobu approach was abandoned and other leaving groups were probed.

Triflation of **39** followed by treatment with Bu_4NN_3 resulted in 53% of **41**.[48] Applying the same two-step procedure to **40** gave **42** in 88%. Reduction of the azide in **41** followed by acetylation gave **45**. Subjecting of **45** to dissolving metal reduction conditions resulted in fully deprotected epoxide **8** (Figure 11).

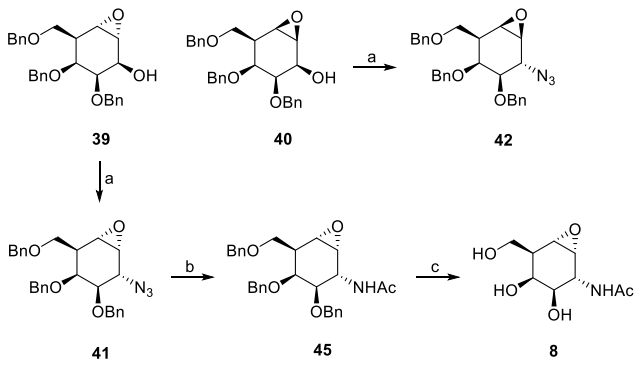


Figure 11 Reagents and conditions: a) i) Tf_2O, pyridine, DCM. ii) Bu_4NN_3, DMF, 53% for **42**, 88% for **43**. b) i) PPh_3, THF/H_2O, 40 °C. ii) Ac_2O, pyridine, DCM, 53%. c) NH_3, Na, *t*-BuOH, THF, -65 °C, 76%.

The synthesis of GlcNAc mimic epoxide **19** commenced with the benzylation of **24** under basic conditions to obtain compound **46**. Oxidative cleavage of the naphthyl group followed by epoxidation of the double bond in **47** with *in situ* generated methyl(trifluoromethyl)dioxirane[49] yielded exclusively epoxide **48**. An attempt to substitute the 2-OH in **48** for an azide with

inversion of configuration using the two-step procedure optimized for compounds **39** and **40** gave a low yield of **49** and several decomposition products.

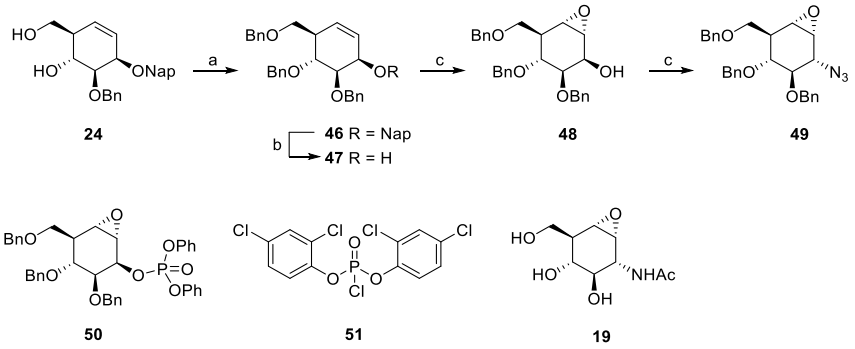


Figure 12 Reagents and conditions: a) BnBr, NaH, TBAI, DMF, 82%. b) DDQ, DCM/H_2O, 76%. c) Oxone, $NaHCO_3$, 1,1,1-trifluoroacetone, EDTA, ACN/H_2O, 68%. d) i) Tf_2O, pyridine, DCM. ii) Bu_4NN_3, DMF, 20%.

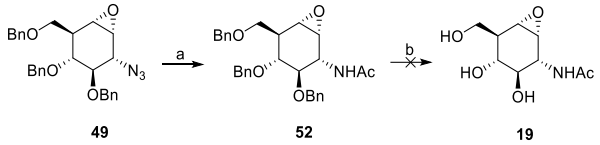
Attempts to optimize this reaction by changing reagents, time and temperature are presented in table 1.

Table 1 Reaction conditions used for the inversion of 2-*O* **48**.

#	Reagents (eq.)	Reaction time	T (°C)	Yield (%)
1	1. Tf_2O (1.5), pyridine (2), DCM (0.3M) 2. Bu_4NN_3 (2), DMF (0.3M)	1. 19h 2. 23h	1. -45 2. RT	19
2	1. Tf_2O (1.5), pyridine (2), DCM (0.3M) 2. Bu_4NN_3 (2), DMF (0.6M)	1. 4.5h 2. 4h	1. -45 2. RT	27
3	1. Tf_2O (1.5), pyridine (2), DCM (0.3M) 2. Bu_4NN_3 (2), DMF (1.5M)	1. 3h 2. 4h	1. -45 2. RT	22
4	1. Tf_2O (1.5), pyridine (2), DCM (0.3M) 2. Bu_4NN_3 (2), DIPEA (2), DMF (0.3M)	1. 4.5 2. 4.5	1. -45 2. RT	21

5	MsCl (1.5), pyridine (2.5), DCM (0.3M)	5h	0 -> RT	decomposition
6	Nf_2O (1.5), pyridine (10), DCM (0.3M)	23h	-78 -> RT	decomposition
7	DPPA (1.2), DBU (1.2), THF (0.3M)	16h	RT	70 of **50** (Figure 12)
8	1. **51** (2.2), NaN_3 (4), DMAP (1.2), DMF (0.3M) 2. Bu_4NN_3 (2), DMF (0.3M)	1. 27h 2. 16h	1. 45 2. RT	19

TLC analysis of entry 1 (see table 1) revealed the formation of several decomposition products. The side products were isolated and analyzed by NMR. One side product could be identified as an opened epoxide. However, characterization of the other products by NMR proved impossible because characteristic peaks could not be discerned. Upscaling the reaction led to even lower yields. Increasing the concentration of the second step (entry 2 and 3) did not result in any significant change in yield. In a final attempt to optimize the initial conditions (entry 4) DIPEA was added as a base to step 2 because during the reaction a red hue was observed. This could indicate the presence of hydrazoic acid which could potentially be the reason for the decomposition of the starting material. Addition of DIPEA did not lead to any improvement in yield. Attempts to change the leaving group to either a mesylate or nonaflate resulted in decomposition in the first step (entry 5 and 6). Thompson *et al*. published a synthetic method for the direct conversion of alcohols into azides using diphenyl phosphorazidate and DBU as an alternative for Mitsunobu reactions.[50] Treatment of **48** with DPPA and DBU resulted in one product which upon purification turned out to be the phosphate triester **50** (entry 7). Yu *et al*. encountered the same issue and developed a more reactive alternative using bis(2-4-dichlorophenyl) phosphate **51** instead of DPPA.[51] Applying these conditions to **48** resulted in the formation of the phosphate triester intermediate. Upon addition of Bu_4NN_3 the desired product **49** was formed in 19% (entry 8).

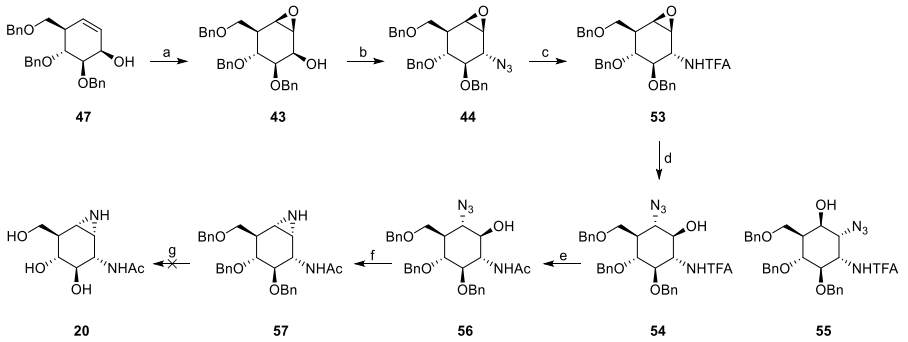


49 52 19

Figure 13 Reagents and conditions: a) i) PPh_3, THF/H_2O, 40 °C. ii) Ac_2O, pyridine, DMAP, DCM, 47%. b) NH_3, Na, *t*-BuOH, THF, -65 °C, decomposition.

Reduction of the azide in **49** and subsequent acetylation resulted in **52**. Unfortunately, subjecting **52** to both dissolving metal reduction conditions or hydrogenation with Pd-OH as catalyst yielded decomposition of the starting material. (Figure 13).

The synthesis of GlcNAc mimic aziridine **20** commenced with the mCPBA-mediated epoxidation of **47** to diastereoselectively yield epoxide **43** (Figure 14).



47 43 44 53 20 57 56 54 55

Figure 14 Reagents and conditions: a) mCPBA, DCM, 0 °C. b) i) Tf_2O, pyridine, DCM. ii) NaN_3, 15-crown-5 ether, DMF, 78% over two steps. c) i) PPh_3, THF/H_2O, 40 °C. ii) Trifluoroacetic anhydride, pyridine, 82% over two steps. d) NaN_3, $LiClO_4$, DMF. e) i) $NH_3.H_2O$, 60 °C. ii) Ac_2O, Et_3N, THF, 20% over two steps. f) PPh_3, ACN, 60 °C, 92%. g) NH_3, Li, *t*-BuOH, THF, -60 °C.

Triflation of **43** followed by treatment with sodium azide resulted in the substitution of the 2-OH in **43** for an azide with inversion of configuration to obtain compound **44**. Reduction of the azide and subsequent acetylation using trifluoroacetic anhydride gave in compound **53**. Opening of the epoxide with sodium azide yielded a mixture of the di-equatorial product **54** and the di-axial regioisomer **55**, with the former being formed predominantly. The isomers were not separated as this proved to be easier after the next step. Treatment of the mixture of **54** and **55** with $NH_3.H_2O$ followed by acetylation resulted in 20% of the di-equatorial product **56** over two steps. Subsequent

treatment with triphenylphosphine gave aziridine **57** in 92% yield.[52] Treatment of **57** with sodium in liquid ammonia at -60 °C resulted in a mixture of the target product and the deacetylated product. Unfortunately, attempts to separate the two compound or re-acetylate the amine have failed so far. Hydrogenation of **57** led to decomposition of the starting material.

4.3 Conclusion

This chapter presents a synthetic route towards a set of potential probes and inhibitors for both retaining *N*-acetyl-α-galactosaminidases and *N*-acetyl-α-glucosaminidases. The key orthogonally protected aldehyde **15** was synthesized from commercially available tetra-*O*-acetyl-ribofuranose **18**. From orthogonally protected aldehyde **15**, a Barbier addition was used to synthesize mannose-configured diene **25**, and an Evans oxazolidinone was used to synthesize talose-configured diene **14**. Both dienes were successfully transformed into their respective cyclohexenes. The α-*N*-acetyl galactosamine epoxide **8** was successfully synthesized. Attempts to synthesize the α-*N*-acetyl glucosamine epoxide **19** stranded when the deprotection of **52** resulted in the decomposition of the starting material. Furthermore, this chapter shows that it is feasible to synthesize the fully protected α-*N*-acetyl glucosamine aziridine **57** from the same cyclohexene. However, also in this case the deprotection resulted in an inseparable mixture of compounds or decomposition. Further work is needed to improve the deprotection steps.

4.4 Acknowledgements

Melanie Groot, Karin Janmaat and Moescha Hoopman are acknowledged for their work on this project.

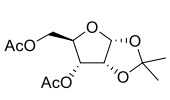
4.5 Experimental methods

4.5.1 Synthesis

General

General synthetic methods were described in Chapter 2.

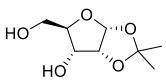
3,5-di-O-acetyl-1,2-isopropylidene-α-D-ribofuranose (17)



1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose **18** (63.6 g, 200 mmol, 1 eq.) was co-evaporated with anhydrous toluene thrice and dissolved in dry acetone (670 mL, 0.3 M). I_2 (17.8 g, 70 mmol, 0.35 eq.) was added and the mixture was stirred at room temperature for 3.5 hours. The reaction was quenched with solid $NaHCO_3$, H_2O and solid $Na_2S_2O_3$. The mixture was concentrated in vacuo until all the acetone was removed. The resulting slurry was diluted with EtOAc and washed with H_2O, sat. $NaHCO_3$, 10% $Na_2S_2O_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 3/20 -> 3/10, v/v) to obtain compound **17** (45.4 g, 166 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, *J* = 3.8 Hz, 1H), 4.83 (dd, *J* = 4.8, 3.8 Hz, 1H), 4.69 (dd, *J* = 9.2, 4.8 Hz, 1H), 4.37 (dd, *J* = 12.2, 2.6 Hz, 1H), 4.32 (ddd, *J* = 9.2, 4.9, 2.5 Hz, 1H), 4.13 (dd, *J* = 12.2, 4.9 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 1.57 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.3, 113.3, 104.3, 77.2, 75.5, 72.3, 62.5, 26.7, 26.7, 20.9, 20.8. HRMS calculated for $[C_{12}H_{18}O_7 + Na]^+$: 297.0950, found 297.0945.

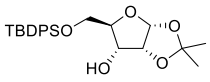
1,2-*O*-isopropylidene-α-D-ribofuranose (26)



To a solution of compound **17** (0.187 g, 0.68 mmol, 1 eq.) in MeOH (2.3 mL, 0.3 M) NaOMe (0.05 mL, 4.4 M, 0.3 eq.) was added and the mixture was stirred overnight. The reaction was quenched Amberlite IR-120 H^+ resin, filtered and concentrated in vacuo. The crude was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (d, *J* = 3.8 Hz, 1H), 4.59 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.06 – 3.91 (m, 2H), 3.85 (ddd, *J* = 8.9, 3.7, 2.6 Hz, 1H), 3.74 (dd, *J* = 12.5, 3.7 Hz, 1H), 1.58 (s, 3H), 1.38 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.9, 104.1, 80.7, 78.9, 70.9, 60.8, 26.6, 26.6. HRMS calculated for $[C_8H_{14}O_5 + Na]^+$: 213.0733, found 213.0733.

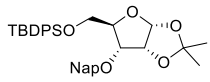
5-*O*-tert-butyldiphenylsilyl-1,2-*O*-isopropylidene-α-D-ribofuranose (27)



Crude **26** (1.94 mmol, 1 eq.) was dissolved in 10 mL anhydrous DMF (0.2 M) and co-evaporated with anhydrous toluene twice to remove any traces of methanol from the starting product. The resulting solution was cooled to -40 °C and imidazole (0.66 g, 9.7 mmol, 5 eq.) and TBDPS-Cl (0.50 mL, 1.94 mmol, 1 eq.) were added. The reaction was left to stir at -40 °C until TLC showed full

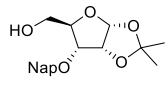
conversion of the starting material. Subsequently the reaction was diluted with H_2O, extracted with diethyl ether thrice, washed with H_2O five times, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 1/9 -> 1/5, v/v) to obtain compound **27** (0.76 g, 1.76 mmol, 91%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 4H), 7.44 – 7.35 (m, 6H), 5.85 (d, *J* = 3.8 Hz, 1H), 4.60 (t, *J* = 5.2, 3.8 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.99 – 3.93 (m, 1H), 3.88 – 3.82 (m, 2H), 2.31 (d, *J* = 9.9 Hz, 1H), 1.56 (s, 3H), 1.38 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.7, 129.8, 129.8, 127.9, 127.8, 104.3, 81.4, 78.9, 71.4, 62.5, 26.9, 26.8, 26.7. HRMS calculated for $[C_{24}H_{32}O_5Si + Na]^+$: 451.1917, found 451.1911.

5-*O*-tert-butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*O*-naphthyl-α-D-ribofuranose (28)



Compound **27** (0.87 g, 2 mmol, 1 eq) was co-evaporated with anhydrous toluene thrice and dissolved in anhydrous DMF (6.7 mL, 0.3 M). The solution was cooled in an ice bath and naphthyl bromide (0.54 g, 2.43 mmol, 1.2 eq.), TBAI (0.037 g, 0.10 mmol, 0.05 eq.) and NaH (60% wt) (0.073 g, 3 mmol, 1.5 eq.) were added. The reaction mixture was left to stir overnight at room temperature. Subsequently the reaction was quenched with MeOH, diluted with H_2O, extracted with diethyl ether thrice, washed with H_2O five times, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 1/20 -> 1/9, v/v) to obtain compound **28** (1.04 g, 1.82 mmol, 90%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 4H), 7.65 – 7.60 (m, 4H), 7.52 – 7.45 (m, 3H), 7.44 – 7.29 (m, 6H), 5.75 (d, *J* = 3.6 Hz, 1H), 4.93 (d, *J* = 12.2 Hz, 1H), 4.77 (d, *J* = 12.2 Hz, 1H), 4.61 (t, *J* = 3.9 Hz, 1H), 4.17 (dt, *J* = 8.8, 2.3 Hz, 1H), 4.10 (dd, *J* = 8.8, 4.2 Hz, 1H), 3.99 (dd, *J* = 11.9, 1.9 Hz, 1H), 3.82 (dd, *J* = 11.8, 2.8 Hz, 1H), 1.61 (s, 3H), 1.38 (s, 3H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.7, 135.3, 133.3, 129.8, 129.7, 128.5, 128.0, 127.9, 127.8, 127.8, 126.9, 126.3, 126.1, 125.9, 104.3, 79.7, 77.9, 76.8, 72.6, 61.9, 27.1, 26.9, 26.7. HRMS calculated for $[C_{35}H_{40}O_5Si + Na]^+$: 591.2543, found 591.2537.

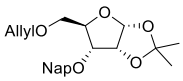
3-*O*-naphtyl-1,2-isopropylidene-α-D-ribofuranose (29)



Compound **28** (0.29 g, 0.50 mmol, 1 eq.) was co-evaporated with anhydrous toluene thrice before being dissolved in anhydrous THF (0.3 M, 1.7 mL). TBAF 1 M in THF (1.5 mL, 1.5 mmol, 3 eq.) was added and the reaction mixture was stirred at RT for 1.5 hours. The reaction mixture was then concentrated under reduced pressure and purified using flash column chromatography (MeOH/DCM, 1/100 -> 3/100, v/v) to obtain compound **29** (0.13 g, 0.41 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 4H), 7.52 – 7.43 (m, 3H), 5.67 (d, J = 3.6 Hz, 1H), 4.87 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 12.1 Hz, 1H), 4.51 (t, J = 4.0 Hz, 1H), 4.13 (dt, J = 9.1, 2.8 Hz, 1H), 3.90 (dd, J = 12.5, 2.5 Hz, 1H), 3.85 (dd, J = 9.0, 4.3 Hz, 1H), 3.69 – 3.61 (m, 1H), 1.59 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.1, 134.9, 133.2, 133.1, 129.6, 128.4, 127.9, 127.8, 126.9, 126.3, 126.1, 125.8, 113.1, 104.1, 78.9, 77.7, 77.4, 76.6, 72.5, 60.6, 26.9, 26.5. HRMS calculated for $[C_{19}H_{22}O_5 + Na]^+$: 353.1365, found 353.1359.

3-*O*-alloxymethyl-5-*O*-tert-butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*O*-naphthyl-α-D-ribofuranose (16)

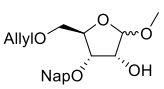


Compound **29** (9.18 g, 27.80 mmol, 1 eq.) was co-evaporated with toluene twice and dissolved in anhydrous DMF (92 mL, 0.3 M). The mixture was cooled to 0 °C and allyl bromide (3.61 mL, 41.70 mmol, 1.2 eq.) was added and the mixture stirred for 5 minutes. NaH (60% wt) (2.22 g, 55.60 mmol, 1.5 eq.) and TBAI (0.51 g, 1.39 mmol, 0.05 eq.) were added and the reaction was allowed to warm to room temperature. After stirring for 5.5 hours TLC showed full conversion of the starting material. The reaction was diluted with H_2O and extracted with diethyl ether thrice. The combined organic layers were washed with water five times, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 1/20 -> 1/5, v/v) to obtain compound **16** (9.46 g, 25.53 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 4H), 7.52 – 7.43 (m, 3H), 5.89 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.80 (d, *J* = 3.7 Hz, 1H), 5.26 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.81 (dd, *J* = 12.4, 0.8 Hz, 1H), 4.71 (dd, *J* = 12.3, 0.8 Hz, 1H), 4.61 (t, *J* = 4.0 Hz, 1H), 4.21 – 4.10 (m, 2H), 4.04 (ddt, *J* = 12.7, 6.0, 1.3 Hz, 1H), 3.90 – 3.81 (m, 2H), 3.65 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.58 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.6, 133.4,

133.1, 128.3, 128.0, 127.8, 126.7, 126.2, 126.0, 125.9, 118.2, 113.0, 104.1, 78.0, 77.6, 77.5, 73.8, 71.8, 68.1, 26.9, 26.62. HRMS calculated for $[C_{22}H_{26}O_5 + Na]^+$: 393.1672, found 393.1671.

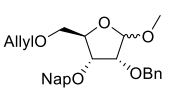
5-*O*-allyl-1-methoxy-3-*O*-naphtyl-α-D-ribofuranose (30)



Compound **16** (0.33 g, 0.62 mmol, 1 eq.) was dissolved in MeOH (0.3 M, 2.1 mL) and CSA (0.043 g, 0.19 mmol, 0.3 eq.) was added. The reaction mixture was stirred at RT for 3 hours before being refluxed for 0.5 hour. The reaction mixture was cooled to RT and quenched with TEA and concentrated in vacuo. The product was purified by column chromatography (EtOAc/pentane, 3/10 -> 1/5, v/v) to yield compound **30** (0.17 g, 0.56 mmol, 90%).

Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 4H), 7.48 – 7.38 (m, 3H), 4.84 (d, J = 3.8 Hz, 1H), 4.71 – 4.62 (m, 2H), 4.21 – 4.14 (m, 2H), 4.11 – 4.02 (m, 1H), 3.73 (dd, J = 11.9, 2.8 Hz, 1H), 3.54 (dd, J = 10.6, 5.4 Hz, 1H), 3.31 (s, 3H), 3.23 – 3.12 (m, 1H), 2.61 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.2, 134.4, 133.1, 133.1, 133.0, 128.5, 128.3, 127.9, 127.8, 127.7, 127.7, 126.9, 126.7, 126.3, 126.2, 126.2, 126.0, 125.7, 125.5, 108.9, 103.0, 83.2, 82.5, 78.2, 63.2, 55.5. HRMS calculated for $[C_{20}H_{24}O_5Na]^+$: 367.1521; found 367.1693.

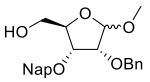
5-*O*-allyl-2-*O*-benzyl-1-methoxy-3-*O*-naphtyl-α-D-ribofuranose (31)



Compound **30** (8.18 g, 23.8 mmol, 1 eq.) was co-evaporated with anhydrous toluene thrice and subsequently dissolved in anhydrous DMF (80 mL, 0.3 M). The reaction mixture was cooled to 0 °C and BnBr (6.5 mL, 54.7 mmol, 2.3 eq.) and TBAI (0.44 g, 1.19 mmol, 0.05 eq.) were added. After 5 minutes, NaH (60% wt) (2.38 g, 59.5 mmol, 2.5 eq.) was also added. The reaction mixture was allowed to warm to RT and stirred overnight. After 16 h, an additional quantity of NaH (60%) (0.95 g, 23.8 mmol, 1.0 eq.) and benzyl bromide (2.3 mL, 23.8 mmol, 1 eq.) was added and the reaction mixture was stirred for 24 h. The reaction was quenched by MeOH and diluted with H_2O. The aqueous phase was extracted with Et_2O thrice and the combined organic layers were washed with H_2O five times and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography (EtOAc/pentane, 1/20 -> 1/5, v/v) to yield compound **31** (8.31 g 19.12 mmol, 80%).

Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.72 (m, 4H), 7.48 – 7.42 (m, 3H), 7.39 – 7.26 (m, 5H), 5.86 (ddt, J = 17.3, 10.4, 5.5 Hz, 1H), 5.24 (dq, J = 17.2, 1.7 Hz, 1H), 5.13 (dq, J = 10.4, 1.4 Hz, 1H), 4.93 (d, J = 1.1 Hz, 1H), 4.75 – 4.57 (m, 4H), 4.35 (ddd, J = 7.1, 5.9, 3.8 Hz, 1H), 4.04 (dd, J = 7.1, 4.7 Hz, 1H), 4.00 (dtd, J = 5.5, 1.5, 0.7 Hz, 2H), 3.86 (dd, J = 4.7, 1.1 Hz, 1H), 3.57 (dd, J = 10.6, 3.8 Hz, 1H), 3.47 (dd, J = 10.6, 5.9 Hz, 1H), 3.32 (s, 3H). ^{13}C NMR (400 MHz, , $CDCl_3$) δ 137.9, 135.4, 134.8, 133.3, 133.1, 128.5, 128.2, 128.0, 128.0, 127.9, 127.8, 126.7, 126.2, 126.0, 125.9, 116.9, 106.4, 80.5, 79.7, 78.4, 72.5, 72.4, 72.3, 71.5, 55.1. HRMS calculated for $[C_{27}H_{30}O_5 + Na]^+$: 457.1991, found 457.1986.

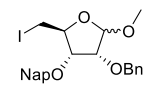
2-*O*-benzyl-1-methoxy-3-*O*-naphtyl-α-D-ribofuranose (32)



Compound **31** (4.32 g, 9.94 mmol, 1.0 eq.) was dissolved in 124 mL MeOH/DCM (1:1, 0.08 M). The reaction mixture was cooled to 0 °C before $Pd(II)Cl_2$ (0.35 g, 1.99 mmol, 0.2 eq.) was added. The reaction mixture was stirred for 17.5 h. The reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The product was purified by flash column chromatography (EtOAc/pentane, 1/10 -> 3/10, v/v) to obtain compound **32** (3.72 g, 9.34 mmol, 94%).

Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.73 (m, 4H), 7.50 – 7.42 (m, 3H), 7.39 – 7.28 (m, 5H), 4.90 (d, J = 1.2 Hz, 1H), 4.74 – 4.58 (m, 4H), 4.32 (dt, J = 6.8, 3.3 Hz, 1H), 4.17 (dd, J = 7.0, 4.7 Hz, 1H), 3.88 (dd, J = 4.8, 1.0 Hz, 1H), 3.81 (ddd, J = 12.0, 4.1, 2.9 Hz, 1H), 3.59 (ddd, J = 12.1, 8.5, 3.9 Hz, 1H), 3.35 (d, J = 0.6 Hz, 3H), 2.04 (d, J = 7.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.8, 135.3, 133.3, 133.2, 128.6, 128.3, 128.1, 128.0, 127.8, 126.7, 126.3, 126.1, 125.8, 106.9, 82.5, 80.3, 77.4, 72.8, 72.7, 62.8, 55.7. HRMS calculated for [C24H26O5 + Na]$^+$: 417.1678; found: 417.1673.

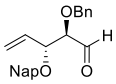
2-*O*-benzyl-5-iodo-1-methoxy-3-*O*-naphtyl-α-D-ribofuranose (33)



Alcohol **32** (3.72 g, 9.34 mmol, 1.0 eq.) was dried by co-evaporation with toluene thrice before being dissolved in 31 mL dry THF (0.3 M). PPh_3 (3.67 g, 14.01 mmol, 1.5 eq.), I_2 (3.56 g, 14.01 mmol, 1.5 eq.) and imidazole (1.27 g, 18.68 mmol, 2.0 eq.) were added and the reaction mixture was heated to reflux. After 2h the reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc and washed with 10% aq. sodium thiosulfate solution. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

product was purified by column chromatography (EtOAC/pentane, 1/20 -> 2/5, v/v) to obtain compound **33** (4.43 g, 8.79 mmol, 94%, α:β; 23:1).
Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 4H), 7.51 – 7.44 (m, 3H), 7.38 – 7.29 (m, 5H), 4.94 (s, 1H), 4.75 – 4.55 (m, 4H), 4.20 (ddd, J = 7.0, 5.6, 4.9 Hz, 1H), 3.99 (dd, J = 6.9, 4.6 Hz, 1H), 3.92 – 3.89 (m, 1H), 3.36 (s, 4H), 3.29 (dd, J = 10.6, 5.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.07, 133.3, 133.2, 128.6, 128.4, 128.1, 128.1, 127.9, 127.0, 126.3, 126.2, 126.0, 106.3, 81.7, 80.5, 80.2, 72.7, 72.5, 55.4, 8.8.
Data for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 4H), 7.51 – 7.41 (m, 3H), 7.39 – 7.26 (m, 5H), 4.92 – 4.86 (m, 2H), 4.72 – 4.66 (m, 1H), 4.63 (d, J = 1.7 Hz, 2H), 4.03 (q, J = 4.3 Hz, 1H), 3.81 (dd, J = 6.9, 4.2 Hz, 1H), 3.69 (dd, J = 7.0, 3.6 Hz, 1H), 3.45 (s, 3H), 3.13 (dd, J = 10.7, 5.0 Hz, 1H), 2.99 (dd, J = 10.7, 4.3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.6, 135.4, 133.1, 133.0, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.0, 126.1, 126.1, 125.9, 102.7, 80.9, 78.5, 77.6, 72.8, 72.7, 55.6, 8.4. HRMS calculated for $[C_{24}H_{25}IO_4 + Na]^+$: 527.0695; found: 527.0690

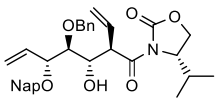
(2R,3R)-2-benzyloxy-3-(naphthalen-2-ylmethoxy)-pent-4-enal (15)



Zinc dust (<10 µm particle size) was placed inside a glass filter and activated with 3M aq. HCl, rinsed with H_2O twice, dioxane twice and Et_2O twice. The activated zinc was then dried at 40 °C under reduced pressure for one hour. It was then placed under argon atmosphere. The following reaction was performed on each anomer separately. It was found that separating the anomers and performing the reactions separately greatly improved the yield. Compound **33α** (9.39 g, 18.6 mmol, 1 eq) was dissolved in THF/H_2O (19/1, 186 mL, 0.1 M) and flushed with argon at 0 °C for 15 minutes. Zinc dust (170 g, 2604 mmol, 140 eq.) was added and the mixture was sonicated for three hours. The mixture was filtered over a pad of celite and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 2/98 -> 1/20, v/v) to obtain compound **15** (4.81 g, 13.9 mmol, 75%). Compound **33β** (0.104 g, 0.206 mmol, 1 eq) was dissolved in THF/H_2O (19/1, 2.06 mL, 0.1 M) and flushed with argon at 0 °C for 15 minutes. Zinc dust (0.269 g, 4.124 mmol, 20 eq.) was added and the mixture was sonicated for 20 minutes. The mixture was filtered over a pad of Celite and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 2/98 -> 1/20, v/v) to obtain compound **15** (0.051 g, 0.147 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.89 – 7.66 (m, 4H), 7.52 – 7.42 (m, 3H), 7.42 – 7.24 (m, 5H), 5.98 – 5.84 (m, 1H), 5.43 – 5.31 (m, 2H) 4.79 (d, *J* = 12.1 Hz, 1H), 4.68 (dd, *J* = 25.6, 11.9 Hz, 2H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.21 (t, *J* = 4.8 Hz, 1H), 3.91 (dd, *J* = 4.8, 2.3 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 137.3, 135.3, 134.1, 133.3, 133.1, 128.6, 128.3, 128.1, 127.9, 127.8, 126.6, 126.2, 126.0, 125.8, 120.3, 85.0, 80.3, 73.1, 70.7. HRMS calculated for $[C_{23}H_{22}O_3 + Na]^+$: 369.1461, found 369.1456.

(S)-3-((2R,3S,4S,5R)-4-benzyloxy-3-hydroxy-5-(naphthalen-2-ylmethoxy)-2-vinylhept-6-enoyl)-4-isopropyloxazolidin-2-one (34)

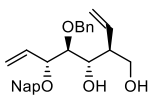


Oxazolidinone (2.52 g, 13.15 mmol, 1.1 eq.) was co-evaporated with toluene 2x under N2, dissolved in anhydrous DCM (22 mL, 0.6 M) and cooled to -78 °C. Bu_2OTf (1.0 M in DCM, 13.15 mL, 13.15 mmol, 1.1 eq.) and Et_3N (2.2 mL, 15.54 mmol, 1.3 eq.) were added and the mixture was stirred at -78 °C for 50 minutes followed by 15 minutes at 0 °C. It was then cooled to -78 °C again. At this temperature compound **15** (4.14 g, 11.95 mmol, 1 eq.), which was co-evaporated with toluene twice and dissolved in anhydrous DCM (21 mL, 0.57 M), was added. The mixture was allowed to warm to -20 °C over one hour and stirred at -20 °C for one hour. The temperature was then allowed to rise to -15 °C and the mixture was stirred at this temperature overnight. A pH 7 phosphate buffer (25 mL) was added at > 0 °C. 50% H_2O_2 was added dropwise and the mixture was stirred for 30 minutes. The mixture was poured into a sat. $NaHCO_3$ and was extracted with DCM thrice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/pentane, 1/20 -> 3/20, v/v) to obtain compound **34** (6.15 g, 11.30 mmol, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.72 (m, 4H), 7.55 – 7.40 (m, 3H), 7.40 – 7.13 (m, 5H), 6.13 – 5.96 (m, 1H), 5.88 (ddd, *J* = 17.1, 10.1, 8.9 Hz, 1H), 5.51 – 5.25 (m, 4H), 5.00 (dd, *J* = 9.8, 6.0 Hz, 2H), 4.81 (d, *J* = 12.1 Hz, 1H), 4.59 (dd, *J* = 11.7, 5.7 Hz, 2H), 4.32 (dd, *J* = 8.2, 3.2 Hz, 1H), 4.24 – 4.01 (m, 2H), 3.86 (dd, *J* = 9.0, 3.1 Hz, 1H), 3.73 (dd, *J* = 8.6, 3.2 Hz, 1H), 3.35 (t, *J* = 8.8 Hz, 1H), 3.03 (d, *J* = 6.5 Hz, 1H), 2.23 (ddq, *J* = 10.2, 7.1, 3.5 Hz, 1H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 153.4, 138.6, 136.2, 134.8, 133.4, 132.9, 132.6, 128.4, 128.2, 127.9, 127.8, 127.6, 127.5, 126.2, 126.1, 125.8, 125.8, 121.6, 120.2, 82.8, 82.1, 73.8, 71.3, 70.6, 62.5,

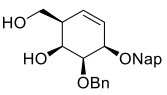
58.1, 49.4, 28.1, 17.9, 14.5. HRMS calculated for $[C_{33}H_{37}NO_6 + Na]^+$: 566.2513, found 566.2510

(2S,3S,4S,5R)-4-benzyloxy-5-(naphthalen-2-ylmethoxy)-2-vinylhept-6-ene-1,3-diol (14)



To a solution of compound **34** (1.40 g, 2.57 mmol, 1 eq.) in THF (18.4 mL, 0.14 M) H_2O (0.86 mL) and $LiBH_4$ (0.140 g, 6.42 mmol, 2.5 eq.) were added at 0 °C and the mixture was stirred at this temperature for one hour. The mixture was allowed to warm to room temperature and stirred for another three hours. The reaction was quenched with 2 M NaOH, diluted with Et_2O and stirred for five minutes. The mixture was diluted with H_2O, poured over Et_2O and washed with sat. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/pentane, 3/20 -> 1/4, v,v) to obtain compound **14** (0.982 g, 2.35 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.74 (m, 4H), 7.52 – 7.41 (m, 3H), 7.36 – 7.22 (m, 5H), 6.11 – 5.95 (m, 2H), 5.46 – 5.37 (m, 2H), 5.26 (dd, *J* = 10.4, 2.1 Hz, 1H), 5.14 (ddd, *J* = 17.4, 2.1, 0.8 Hz, 1H), 4.87 – 4.77 (m, 2H), 4.61 – 4.49 (m, 2H), 4.25 (ddt, *J* = 7.9, 4.1, 0.9 Hz, 1H), 3.95 (ddd, *J* = 8.9, 3.3, 2.2 Hz, 1H), 3.85 – 3.70 (m, 2H), 3.59 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.32 (d, *J* = 3.4 Hz, 1H), 2.69 (dtd, *J* = 7.6, 5.3, 2.1 Hz, 1H), 2.22 (dd, *J* = 7.1, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 135.6, 135.5, 135.2, 133.4, 133.1, 128.5, 128.4, 128.0, 128.0, 127.8, 127.8, 126.7, 126.3, 126.0, 125.9, 120.0, 119.2, 83.2, 81.0, 74.0, 73.8, 70.8, 66.1, 58.30. HRMS calculated for $[C_{27}H_{30}O_4 + Na]^+$: 441.2036, found 441.2036.

3-*O*-benzyl-2-*O*-naphthyl-talo-cyclophellitol-alkene (13)

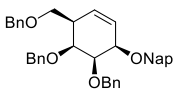


Compound **14** (4.84 g, 11.56 mmol, 1 eq.) was co-evaporated with toluene twice and dissolved in anhydrous DCM (460 mL, 0.025M) and flushed with argon for 15 minutes at 0 °C. Grubbs catalyst 2nd generation (0.490 30 g, 0.578 mmol, 0.05 eq.) was added and mixture was warmed to 40 °C to stir overnight in the dark. The mixture was concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 7/20 -> 1/2, v,v) to obtain compound **13** (4.47 g, 11.45 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.75 (m, 4H), 7.56 – 7.45 (m, 3H), 7.45 – 7.27 (m, 5H), 6.01 (ddd, *J* = 10.0, 5.1, 2.9 Hz, 1H), 5.76 (dt, *J* = 10.1, 1.8 Hz,

1H), 4.97 (dd, *J* = 30.2, 11.7 Hz, 2H), 4.79 (d, *J* = 12.1 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.51 – 4.43 (m, 1H), 4.36 (d, *J* = 7.6 Hz, 1H), 4.22 (dt, *J* = 5.2, 2.7 Hz, 1H), 4.04 – 3.82 (m, 2H), 3.59 (dd, *J* = 4.0, 2.1 Hz, 1H), 3.23 – 3.11 (m, 1H), 2.30 (pt, *J* = 3.6, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 135.9, 133.3, 130.4, 128.6, 128.4, 128.0, 127.9, 127.8, 127.8, 126.9, 126.3, 126.2, 126.1, 126.1, 77.3, 73.2, 71.9, 70.5, 70.5, 64.3, 44.2. HRMS calculated for $[C_{25}H_{26}O_4 + Na]^+$: 413.1723, found 413.1720.

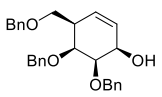
3,4,6-*O*-benzyl-2-*O*-naphthyl-talo-cyclophellitol-alkene (37)



Compound **13** (0.50 g, 1.25 mmol, 1 eq.) was co-evaporated with toluene twice and dissolved in anhydrous DMF (12.8 mL, 0.1 M) and cooled to 0 °C. BnBr (1.75 g, 10.2 mmol, 8 eq.) and TBAI (0.047 g, 0.13 mmol, 0.1 eq.) were added and the mixture was stirred for five minutes. NaH (60% wt) (0.153 g, 3.84 mmol, 3 eq.) was added and the mixture was allowed to warm to room temperature. After four hours of stirring, the reaction was quenched with H_2O and extracted with EtOAc thrice. The combined organic layers were washed with H_2O five times, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 1/20 -> 3/10, v/v) to obtain compound **37** (0.488 g, 0.856 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.71 (m, 4H), 7.50 – 7.41 (m, 3H), 7.37 (dq, *J* = 6.7, 2.9, 2.5 Hz, 2H), 7.35 – 7.21 (m, 13H), 5.92 (ddd, *J* = 10.2, 3.7, 1.8 Hz, 1H), 5.81 (dt, *J* = 10.3, 2.5 Hz, 1H), 4.78 (s, 1H), 4.76 (s, 3H), 4.69 (d, *J* = 2.3 Hz, 2H), 4.49 (s, 2H), 4.13 (dq, *J* = 4.5, 2.0 Hz, 1H), 4.02 – 3.93 (m, 2H), 3.86 (d, *J* = 5.6 Hz, 1H), 3.74 (t, *J* = 8.6 Hz, 1H), 2.77 (tt, *J* = 8.3, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 138.9, 138.7, 136.3, 133.4, 132.9, 129.4, 128.5, 128.3, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 126.3, 126.1, 125.9, 125.8, 77.4, 75.7, 74.4, 73.4, 72.6, 71.6, 71.4, 71.0, 40.9. HRMS calculated for $[C_{39}H_{38}O_4 + Na]^+$: 593.2662, found 593.2664.

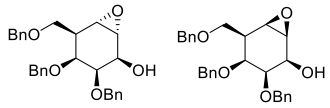
3,4,6-*O*-benzyl-talo-cyclophellitol-alkene (38)



To a solution of **37** (0.12 g, 0.20 mmol, 1 eq.) in DCM/H_2O (19/1, 2.0 mL, 0.1 M) DDQ (0.054 g, 0.24 mmol, 1.2 eq.) was added. After two hours the reaction mixture was diluted with DCM and washed with 2 M NaOH thrice, brine, dried over $MgSO_4$, filtered and concentrated under in vacuo. The crude product was purified

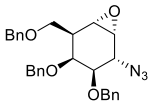
using flash column chromatography (EtOAc/pentane, 1/20 -> 1/10, v/v) to obtain compound **38** (0.071 g, 0.16 mmol, 82%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.24 (m, 15H), 5.94 (ddd, *J* = 10.1, 4.9, 2.8 Hz, 1H), 5.50 (d, *J* = 9.8 Hz, 1H), 4.88 (dd, *J* = 26.8, 11.5 Hz, 2H), 4.62 (dd, *J* = 29.5, 11.5 Hz, 2H), 4.49 (s, 2H), 4.33 – 4.26 (m, 1H), 4.21 (dd, *J* = 4.2, 1.7 Hz, 1H), 3.68 (t, *J* = 8.9 Hz, 1H), 3.59 (dd, *J* = 4.6, 1.6 Hz, 1H), 3.53 (dd, *J* = 8.8, 6.3 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 2.64 (dtt, *J* = 6.5, 4.6, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 138.4, 138.2, 129.5, 128.6, 128.6, 128.5, 128.2, 127.9, 127.9, 127.9, 127.8, 127.8, 126.5, 77.5, 77.0, 74.8, 73.5, 70.3, 70.1, 65.4, 42.2. HRMS calculated for $[C_{28}H_{30}O_4 + Na]^+$: 453.2036, found 453.2039.

3,4,6-*O*-benzyl-talo-(*epi*)-cyclophellitol (39 and 40)



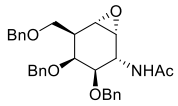
To a solution of **38** (0.88 g, 2.05 mmol, 1 eq.) in DCM (20.5 mL, 0.1 M) mCPBA (0.702 g, 4.10 mmol, 2 eq.) was added. The reaction was stirred at 4 °C for 3 days. The mixture was diluted with DCM and washed with $NaHCO_3$ and brine. The combined water layers were extracted with DCM thrice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 1/10 -> 3/10, v/v) to obtain compounds **32** and **33** as a diastereomeric mixture (**39**: 0.13 g, 0.28 mmol, 14%, **40**: 0.70 g, 1.58 mmol, 77%)
39: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 15H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.78 – 4.69 (m, 1H), 4.60 – 4.48 (m, 4H), 4.45 (d, *J* = 4.2 Hz, 1H), 3.99 – 3.96 (m, 1H), 3.72 – 3.62 (m, 2H), 3.49 (dd, *J* = 4.2, 1.5 Hz, 1H), 3.41 (dd, *J* = 3.6, 1.9 Hz, 1H), 2.94 (d, *J* = 3.5 Hz, 1H), 2.40 (td, *J* = 8.0, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 137.9, 137.8, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 127.9, 127.9, 127.9, 127.8, 76.7, 75.5, 74.9, 73.5, 70.7, 68.4, 66.1, 56.9, 52.4, 40.8. HRMS calculated for $[C_{28}H_{30}O_5 + Na]^+$: 469.1985, found 469.1989.
40: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 15H), 4.84 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.54 – 4.44 (m, 2H), 4.31 (t, *J* = 4.9 Hz, 1H), 3.89 (s, 1H), 3.85 – 3.75 (m, 2H), 3.42 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.36 (s, 1H), 3.29 (t, *J* = 3.2 Hz, 1H), 2.40 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 138.2, 138.2, 133.5, 128.6, 128.6, 128.5, 128.3, 127.9, 127.9, 127.9, 127.8, 127.8, 77.3, 76.0, 74.5, 73.7, 68.9, 65.7, 53.8, 53.7, 30.3. HRMS calculated for $[C_{28}H_{30}O_5 + Na]^+$: 469.1985, found 469.1987.

2-azido-3,4,6-*O*-benzyl-*epi*-cyclophellitol (41)



Compound **40** (0.035 g, 0.080 mmol, 1 eq.) was co-evaporated with toluene thrice and dissolved in anhydrous DCM (0.80 mL, 0.1 M). Pyridine (0.013 mL, 0.16 mmol, 2 eq.) was added and the mixture was cooled to -45 °C. Tf_2O (0.020 mL, 0.12 mmol, 1.5 eq.) in dry DCM (0.06 mL, 1.75 M) was added dropwise. After 5 hours more pyridine (0.013 mL, 0.16 mmol, 2 eq.) and Tf_2O (0.020 32 mL, 0.12 mmol, 1.5 eq.) in dry DCM (0.06 mL, 1.75M) were added. The reaction was stirred for another hour and quenched with H_2O. The mixture was diluted with DCM, washed with 1 M HCl and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude was co-evaporated with toluene thrice and dissolved in anhydrous DMF (0.27 mL, 0.3 M). Bu_4NN_3 (0.045 g, 0.16 mmol, 2 eq.) was added quickly and the reaction was stirred overnight. The mixture was diluted with Et_2O and washed with H_2O five times, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 1/20 -> 1/10, v/v) to obtain compound **41** (0.026 g, 0.057 mmol, 53%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 15H), 4.84 (d, *J* = 11.9 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.46 (s, 2H), 4.16 (d, *J* = 9.6 Hz, 1H), 4.01 (dd, *J* = 4.3, 2.0 Hz, 1H), 3.73 – 3.63 (m, 2H), 3.36 (dd, *J* = 9.7, 2.0 Hz, 1H), 3.11 – 3.08 (m, 2H), 2.28 (dddd, *J* = 8.2, 6.2, 4.3, 1.6 Hz, 1H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.71, 138.04, 137.47, 128.65, 128.59, 128.34, 128.11, 128.05, 128.02, 127.94, 127.80, 127.55, 82.80, 74.66, 73.67, 72.17, 71.43, 68.84, 59.03, 54.39, 52.21, 40.47. HRMS calculated for [for $C_{28}H_{29}N_3O_4$ + Na]$^+$: 494.2050, found 494.2053.

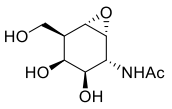
2-*N*-acetyl-3,4,6-*O*-benzyl-*epi*-cyclophellitol (45)



To a solution of **41** (0.045 g, 0.096 mmol, 1 eq.) in THF/H_2O (20/1, 1.37 mL, 0.07 M) PPh_3 (polymer bound, 3 mmol/g, 0.064 g, 0.19 mmol, 2 eq.) was added. The reaction was stirred overnight at 40 °C. The mixture was filtered and concentrated under reduced pressure. The crude was co-evaporated with toluene five times and dissolved in anhydrous DCM (0.96 mL, 0.1 M) and was cooled to 0 °C. Ac_2O (0.018 mL, 0.19 mmol, 2 eq.) and pyridine (0.023 mL, 0.29 mmol, 3 eq.) were added and the mixture was allowed to warm to room temperature. After 4 hours of stirring, the reaction was diluted with DCM and washed with 1 M HCl, $NaHCO_3$ and brine. The organic layer was dried over

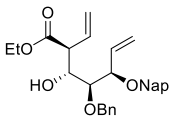
$MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using flash column chromatography (EtOAc/pentane, 2/5 -> 3/5, v/v) to obtain compound **45** (0.025 g, 0.051 mmol, 53%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 15H), 5.40 (d, J = 8.7 Hz, 1H), 4.88 (d, J = 11.5 Hz, 1H), 4.78 (td, J = 8.7, 2.8 Hz, 1H), 4.70 (d, J = 12.4 Hz, 1H), 4.56 – 4.46 (m, 3H), 4.39 (d, J = 12.4 Hz, 1H), 3.90 (dd, J = 3.3, 1.7 Hz, 1H), 3.65 (dd, J = 7.8, 3.7 Hz, 2H), 3.39 (dd, J = 3.8, 2.8 Hz, 1H), 3.22 (d, J = 1.3 Hz, 1H), 3.03 (d, J = 3.9 Hz, 1H), 2.28 (td, J = 7.8, 3.8 Hz, 1H), 1.94 (s, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.12, 138.57, 138.11, 138.05, 128.61, 128.40, 128.07, 128.04, 128.00, 127.95, 127.72, 78.79, 73.87, 73.55, 72.89, 71.69, 68.76, 56.25, 55.29, 48.35, 40.96, 23.57. HRMS calculated for $[C_{30}H_{33}NO_5 + H]^+$: 488.2431, found 488.2431.

2-*N*-acetyl-*epi*-cyclophellitol (8)



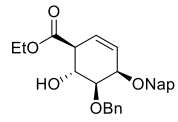
An oven dried 25 mL flask with a glass stirring bar was cooled to -65°C. A flow of NH_3 was passed through the flask until half of it was filled with liquid NH_3. Na(s) (0.009 g, 0.43 mmol, 30 eq.) was added and the mixture turned blue. Compound **45** (0.007 g, 0.014 mmol, 1 eq.) was co-evaporated with anhydrous toluene thrice and dissolved in anhydrous THF (0.59 mL, 0.024M) and *t*-BuOH (0.05 mL, 0.58 mmol, 40 eq.) This mixture was slowly added to the blue solution. After 15 min the reaction was quenched with NH_4Cl (0.031 g, 0.58 mmol, 40 eq.) in H_2O and the mixture turned colorless. The solution was stirred in a warm-water bath to remove any residual ammonia. The remaining solvents were removed in vacuo. The crude residue was purified using flash column chromatography (MeOH/DCM, 1/5, v/v) with neutralized silica and an AmberLite MAC-3 H plug was used to remove most of the salts. A second round of purification by size exclusion Sephadex biogel P-2 (1% AcOH) and freeze drying yielded compound **8** (0.00257 g, 0.011 mmol, 76%).
^{1}H NMR (850 MHz, D_2O) δ 4.39 (dd, J = 9.6, 2.5 Hz, 1H), 3.92 (dt, J = 3.4, 1.7 Hz, 1H), 3.76 (ddd, J = 24.8, 11.3, 7.4 Hz, 2H), 3.51 (dd, J = 9.7, 1.8 Hz, 1H), 3.42 (dd, J = 4.0, 2.4 Hz, 1H), 3.15 (dd, J = 4.0, 1.6 Hz, 1H), 2.16 (td, J = 7.8, 3.4 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (214 MHz, D_2O) δ 175.68, 71.05, 70.60, 61.12, 57.46, 55.13, 49.65, 42.80, 22.89. HRMS calculated for $[C_9H_{15}NO_5 + Na]^+$: 218.1023; found: 218.1023.

ethyl 4-(benzyloxy)-3-hydroxy-5-(naphthalen-2-ylmethoxy)-2-vinylhept-6-enoate (25)



Aldehyde **15** (4.07 g, 11.75 mmol, 1 eq.) was dissolved in H_2O (0.3 M, 40 mL). In powder (3.10 g, 27.03 mmol, 2.3 eq.), $La(OTf)_3$ (14.46 g, 24.68 mmol, 2.1 eq.) and ethyl-4-bromobut-2-enolate (5.18 mL, 37.60 mmol, 3.2 eq.) were added to the reaction mixture while vigorously stirring. When TLC analysis indicated full conversion of the starting material, the reaction mixture was filtered through Celite® and rinsed thoroughly with Et_2O. The filtrate was washed with H_2O and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified using flash column chromatography (EtOAc/pentane, 1/10, v/v) to obtain compound **25** (3.00 g, 6.51 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 4H), 7.48 – 7.40 (m, 3H), 7.32 – 7.23 (m, 5H), 5.90 (ddd, J = 17.4, 10.3, 7.2 Hz, 1H), 5.73 (ddd, J = 17.1, 10.2, 9.4 Hz, 1H), 5.45 – 5.35 (m, 2H), 5.15 – 5.03 (m, 2H), 4.78 (d, J = 11.9 Hz, 1H), 4.65 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 11.3 Hz, 1H), 4.29 (ddd, J = 9.5, 6.8, 1.3 Hz, 1H), 4.21 (dd, J = 7.2, 5.7 Hz, 1H), 4.09 (dq, J = 14.7, 7.1 Hz, 2H), 3.46 (dd, J = 5.6, 1.3 Hz, 1H), 3.37 (t, J = 9.4 Hz, 1H), 3.24 (d, J = 6.8 Hz, 1H), 1.20 (td, J = 7.1, 2.7 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.4, 137.8, 135.4, 135.3, 133.2, 133.0, 132.9, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6, 126.5, 126.0, 125.9, 125.8, 119.8, 119.5, 80.1, 78.9, 73.0, 71.9, 70.9, 60.7, 54.8, 14.1. HRMS calculated for $[C_{29}H_{32}O_5Na]^+$: 483.2147; found: 483.2142.

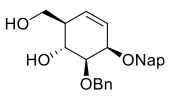
3-*O*-benzyl-6-ethyl-formate-2-*O*-naphthyl-manno-cyclophellitol-alkene (35)



Compound **25** (1.49 g, 3.24 mmol, 1.0 eq.) was co-evaporated thrice with anhydrous toluene and subsequently dissolved in anhydrous DCM (0.2 M, 16 mL). The reaction mixture was flushed with argon for 20 minutes. Afterwards, 2nd gen. Grubbs catalyst (0.11 g, 0.13 mmol, 0.04 eq.) was added and the reaction mixture was heated to reflux under argon atmosphere in the dark for 20 h. The reaction mixture was concentrated in vacuo and purified using flash column chromatography (EtOAc/pentane, 1/5 -> 2/3, v/v) to obtain compound **35** (1.39 g, 3.22 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 4H), 7.53 – 7.41 (m, 3H), 7.39 – 7.23 (m, 5H), 5.90 (ddd, J = 9.9, 5.1, 2.8 Hz, 1H), 5.82 (dd, J = 9.9, 2.4 Hz, 1H), 4.84 (s, 2H), 4.74 (d, J = 11.8 Hz, 1H), 4.67 – 4.53 (m, 2H), 4.27 – 4.14 (m, 2H), 4.17 – 4.08 (m, 1H), 3.47 (dd, J = 10.3, 3.8 Hz, 1H), 3.14 (dt, J = 8.8, 2.8 Hz, 1H), 2.94 (d, J = 1.9 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.6, 138.2, 136.1, 133.3, 133.1, 128.6, 128.3, 128.0, 127.9, 127.8, 127.6, 126.8, 126.7, 126.2, 126.1, 126.0, 80.4, 72.2, 72.0, 69.7, 67.3, 61.4, 51.2, 14.3. HRMS calculated for $[C_{27}H_{28}O_5Na]^+$: 455.1834; found: 455.1829.

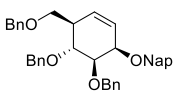
3-*O*-benzyl-2-*O*-naphthyl-manno-cyclophellitol-alkene (24)



Compound **35** (0.56 g, 1.29 mmol, 1 eq.) was co-evaporated thrice with anhydrous toluene and subsequently dissolved in anhydrous THF (0.1 M, 13.0 mL). DIBAL-H (25 wt% in toluene, 5.2 mL, 7.74 mmol, 6 eq.) was added at 0 °C. The reaction mixture was stirred at 0 °C under N_2 atmosphere for 0.5 h and subsequently warmed up to RT. After 0.5 h, the reaction mixture was quenched with EtOAc. H_2O (7.5 mL) and $NaBH_4$ (0.32 g, 8.39 mmol, 6.5 eq.) were added and the reaction mixture was stirred at RT for 2.5 h. The reaction mixture was diluted with EtOAc and washed with 1 M aq. HCl (vigorous reaction with gas production). The aqueous phase was extracted with EtOAc thrice and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified using flash column chromatography (EtOAc/pentane, 2/3 -> 3/5, v/v) to yield compound **24** (0.472 g, 1.21 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (ddd, J = 13.8, 9.4, 5.1 Hz, 4H), 7.52 – 7.42 (m, 3H), 7.39 – 7.25 (m, 5H), 5.88 (ddd, J = 9.9, 5.2, 2.7 Hz, 1H), 5.64 (dd, J = 9.9, 2.2 Hz, 1H), 4.85 – 4.48 (m, 4H), 4.16 – 4.08 (m, 2H), 3.83 – 3.70 (m, 2H), 3.45 (dd, J = 10.2, 3.9 Hz, 1H), 3.11 (s, 1H), 2.81 (s, 1H), 2.39 (dddt, J = 9.4, 7.3, 5.0, 2.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.0, 136.1, 133.3, 133.1, 130.8, 128.6, 128.5, 128.3, 128.0, 128.0, 127.8, 126.8, 126.2, 126.1, 126.0, 81.2, 71.9, 71.8, 69.9, 69.6, 65.6, 46.6. HRMS calculated for $[C_{25}H_{26}O_4Na]^+$: 413.1729; found: 413.1722.

3,4,6-tri-*O*-benzyl-2-*O*-naphthyl-manno-cyclophellitol-alkene (46)

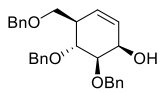


Compound **24** (1.57 g, 4.03 mmol, 1 eq.) was co-evaporated thrice with anhydrous toluene before being dissolved in anhydrous DMF (0.3 M, 13.4 mL) at 0 °C. TBAI (0.15 g. 0.40

mmol, 0.1 eq.) and BnBr (1.92 mL, 2.76 mmol, 16 eq.) were added to the reaction mixture. After 5 minutes, NaH (60% dispersion in mineral oil, 0.48 g, 12.09 mmol, 3 eq.) was added and the reaction mixture was stirred at RT under N_2 atmosphere for 2.5 h. The reaction mixture was quenched with MeOH and diluted with H_2O. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified using flash column chromatography (EtOAc/pentane, 1/50 -> 1/10, v/v) to yield compound **46** (1.88 g, 3.29 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 4H), 7.55 – 7.43 (m, 3H), 7.38 – 7.23 (m, 16H), 5.88 – 5.77 (m, 2H), 4.97 – 4.85 (m, 3H), 4.71 (d, J = 1.8 Hz, 2H), 4.58 – 4.41 (m, 3H), 4.15 (d, J = 4.1 Hz, 1H), 3.97 (td, J = 9.4, 4.9 Hz, 1H), 3.66 (dddd, J = 22.8, 9.0, 4.4, 1.9 Hz, 2H), 3.52 – 3.43 (m, 1H), 2.50 (q, J = 6.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.9, 138.8, 138.6, 136.6, 133.4, 133.1, 131.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.8, 127.7, 126.6, 126.2, 125.9, 125.4, 81.4, 75.4, 74.7, 73.1, 72.5, 71.7, 71.7, 70.6, 44.8. HRMS calculated for $[C_{39}H_{38}O_4Na]^+$: 593.2668; found: 593.2662.

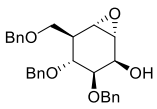
3,4,6-tri-*O*-benzylo-manno-cyclophellitol-alkene (47)



Compound **46** (1.88 g, 3.29 mmol, 1 eq.) was dissolved in DCM/H_2O (18:1, 0.1 M, 33 mL). DDQ (0.90 g, 3.95 mmol, 1.2 eq.) was added to the stirred reaction mixture. After 2.5 h, the reaction mixture was diluted with DCM and washed with 2 M aq. NaOH (3x) and sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified using flash column chromatography (EtOAc/pentane, 1/10 -> 1/5, v/v) to yield compound **47** (1.1 g, 2.48 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (td, J = 14.6, 12.5, 6.8 Hz, 15H), 5.95 – 5.79 (m, 2H), 4.88 (d, J = 11.0 Hz, 1H), 4.80 – 4.66 (m, 2H), 4.55 – 4.43 (m, 3H), 4.32 (qd, J = 6.6, 4.5, 3.2 Hz, 1H), 3.81 (t, J = 8.8 Hz, 1H), 3.65 (dd, J = 9.5, 4.2 Hz, 1H), 3.58 (dd, J = 8.9, 4.3 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.66 (d, J = 3.5 Hz, 1), 2.49 (ddd, J = 8.4, 6.4, 4.1 Hz, 1H. ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.7, 138.4, 138.2, 131.8, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 127.8, 126.4, 81.8, 74.8, 74.7, 73.1, 72.8, 70.1, 65.6, 44.4. HRMS calculated for $[C_{28}H_{30}O_4Na]^+$: 453.2042; found: 453.2036.

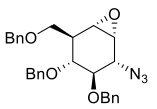
3,4,6-tri-*O*-benzylo-manno-*epi*-cyclophellitol (48)



Compound **47** (0.043 g, 0.1 mmol, 1.0 eq.) was dissolved in MeCN (0.1 M, 1.0 mL) and 0.4 mM EDTA (0.4 mL, 0.4 mL/1mL ACN) was added. To obtain a clear solution, the reaction mixture was cooled to 0 °C and five drops of dioxane were added to the reaction mixture. Using a precooled syringe, 1,1,1-trifluoroacetone (0.089 mL, 1.0 mmol, 10 eq.) was added. $NaHCO_3$ (0.059 g, 0.7 mmol, 7.0 eq.) and oxone (0.31 g, 0.5 mmol, 5.0 eq.) were grinded to a fine powder and added to the reaction mixture in six portions during one hour. The reaction mixture was stirred at RT under N_2 atmosphere for 23h, after which it was diluted with Et_2O and washed with H_2O. The aqueous phase was extracted with Et_2O thrice and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified using flash column chromatography (EtOAc/pentane, 1/10 -> 1/5, v/v) to yield epoxide **48** (0.0304 g, 0.068 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 13H), 7.23 – 7.19 (m, 2H), 4.82 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.51 – 4.39 (m, 4H), 3.72 (dd, J = 10.0, 8.8 Hz, 1H), 3.66 – 3.49 (m, 3H), 3.35 (t, J = 3.1 Hz, 1H), 3.20 (d, J = 3.5 Hz, 1H), 2.26 (ddd, J = 8.9, 5.6, 3.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.6, 138.1, 138.0, 133.7, 130.3, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 80.3, 75.2, 73.7, 73.2, 72.9, 68.9, 66.6, 55.1, 55.0, 42.7. HRMS calculated for $[C_{28}H_{30}O_5Na]^+$: 469.1991; found: 469.1986.

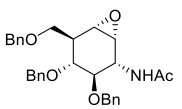
2-azido-3,4,6-tri-*O*-benzylo-*epi*-cyclophellitol (49)



Epoxide **48** (0.045 g, 0.1 mmol, 1 eq.) was co-evaporated thrice with anhydrous toleune prior to solvation in anhydrous DCM (1.0 mL, 0.3 M). Pyridine (0.081 mL, 1.0 mmol, 2 eq.) was added and the reaction mixture was cooled to -45 °C. Tf_2O (0.034 mL, 0.2 mmol, 1.5 eq.) was added dropwise and the reaction mixture was stirred at -45 °C under N_2 atmosphere. After 3 h, the temperature was increased to -10 °C. When full conversion of the starting material was reached, the reaction mixture was quenched with H_2O and washed with 1 M aq. HCl and sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo at 30 °C. The residue was was co-evaporated with anhydrous toluene thrice and subsequently dissolved in dry DMF (0.17 mL, 0.6 M). Bu_4NN_3 (0.057 g, 0.2 mmol, 2 eq.) was weighed and

immediately added to the reaction mixture (hygroscopic compound). The resulting mixture was stirred at RT under N_2 atmosphere. After 5 h, the reaction mixture was diluted with Et_2O and washed with H_2O/brine (3:1). The aqueous phase was extracted with Et_2O thrice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified using flash column chromatography (EtOAc/pentane, 1/19 -> 1/10, v/v) to yield azide **49** (0.012 g, 0.027 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 15H), 4.89 – 4.76 (m, 3H), 4.45 – 4.30 (m, 3H), 3.81 (dd, J = 8.9, 1.8 Hz, 1H), 3.66 (dd, J = 10.0, 9.0 Hz, 1H), 3.58 – 3.50 (m, 3H), 3.36 (dd, J = 3.9, 1.8 Hz, 1H), 3.16 (d, J = 3.9 Hz, 1H), 2.23 (dt, J = 9.7, 3.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 128.6, 128.6, 128.4, 128.1, 128.0, 128.0, 127.9, 81.4, 78.0, 75.8, 75.5, 73.3, 68.2, 64.0, 55.5, 54.8, 43.0. HRMS calculated for $[C_{28}H_{29}N_3O_4Na]^+$: 494.2056; found: 494.2050.

2-*N*-acetyl-3,4,6-tri-*O*-benzylo-*epi*-cyclophellitol (52)

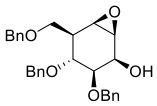


Azide **49** (33 mg, 70.0 µmol, 1 eq.) was dissolved in THF/H_2O (20:1, 0.07 M, 1.0 mL). PPh_3 on beads (3 mmol/g, 28 mg, 84 µmol, 1.2 eq.) was added and the reaction mixture was heated to 40 °C. After 49 h, the mixture was filtered over a glass filter and the filtrate was concentrated under reduced pressure. The residue was co-evaporated five times with anhydrous toluene prior to solvation in anhydrous DCM (0.1 M, 0.7 mL). To the reaction mixture was added: Ac_2O (66 µL, 0.70 mmol, 10 eq.), pyridine (85 µL, 1.05 mmol, 15 eq) and DMAP (4.3 mg, 35 µmol, 0.05 eq.). The reaction mixture was stirred at RT under N_2 atmosphere. After five days, the solvent was evaporated and additional pyridine (0.14 mL, 1.8 mmol, 26 eq.) and Ac_2O (20 µL, 0.21 mmol, 3 eq.) was added because the progress of the reaction stagnated. The reaction mixture was stirred under N_2 atmosphere for two more days at RT. The reaction mixture was subsequently quenched with MeOH and concentrated in vacuo. The residue dissolved in EtOAc and washed with 1 M aq. HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (EtOAc/pentane, 3/10 -> 1/2, v/v) to yield compound **52** (7.6 mg, 15.6 µmol, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 13H), 7.22 (dd, J = 7.6, 1.9 Hz, 2H), 5.23 (d, J = 8.6 Hz, 1H), 4.85 (dd, J = 11.5, 6.5 Hz, 2H), 4.57 (d, J = 12.0 Hz, 1H), 4.48 – 4.35 (m, 4H), 3.61 – 3.54 (m, 3H), 3.35 (t, J = 9.4 Hz, 1H), 3.31

(dd, J = 3.7, 2.1 Hz, 1H), 3.18 (d, J = 3.9 Hz, 1H), 2.21 (dt, J = 9.6, 3.9 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.1, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 79.4, 78.4, 75.3, 74.8, 73.3, 68.3, 56.4, 55.7, 51.2, 42.9, 23.4. HRMS calculated for $[C_{30}H_{33}NO_5Na]^+$: 510.2256; found: 510.2251.

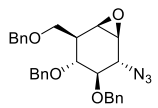
3,4,6-tri-*O*-benzylo-manno-cyclophellitol (43)



To a solution of **47** (0.043 g, 0.1 mmol,1 eq.) in DCM (0.3 M, 0.33 mL) was added *m*-CPBA (0.052 g, 0.3 mmol, 3 eq.). The reaction mixture was stirred at 4 °C for 23 h, after which it was diluted with DCM. The reaction mixture was washed with sat. aq. $NaHCO_3$ and brine and the combined aqueous layers were extracted with DCM thrice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified using flash column chromatography (EtOAc/pentane, 3/20 -> 1/4, v/v) to obtain epoxide **43** (0.0359 g, 0.080 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 16H), 4.74 – 4.41 (m, 6H), 4.29 – 4.25 (m, 1H), 3.73 – 3.63 (m, 2H), 3.57 – 3.48 (m, 3H), 3.38 (t, J = 4.0 Hz, 1H), 2.37 – 2.29 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.3, 138.2, 137.7, 128.6, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.7, 79.9, 74.1, 73.3, 73.3, 73.1, 69.1, 65.5, 55.5, 53.5, 41.4. HRMS calculated for $[C_{28}H_{30}O_5Na]^+$: 469.1991; found: 469.1986.

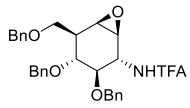
2-azido-3,4,6-tri-*O*-benzylo-cyclophellitol (44)



Epoxide **43** (3.53 g, 1.2 mmol, 1 eq.) was co-evaporated thrice with anhydrous toleune prior to solvation in anhydrous DCM (79 mL, 0.3 M). Pyridine (2.6 mL, 41.5 mmol, 4 eq.) was added and the reaction mixture was cooled to -45 °C. Tf_2O (2.0 mL, 11.9 mmol, 1.5 eq.) was added dropwise and the reaction mixture was stirred at -45 °C. After 3 h, the temperature was increased to -10 °C. When full conversion of the starting material was reached, the reaction mixture was quenched with H_2O and washed with 1 M aq. HCl and sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo at 30 °C. The residue was was co-evaporated with anhydrous toluene thrice and subsequently dissolved in dry DMF (26.4 mL, 0.3 M). To this solution 15-crown-5 ether (6.3 mL, 31.6 mmol, 4 eq.) and NaN_3 (2.1 g, 31.6 mmol, 4 eq.) were added. The resulting mixture was stirred at RT. After 5 h, the reaction mixture was diluted with Et_2O and washed with H_2O/brine

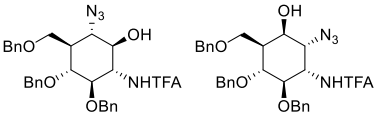
(3:1). The aqueous phase was extracted with Et_2O thrice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified using flash column chromatography (EtOAc/pentane, 0/1 -> 1/20, v/v) to yield azide **44** (2.9 g, 6.2 mmol, 78%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 12H), 7.20 – 7.14 (m, 3H), 4.90 – 4.73 (m, 3H), 4.55 – 4.47 (m, 2H), 4.41 (d, J = 11.0 Hz, 1H), 3.85 (d, J = 8.8 Hz, 1H), 3.72 (dd, J = 8.8, 3.5 Hz, 1H), 3.55 (t, J = 8.7 Hz, 1H), 3.46 – 3.38 (m, 2H), 3.31 (t, J = 9.9 Hz, 1H), 3.09 (d, J = 3.5 Hz, 1H), 2.31 – 2.23 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 138.0, 137.8, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 84.4, 76.0, 75.5, 73.3, 68.5, 63.1, 55.7, 54.2, 42.7.

3,4,6-*O*-benzyl-2-*N*-trifluoroacetyl-cyclophellitol (53)



Azide **44** (0.26, 0.54 mmol, 1 eq.) was dissolved in THF/H_2O (20:1, 0.07 M, 7.8 mL). PPh_3 (0.85 g, 3.3 mmol, 6 eq.) was added and the reaction mixture was heated to 40 °C. After 49 h, the mixture was concentrated in vacuo. The residue was co-evaporated five times with anhydrous toluene prior to solvation in pyridine (0.1 M, 3.9 mL). Trifluoroacetic acid anhydride (0.11 mL, 0.79 mmol, 2 eq.) was added and the reaction was stirred overnight at RT. The reaction mixture was subsequently quenched with MeOH and concentrated in vacuo. The residue dissolved in EtOAc and washed with 1 M aq. HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (Et_2O/pentane, 1/2, v/v) to yield compound **53** (0.18 g, 0.32 mmol, 82%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 14H), 7.02 (d, J = 8.2 Hz, 1H), 4.68 (dd, J = 11.4, 3.4 Hz, 2H), 4.58 – 4.44 (m, 4H), 4.24 (t, J = 7.5 Hz, 1H), 3.72 – 3.62 (m, 2H), 3.59 – 3.47 (m, 2H), 3.41 (t, J = 3.2 Hz, 1H), 3.08 (d, J = 3.7 Hz, 1H), 2.50 – 2.41 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 157.3, 156.9, 156.6, 138.2, 137.6, 137.5, 128.7, 128.6, 128.5, 128.1, 128.1, 128.1, 128.1, 128.0, 127.7, 79.0, 75.3, 74.3, 74.1, 73.3, 68.6, 53.9, 53.7, 50.6, 40.8.

7-azido-3,4,6-*O*-benzyl-2-*N*-trifluoroacetyl-cyclophellitol (54 and 55)

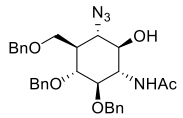


Epoxide **53** (0.20 g, 0.37 mmol, 1 eq.) was dissolved in DMF (0.1 M, 3.7 mL) and to this solution $LiClO_4$ (0.39 g, 3.7 mmol, 10 eq.) and NaN_3 (1.20 g, 18.5 mmol, 50 eq.)

were added. The reaction mixture was heated to 80 °C and stirred overnight. After TLC revealed full conversion of the starting material, the reaction mixture was cooled to RT, diluted with H_2O and extracted thrice with Et_2O. The combined organic layers were washed with H_2O five times, brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified using flash column chromatography (Et_2O/pentane, 1/10 -> 3/10, v/v) to obtain compound **54** (0.13 g, 0.22 mmol, 58%). The diaxial regioisomer **55** was also isolated as a mixture with the diequatorial regioisomer (0.054 g, 0.09 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 15H), 4.87 (d, J = 11.5 Hz, 1H), 4.80 – 4.74 (m, 2H), 4.67 (d, J = 11.5 Hz, 1H), 4.58 – 4.40 (m, 4H), 4.39 (d, J = 3.4 Hz, 1H), 3.95 – 3.82 (m, 2H), 3.77 (d, J = 4.0 Hz, 1H), 3.68 (dd, J = 9.2, 3.5 Hz, 1H), 3.57 (t, J = 7.0, 6.1 Hz, 1H), 2.00 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 155.0, 138.3, 137.7, 137.4, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 117.8, 83.9, 83.2, 74.8, 74.1, 73.8, 73.4, 69.4, 69.3, 69.0, 41.4, 29.8.

2-*N*-acetyl 7-azido-3,4,6-*O*-benzyl-cyclophellitol (56)

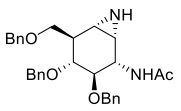


A mixture of **54** and **55** (0.32 g, 0.55 mmol, 1 eq.) was dissolved in $NH_3.H_2O$ (0.3 M, 1.8 mL), heated to 60 °C and stirred overnight. The solution was concentrated in vacuo and co-evaporated five times with anhydrous toluene. Subsequently, the crude residue was dissolved in THF (0.1 M, 7 mL and Ac_2O (3.11 mL, 33 mmol, 60 eq.) and Et_3N (1.06 mL, 7.7 mmol, 14 eq.) were added. The reaction mixture was stirred overnight and subsequently concentrated in vacuo. The crude residue was re-dissolved in EtOAc en washed with 1M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified using flash column chromatography (EtOAc/pentane, 1/10 -> 1/2, v/v) to obtain compound **56** (0.06 g, 0.11 mmol, 20% over two steps). The diaxial regioisomer was isolated as an impure mixture (0.094 g, 18 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.16 (m, 15H), 5.20 (d, J = 7.9 Hz, 1H), 4.91 – 4.83 (m, 2H), 4.62 (d, J = 11.8 Hz, 1H), 4.55 – 4.43 (m, 4H), 4.20 – 4.16 (m, 1H), 4.09 – 3.96 (m, 4H), 3.70 (dd, J = 9.2, 2.7 Hz, 1H), 3.50 (dd, J = 10.6, 8.8 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 138.4, 138.3, 137.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3,

128.2, 128.1, 128.0, 127.9, 127.8, 80.9, 77.6, 75.4, 74.8, 73.8, 71.8, 69.5, 64.0, 50.1, 41.8, 23.4.

2-*N*-acetyl-3,4,6-*O*-benzyl-*epi*-cyclophellitol-aziridine (57)



PPh_3 (0.033 g, 0.12 mmol, 2 eq.) was added to azido alcohol **56** (0.033 g, 0.062 mmol, 1 eq.). The combined residue was co-evaporated thrice with anhydrous toluene and subsequently dissolved in anhydrous ACN (0.05 M, 1.2 mL). The resulting solution was heated to 60 °C and stirred overnight. The solution was concentrated in vacuo and the crude product was purified using flash column chromatography (EtOAc/pentane, 3/10 -> 1/2, v/v) to obtain aziridine **57** (0.028 g, 0.057 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 15H), 4.83 (dd, J = 11.4, 3.7 Hz, 2H), 4.57 (d, J = 11.8 Hz, 1H), 4.49 – 4.41 (m, 3H), 4.37 (td, J = 9.0, 3.8 Hz, 1H), 3.61 – 3.55 (m, 1H), 3.55 – 3.51 (m, 1H), 3.44 (t, J = 9.7 Hz, 1H), 3.34 (t, J = 9.4 Hz, 1H), 2.55 – 2.51 (m, 1H), 2.36 – 2.30 (m, 1H), 2.14 – 2.10 (m, 1H), 1.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 138.7, 138.4, 138.3, 128.6, 128.5, 128.5, 128.5, 128.3, 128.0, 127.9, 127.8, 80.6, 79.4, 77.4, 77.2, 76.9, 75.1, 74.8, 73.2, 69.7, 51.2, 43.7, 35.1, 33.0, 23.6.

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