Design and synthesis of next generation carbohydrate-mimetic cyclitols: towards deactivators of inverting glycosidases and glycosyl transferases

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Chapter 8

Summary and future prospects

Cyclophellitol and its analogues are established inactivators of retaining glycosidases (GHs) often showing excellent potencies and selectivities.[1–6] Over the years, understanding of their mode of action has allowed for the design of analogues tailored towards predetermined glycosidases and for specific purposes.[2,3,7–11] In this way, inhibitors and probes targeting specific *endo*- or *exo*-glycosidases,[12,13] but also reagents to study broader ranges of glycosidases have been constructed and applied successfully.[14,15] The work described in this thesis focusses on novel designs and the development of synthetic methodologies in order to widen the palette of inhibitors and probes targeting glycol-processing enzymes. Putative inhibitors are described envisioned as covalently binding deactivators of inverting glycosidases, enzyme families as large and diverse as retaining ones, but for which no covalent and irreversible inhibitors exist to date. In addition, the design and synthesis of a new class of conformationally constrained glycosyl transferase (GT) donor analogues, envisioned as putative GT inhibitors, is presented. In all, the work presented expands on the growing list of retaining GH inhibitors and activity-based probes, presents the first steps towards

the complementary inverting GH ones and reports on the design of a new class of potential, conformationally biased, competitive GT inhibitors.

1 | **Chapter 1** provides a global overview of literature precedents regarding the synthesis of carbasugar motifs. The main focus lies on the developed synthetic methodologies towards carbaglucose and carbagalactose backbones – substructures that also feature as discriminating motifs in most of the experimental work of this thesis.

2 | A new route towards an orthogonal cyclophellitol building block from commercially available tri-*O*-acetyl-D-glucal is described in **Chapter 2**. The key transformation of this synthesis route relies on a Claisen rearrangement, effectively transforming D-glucal to carba-D-glucal. Subsequent transposition of the 1,2-alkene to the 1,7-position afforded a key orthogonal building block in an overall yield of 19% over 12 steps. Due to the full orthogonality of all four hydroxyl protecting groups in this glucopyranose-configured cyclohexene, regioselective manipulations are feasible and gave rise to a small series of α-(1,3)-linked di- and trisaccharide nigerose and dextran mimetics. As well, making judicious use of neighboring group participation potential (utilizing the allylic secondary alcohol, available by selective deprotection) allowed for the stereoselective introduction of both epoxide and aziridine warheads to emulate α-glucopyranosides.

The set of established di- and trisaccharide structures are, besides a demonstration of the ease of use of the orthogonal building block, envisioned as potential inhibitors of the corresponding nigerase and dextranase enzymes. To further capitalize on the novel methodology described in this chapter, and to study these relatively underexplored enzyme families, a set of probes is proposed as shown in figure 1. The proposed set of probes cover three different glucoside-backbones, consisting of α-(1,3)-linked glucosides (**1** – **4**), α-(1,6)-linked glucosides (**5** – **8**) and a combination of the two (**9** – **12**), relating to nigerose, pullulan and dextran respectively. The proposed nigerase, pullulanase and dextranase probes could find use in studying and identifying glycosidases involved in the degradation of common cell wall polysaccharides of fungi and bacteria. An important component of cell wall polysaccharides of numerous eukaryotic and bacterial organisms is repeating α-(1,3)-linked glucan (also called mutan) with a high degree of branching (for instance, α-(1,6)-linked glucosides forming dextran).[16–21] These polysaccharides are widely found in both fungi (for instance, *Aspergillus niger*, *Agrocybe cylinducea* and *Piptoporus betulinus*) and bacteria (for instance, *Streptococci*, the main causal agent of dental plaques). A high degree of branching is crucial for organismal survival, since it correlates to low substrate

recognition by glycosidases.[16,22,23] As a result, low turn-over rates are generally observed by host enzymes, effectively making the cell wall impenetrable. In contrast, some microorganisms produce *exo*- and *endo*-mutan and dextran processing enzymes, which allows them to use these polysaccharides as their main carbon source.[22,24–26] Knock-out strains, lacking enzymes competent in processing α-(1,3)-linked glucans, generally show poor growth and are less or not viable.[23,26] This has marked these enzymes as interesting therapeutic targets. To this end, the probes described here could assist in the development of much needed novel antibiotics targeting these glycan cell wall processing enzymes. As aforementioned, crippling of this pathway will constitute serious limitations for the pathogenic micro-organisms.

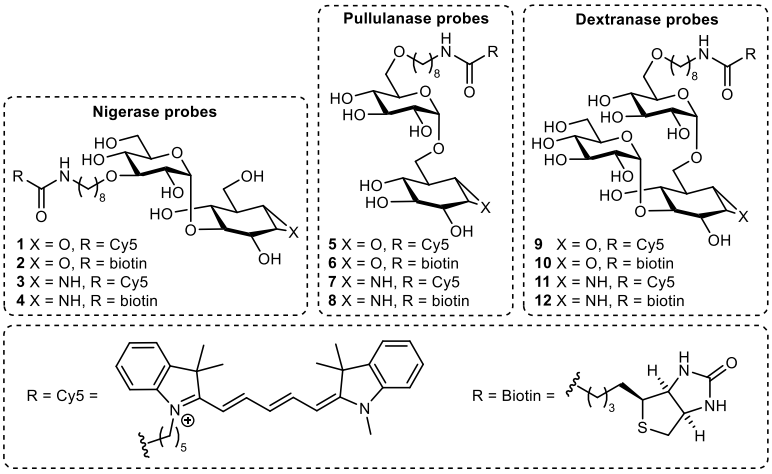
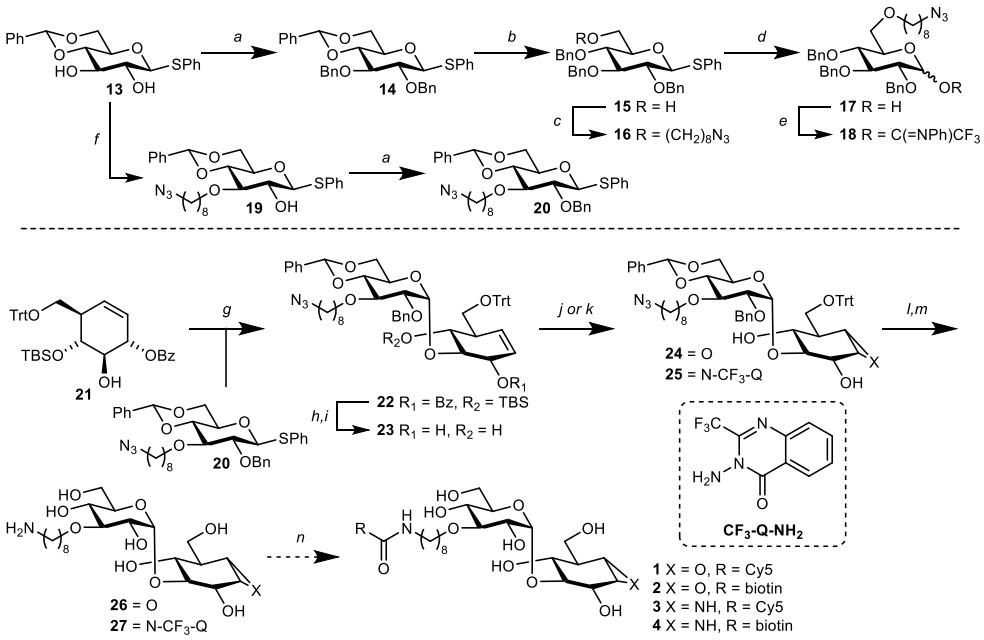


Figure 1. Library of twelve probes, envisioned as suitable mimetics of nigerose (**1** – **4**), pullulan (**5** – **8**) and dextran (**9** – **12**). The probes are either equipped with a fluorescent Cy5 tag for visualisation, or equipped with a biotin tag, allowing for pull-down and isolation.

Initial studies towards these aims have been conducted and comprised the synthesis of disaccharide ABPs having a nigerose, pullulan or dextran configuration with reporter tags installed at the appropriate non-reducing alcohol (Figure 1). The synthesis of these compounds commenced with preparation of donor glucosides **18** and **20** (Scheme 1) that allow the introduction of the reporter entities (fluorophore or biotin) in later stages of the synthesis schemes. To this end, the 2- and 3-OH of thiophenol donor **13** were protected as benzyl ethers[27] after which the benzylidene was reductively opened aided by cobalt chloride and a small hydride donor (BH_3·THF) in quantitative yield.[28] Alkylation of the 6-OH using 1-azido-8-iodooctane, prepared in two steps from commercially available 8-chloro-octanol,[14] and NaH afforded azide **16** in 80% yield. Subsequent hydrolysis of the thiophenol aglycon under the aegis of trichloroisocyanuric acid (TCCA) in aqueous acetone afforded construct **17** as a mixture of α/β anomers in 74% yield.

Treatment of compound **17** with 2,2,2-trifluoro-*N*-phenylacetimido-yl chloride in aqueous acetone and aided by a mild base (Cs_2CO_3) yielded donor **18** in near-quantitative yield. In parallel, compound **13** was regioselectively equipped with an azide spacer *via* an one-pot two-step procedure. Here, installation of a tin ketal over the 2- and 3-position provided the necessary regioselectivity to yield compound **19** upon exposure to 1-azido-8-iodooctane and cesium fluoride in 61% yield. Subsequent protection of the 2-OH as a benzyl ether under standard Williamson etherification conditions (BnBr, NaH) afforded donor **20** in 81% yield.[29]

Scheme 1. Preparation of donor glucosides **18** and **20** and proposed construction of nigerase probes **1** – **4**.

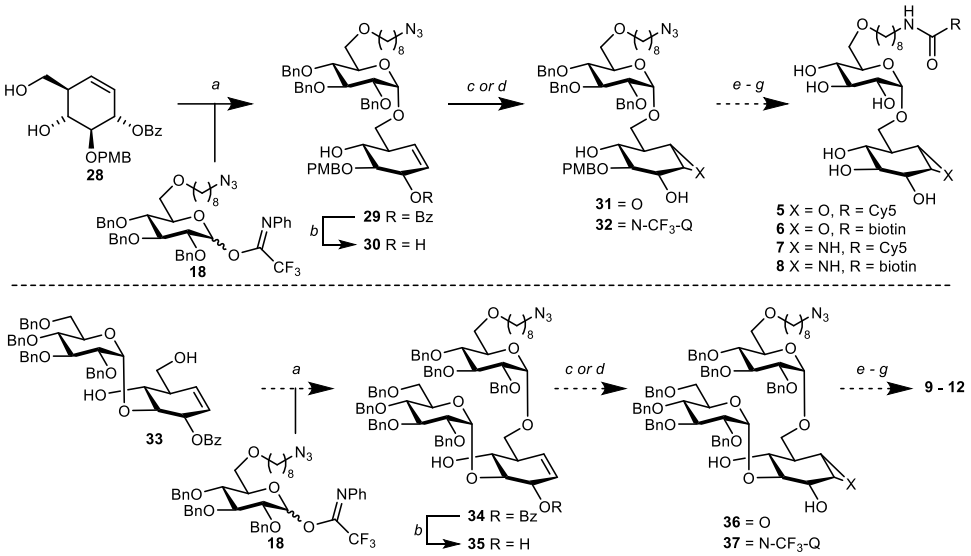


Reagents and conditions: a) BnBr, NaH, DMF, rt, 16 h, **14** (83%), **20** (81%); *b)* $CoCl_2$, BH_3·THF, rt, 15 min (quant.); *c)* 1-azido-8-iodooctane, NaH, DMF, rt, 16 h (80%); *d)* TCCA, acetone:H_2O (4:1 v:v), rt, 2 h (74%); *e)* 2,2,2-trifluoro-*N*-phenylacetimido-yl chloride, Cs_2CO_3, acetone:H_2O (50:1 v:v), rt, 16 h (96%); *f) i.* $(n\text{-Bu})_2SnO$, toluene, reflux 4 h, *ii.* 1-azido-8-iodooctane, CsF, DMF, rt, 3 days (61%); *g)* TTBP, Ph_2SO, donor **20**, 3Å molecular rods, DCM, -78 °C, *then* **21**, 2 h, -78 °C to -10 °C (57%); *h)* TBAF, THF, 1 h, rt; *i)* NaOMe, DCM, MeOH, 16 h, rt (77% over two steps); *j) m*-CPBA, $NaHCO_3$, DCM, 16 h, rt, **24** (96%); *k)* BAIB, CF_3-Q-NH_2, DCM, 48 h, -40 °C to rt; *l)* PtO_2, H_2, THF, 4h, rt; *m)* Na, *t*-BuOH, NH_3, 2 h, -60 °C, **26** (96%); *n)* Cy5-COOH *or* biotin-COOH, COMU, DIPEA, DMF, 4 h, rt.

Initial glycosylation experiments between donor **20** and acceptor **21** resulted in clean conversion to compound **22** with the 1,2-*cis*-linked product as the only observable isomer formed. Liberation of the 2- and 4-OH, aided by TBAF and subsequent treatment with methanolic NaOMe, yielded construct **23** in 77% yield over two steps. Construct **23**

could be used to produce, in parallel fashion and aided by neighbouring group participation of the 2-OH, both epoxide **24** and aziridine **25**. The former was synthesized by subjecting alkene **23** to *m*-CPBA, affording solely epoxide **24** in near-quantitative yields. An azide reduction catalysed by PtO_2 under H_2 atmosphere followed by a global deprotection under Birch condition[30] afforded disaccharide **26** in near-quantitative yield. All that remains to do comprises condensation with either Cy5-COOH or biotin-COOH utilizing a suitable coupling reagent[31] to afford probes **1** and **2**. In addition, aziridine formation (compound **25**) aided by CF_3-Q-NH_2 and BAIB,[32] followed by identical transformations as for the epoxide probes, the construction of the aziridine probes **3** and **4** should be feasible.

Scheme 2. Proposed construction of pullulanase probes **5** – **8** and dextranase probes **9** – **12**.



Reagents and conditions: a) donor **18**, PPh_3O, TMSI, 3Å molecular rods, DCM, 48 h, rt, **29** (68%); *b)* NaOMe, MeOH, DCM, 16 h, rt, **30** (86%); *c) m*-CPBA, $NaHCO_3$, DCM, 48 h, 5 °C, **31** (86%); *d)* BAIB, CF_3-Q-NH_2, DCM, 48 h, -40 °C to rt; *e)* PtO_2, H_2, THF, 4 h, rt; *f)* Na, *t*-BuOH, NH_3, 2 h, -60 °C; *g)* Cy5-COOH *or* biotin-COOH, COMU, DIPEA, DMF, 4 h, rt.

In line with the synthetic methodology described in chapter 2, a synthesis of pullulanase probes is proposed in scheme 2. Initial studies to regio- and stereoselectively couple imidate donor **18** with acceptor **28**, modulated by PPh_3O and TMSI, yielded disaccharide **29** in 68% yield. Hydrolysis of the benzoyl protecting group of the 2-position, followed by a stereoselective epoxidation afforded epoxide **31** in 86% yield. In a divergent manner, compound **31** is expected to undergo stereoselective aziridination with CF_3-Q-NH_2 and BAIB. A PtO_2 catalysed azide reduction followed by global deprotection would then result, after coupling to either Cy5-COOH or biotin-COOH, in epoxide and aziridine

probes **5** – **8**. Putative dextranase probes are in turn considered accessible when disaccharide **33** is used as acceptor in the PPh_3O/TMSI modulated glycosylation with imidate donor **18**. Following identical transformations as for the pullulanase probes, the construction of the dextranase probes **9** – **12** should be feasible.

3 | **Chapter 3** describes a study exploring the use of 1,2- and 1,7-cyclophellitols as potential α-glucosidase inhibitors. To this end, a series of twenty configurational and functional cyclophellitol analogues, featuring a systematic array of electrophiles were synthesized and studied in *in vitro* assays for their inhibitory potencies against human acid α-glucosidase (GAA) and ER α-glucosidase II (ER-II). Subsequently, the conformational free energy landscapes of the most active compounds were mapped. Although no potent inhibitors were found, low micromolar affinity was observed for some of the cyclophellitols. A systematic shift in lowest energy conformation of the 1,2-cyclophellitols in contrast to their 1,7-counterparts was observed during metadynamic simulations. As a result of this shift, the conformation does not resemble that of either the Michaelis complex or transition state during hydrolysis. This conformational shift may explain the overall reduction in observed inhibitory potency of the 1,2-cyclophellitols in comparison to their 1,7-counterparts.

In order to further study the effect of conformational change of the inhibitors on the binding in the enzyme, it would be of interest to obtain crystal structures of the most prominent 1,2-cyclitols. Covalent binding within the active site, combined with the binding interactions within the enzyme active site could shed light on the binding mode of the 1,2-cyclitols. This may allow for the identification of novel binding interactions which can be exploited in future inhibitor designs.

4 | Eight exocyclic aziridine cyclitols were synthesized in **Chapter 4**, envisioned to be selective deactivators of inverting α- and β-glycosidases, enzymes for which no mechanism-based, covalent and irreversible inhibitors exist to date. It was hypothesized that by transpositioning the electrophilic site from the anomeric center to a more distal position through the appendage of an exocyclic aziridine, covalent bond formation could be evoked with the more distal nucleophilic acid/base residue that characterizes inverting GH active site pockets when compared to retaining ones. The key step in the synthesis route employed a divergent *aza*-Michael initiated ring closure reaction (*aza*-MIRC) between unprotected validamine or 1-*epi*-validamine and a small series of dibromide coupling partners bearing a diverse selection of electron withdrawing functionalities. In this fashion, all eight foreseen deactivators were obtained in excellent yield proving the mildness and robustness of the aziridine forming reactions on complex, unprotected substrates.

It is hypothesized that the developed methodology can be easily extended to various substrates bearing primary amines. An interesting substrate for this would be valiolamine (**38**, Figure 2) which is a potent, competitive inhibitor of ER-I and ER-II α-glucosidases with an IC_{50} value of 12 µM for both glucosidases.[33] In addition, *N*-substitution of valiolamine is widely accepted by the glucosidases as nanomolar potencies have been reported.[34–37] This has even resulted in the admission of the α-glucosidase inhibitor Voglibose (**39**, Figure 2), as a drug to treat diabetes mellitus type 2.[38–40] *Via* the described *aza*-MIRC reaction, employing a series of dibromides, valiolamine could be converted in a divergent manner to a series of putative irreversible inhibitors of ER-I (**40** – **43**, Figure 2).

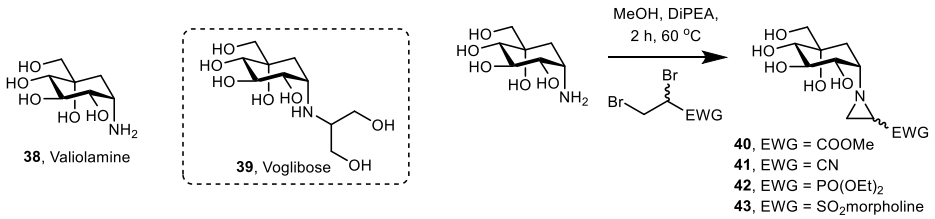
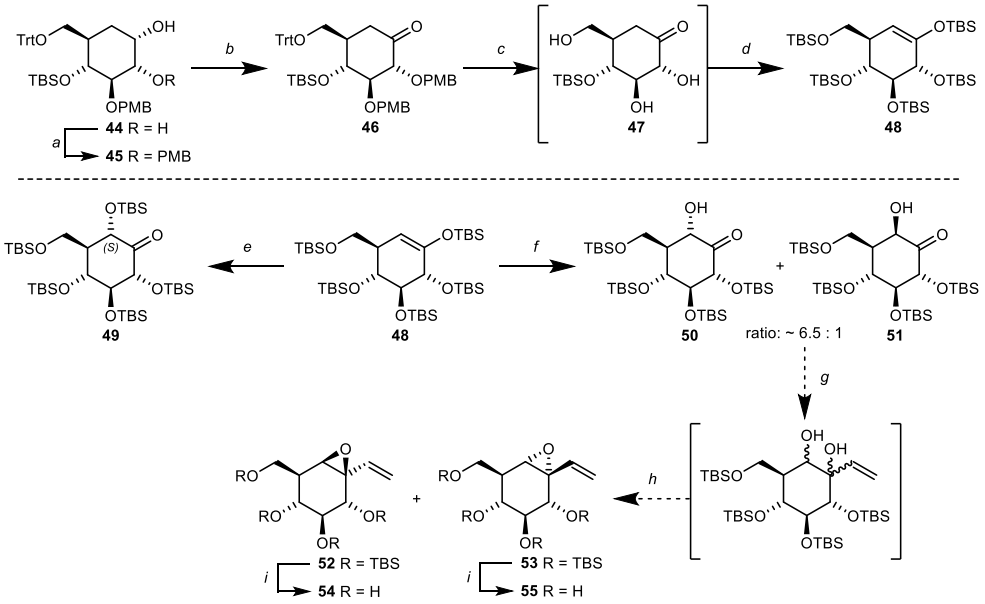


Figure 2. Valiolamine **38**, a potent, reversible inhibitor of ER-I and ER-II, and Voglibose **39**, an α-glucosidase inhibitor used as a drug to treat diabetes mellitus type 2. Proposed putative covalent inhibitors **40** – **43** of ER-I bearing the valiolamine backbone accessible *via* the in chapter 5 described *aza*-MIRC reaction.

5 | As an extension of the studies towards putative inhibitors of inverting α- and β-glucosidases subject of Chapter 4, **Chapter 5** describes the synthesis of a small series of compounds bearing an anomeric vinyl moiety in addition to a range of electrophilic warheads spanning the 1,2-position. It was hypothesized that *via* a conjugated addition the terminal side of the alkene could, due its size and distance from the anomeric center, be attacked by the distal acid/base residue in the enzyme active site, thereby effectively incapacitating the enzyme. The constructs were synthesized in a divergent manner from carbaglucose derivatives that were synthesized as described in Chapter 3. Subjection of the validone analogues with vinyl Grignard reagent neatly provided the vinyl adducts. Warhead installation proceeded smoothly as mesylation or carbonylation of diol intermediates provided the vinyl-epoxides or -carbonates. A Staudinger induced ring closure on the azido-alcohol allowed for isolation of the desired vinyl-aziridine. Due to the intrinsic reactivity of the proposed warheads, and the consequent synthetic challenges that arose during the global deprotection step, the use of silyl protection groups proved crucial allowing the use of a mild fluoride based deprotection step.

To further capitalize on the developed synthetic methodology and inhibitor design, it was hypothesized that transposition of the warhead to the 1,7-position will yield putative potential inhibitors bearing a conjugate addition warhead while closely resembling cyclophellitol. To this end, carbaglucose **44**, previously synthesized in Chapter 2, was transformed in two steps into protected validone **46** (Scheme 3). Here, tin-ketal chemistry provided the necessary regioselectivity during PMB protection of the 2-OH after which a Dess-Martin oxidation yielded construct **46** in quantitative yield.[41] Acid treatment (TFA, TES) removed all acid labile protecting groups to provide partially protected validone **47**. This intermediate was directly subjected to strong silylating conditions (TBSOTf, 2,6-lutidine). Here, not only protection of the primary and secondary hydroxyls was achieved, but formation of the silyl enolate was observed. The regioselectivity was remarkable, as the desired 1,7-silylenolate was the only observed product, yielding **48** in 88% yield. The regioselectivity could be explained by the better accessibility of H-7 by the sterically hindered base, resulting in the formation of the kinetic 1,7-enolate.[42] Subsequent oxidation of the enolate towards the α-hydroxy ketone was attempted. To this end, enolate **48** was subjected to a range of epoxidation conditions (*m*-CPBA, oxone, DMDO), all of which resulted in the formation of α-hydroxy ketone **49** as the single diastereomer. Here, migration of the silyl moiety towards the newly introduced hydroxyl was observed. This would prevent the foreseen orthogonal functionalization of the 7-OH. Migration of the silyl functionality could be circumvented by subjecting silylenolate **48** to dihydroxylating conditions (OsO_4, NMO), providing a diastereomeric mixture of the α-hydroxy ketones **50** and **51** as an inseparable mixture. It was foreseen that subsequent exposure of the α-hydroxy ketones **50** and **51** to the vinyl Grignard conditions described in Chapter 5 would provide an anomeric mixture of the vinyl adducts.

Scheme 3. Proposed synthetic scheme for the preparation of putative inverting α- and β-glucosidase inhibitors.



Reagents and conditions: a) i. (n-Bu)$_2$SnO, toluene, 4 h, reflux; *ii.* PMBCl, CsF, DMF, 16 h, rt (33%); *b)* DMP, NaHCO$_3$, DCM, 2 h, rt (quant.); *c)* TFA, TES, DCM, 3.5 h, 0 °C (93%); *d)* TBSOTf, 2,6-lutidine, DCM, 16 h, rt (88%); *e)* *m*-CPBA, DCM, 2 h, 0 °C (53%); *f)* OsO$_4$, NMO, acetone, 20 h, 75 °C (50%, 79% brsm); *g)* vinyl Grignard, THF, 20 h, -78 °C → 0 °C; *h)* MsCl, Et$_3$N, DCM, 1 h, 0 °C; *i)* TBAF, THF, 2 h, rt.

In a convergent manner, a subsequent intramolecular substitution aided by MsCl would provide a separable mixture of both the α- and β- epoxide, **52** or **53**. Subsequent removal of the silyl protecting groups would yield target structures **54** and **55**.

6 | **Chapter 6** describes the design and synthesis of a series of eight conformational donor mimetics of glucosyl and galactosyl transferases. The design of these structures is based on crystallographic data, suggesting the UDP-glucose or UDP-galactose donor substrates to adopt a concave orientation upon formation of a Michaelis complex with some glucosyl- or galactosyl transferases. Key to the design is the conformational restriction induced by a cyclic carbamate or -sulfamidate functionality, bridging the C1 and C2 position. In addition, the amide is further functionalized with a uridine 5'-monophosphate moiety. Amongst the key transformations are a Sharpless aminohydroxylation, which appeared completely stereoselective on protected carba-D-glucal and carba-D-galactal and yielded almost equimolar quantities of both α-cis-aminohydroxylated regio-isomers in excellent yield. In a divergent and parallel manner, the regio-isomers were transformed to both the cyclic carbamates and sulfamidates. In the next step, Atherton-Todd *N*-phosphorylation

allowed for the efficient condensation of the cyclic carbamate or sulfamidate with a suitably protected H-phosphonate diester. Finally, and using a mild and efficient two-step one-pot deprotection method, all eight complex target structures were successfully deprotected and isolated.

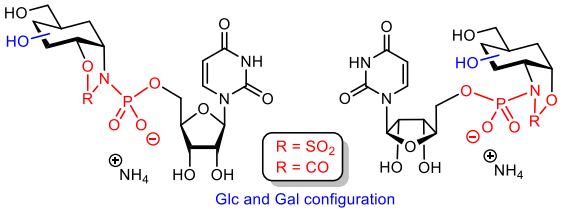
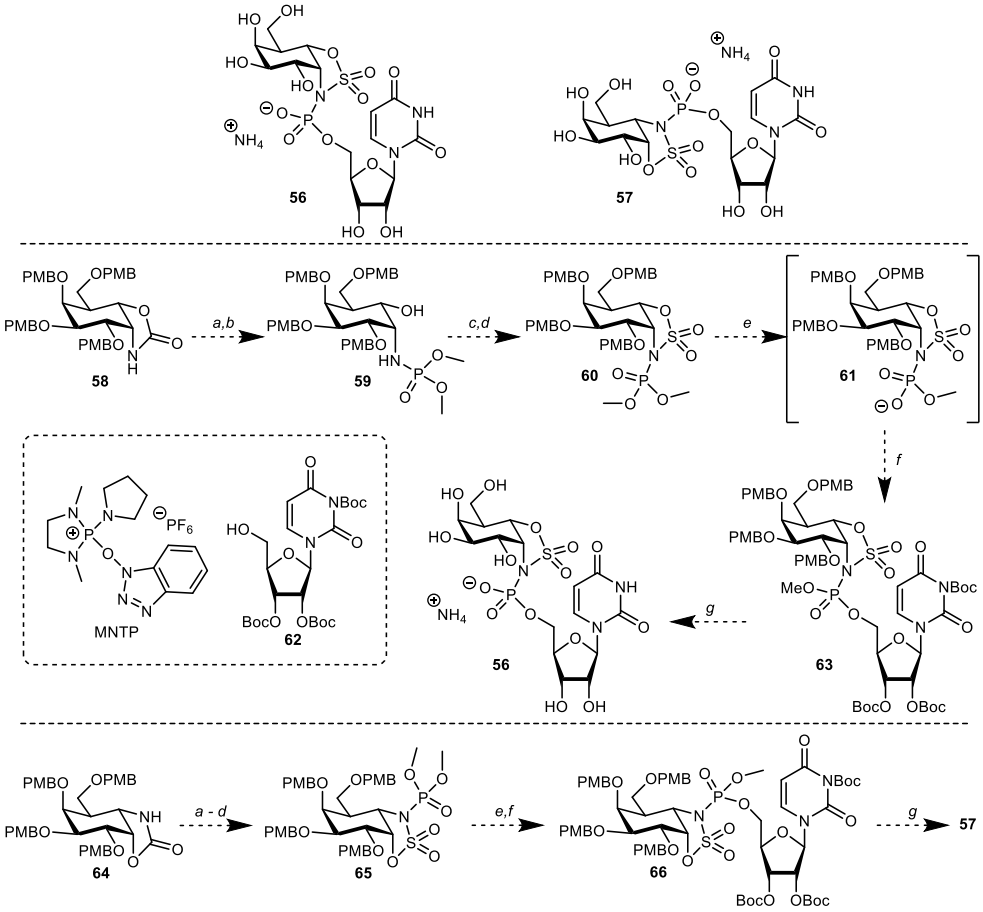


Figure 3. Library of eight complex glucosyl and galactosyl transferase donor mimetics, the synthesis of which is described in Chapter 6.

7 | To further expand on the 1,2-carbamate and sulfamidate inhibitors described in Chapter 6, **Chapter 7** describes synthetic studies towards the corresponding regio-isomers in which the cyclic carbamate or sulfamidate occupies the 1,7-position. It was hypothesized that, by translocating the bicycle over the carba-backbone, a larger chemical space can be probed. In contrast to what was observed in Chapter 6, Sharpless aminohydroxylation proved abortive when attempted on cyclophellitol cyclohexenes. Therefore, somewhat lengthy literature procedures were followed to gain access to the cyclic carbamate building blocks. The use of a TIPDS protecting group on the 4- and 6-position of the carbaglucose analogues proved key for subsequent productive execution of both the Atherton-Todd reaction and the global deprotection sequence, allowing for the isolation of the first target structure. In parallel, both regio-isomers of the carbagalactose carbamate were synthesized following the aforementioned procedures. Atherton-Todd phosphorylation of the first cyclic carbamate and a subsequent global deprotection yielded the first carbagalactose target structure. Atherton-Todd phosphorylation attempts with the second carbamate, as well as with the sulfamidate analogue, proved unsuccessful. Therefore, new routes towards the remaining carbagalactose-configured cyclic carbamate and cyclic sulfamidate constructs are required.

Scheme 4. Proposed synthesis of carbagalactose cyclic sulfamidate constructs **56** and **57**.



Reagents and conditions: a) NaOH, EtOH:H_2O (4:1 v:v), 70 °C, 2 h; *b)* dimethyl phosphite, $BrCCl_3$, DiPEA, DCM, 0 °C, 15 min; *c)* $SOCl_2$, -40 °C → 0 °C, 16 h; *d)* $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 0 °C, 20 min; *e)* Et_3N, CH_3CN, 70 °C, 2 h; *f)* MNTP, 2,6-lutidine, CH_3CN, rt, 2 h; *g)* TFA (30% v:v), TES, DCM, rt, 24 h *then* pyridine, 35 °C, 24 h.

Taken all developed methodology and the identified pitfalls into account, an alternative synthesis route towards carbagalactose cyclic sulfamidate construct **56** and **57** is proposed (Scheme 4). As previously observed in Chapter 7, hydrolysis of carbamate **58** under alkaline conditions produces an amino-alcohol that can be easily converted into the corresponding phosphoramidate through an Atherton-Todd phosphorylation.

It is postulated that dimethyl phosphite would be a suitable coupling partner, yielding the dimethyl phosphoramidate intermediate **59**.[43] Following procedures as described in chapter 7, treatment of crude **59** with thionyl chloride would provide the corresponding cyclic sulfamidite. Here, an $RuCl_3/NaIO_4$ oxidation is expected to result in

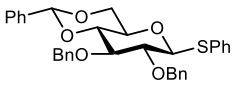
the formation of cyclic sulfamidate **60**.[44,45] After the S(IV) oxidation, the uridine moiety is envisioned to be installed *via* hydrolysis of a single phosphoramidate methyl ester.[46] A subsequent coupling using a phosphonium-type condensing agent (for instance, MNTP)[47] allows for coupling with the primary hydroxyl of protected uridine **62**, previously synthesized in Chapter 6, to provide sulfamidate **63**. The one-pot two-step global deprotection procedure (TFA, TES *then* pyridine), optimized in Chapter 6, is expected to remove all acid labile protecting groups (PMB and Boc) allowing the subsequent nucleophilic removal of the final phosphoramidate methyl ester to yield *N*-UMP-1'',7''-(*N,O*)-sulfamidate carba-α-D-galactopyranoside **56**. Following identical transformations, the synthesis of the 1,7-regioisomer could be feasible, starting from cyclic carbamate **64**, to yield *N*-UMP-1'',7''-(*O,N*)-sulfamidate carba-α-D-galactopyranoside **57**.

Acknowledgements

I extend my acknowledgments to Florian Küllmer for our joint efforts in the partial synthesis of di- and trisaccharide probes, as well as in developing conjugate addition-type inverting glycosidase inhibitors. Our invaluable discussions greatly contributed to these endeavours. I also wish to express gratitude to Madouc Bergers for her synthetic work during her BSc internship.

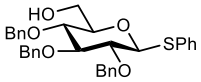
Synthetic procedures.

Phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranose (14).



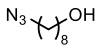
Compound **13** (1.1 g, 3.0 mmol) was dissolved in anhydrous DMF (10 mL, 0.3 M) and cooled on ice. Subsequently, benzyl bromide (1.1 mL, 9.0 mmol, 3.0 eq.) and NaH (60 wt% in mineral oil, 0.36 g, 9.0 mmol, 3.0 eq.) were added respectively. The reaction was stirred overnight while allowed to attain to room temperature. Upon full conversion was observed (R_f 0.6 (EtOAc:pentane, 1:9, v:v)), the reaction was cooled on ice and quenched with water and subsequently diluted further with Et_2O. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 Et_2O:pentane → 30:70 Et_2O:pentane) yielded the donor **14** as a white solid (1.35 g, 2.5 mmol, 83%). Analytical data was determined to be in full agreement with literature data.[27]

Phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranose (15).



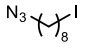
Compound **14** (0.54 g, 1.0 mmol) was combined with $CoCl_2$ (0.39 g, 3.0 mmol, 3.0 eq.) prior to the addition of BH_3·THF (1.0 M, 6.0 mL, 6.0 mmol, 6.0 eq.) and the reaction mixture was stirred for 15 minutes upon TLC confirmed full conversion (R_f 0.2 (Et_2O:pentane, 2:8, v:v)). The mixture was diluted with sat. aq. $NaHCO_3$ and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 Et_2O:pentane → 30:70 Et_2O:pentane) yielded compound **15** (0.55 g, 1.0 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.62 – 7.16 (m, 20H, CH_{arom}), 4.98 – 4.86 (m, 4H, C*H*H Bn, C*H*H Bn, CH*H* Bn, H-1), 4.78 (m, 4H, C*H*H Bn, CH*H* Bn), 4.69 (d, *J* = 11.0 Hz, 1H, CH*H* Bn), 3.91 (ddd, *J* = 12.1, 6.1, 2.6 Hz, 1H, H-6), 3.80 – 3.69 (m, 2H, H-3, H-6), 3.62 (dd, *J* = 9.3, 9.3 Hz, 1H, H-4), 3.53 (dd, *J* = 10.1, 8.7 Hz, 1H, H-2), 3.43 (ddd, *J* = 9.7, 4.8, 2.0 Hz, 1H, H-5), 2.00 (s, 1H, 6-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 138.4, 138.0, 137.9, 133.6, 131.9 ($C_{q\text{-}arom}$), 129.2, 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8 (CH_{arom}), 87.7 (C-1), 86.7 (C-3), 81.2 (C-2), 79.4 (C-5), 77.7 (C-4), 75.9, 75.7, 75.2 (CH_2Bn), 62.2 (C-6); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{33}H_{34}NaO_5S$ 565.2025; found 565.2036.

8-Azido-octanol.



8-Chlorooctanol (24 g 148 mmol) was dissolved in DMSO (37 mL, 4.0 M). NaN_3 (14 g, 222 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 17 hours at 80 °C. After TLC-MS confirmed full conversion, the reaction was diluted with EtOAc and H_2O. The organic layer was washed with water ten times and subsequently dried over $MgSO_4$, filtered and concentrated. Yielding 8-azido-octanol as an colourless oil and was used in the next step without further purification (26 g, 150 mmol quant.). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 3.66 – 3.55 (m, 2H, C*H*$_2$OH), 3.26 (m, 3H, CH_2N_3, OH), 1.67 – 1.47 (m, 4H, spacer), 1.43 – 1.30 (m, 8H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): *δ* 62.7 (CH_2OH), 51.4 (CH_2N_3), 32.6, 29.2, 29.1, 28.8, 26.6, 25.6.

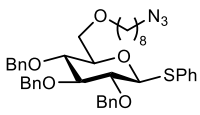
1-Azido-8-iodooctane.



8-azido-octanol (8.5 g, 50 mmol) was dissolved in DCM (150 mL, 0.3 M) and Et_3N (11 mL, 79 mmol, 1.6 eq.) was added. The mixture was cooled on ice and MsCl (5.7 mL, 74 mmol, 1.5 eq.) was added dropwise to the cooled reaction mixture. The reaction mixture was stirred for 3 hours, while allowing to attain room temperature. TLC-MS confirmed full conversion (R_f 0.3 (MeOH:DCM, 1:99, v:v). The reaction mixture was quenched with H_2O and further diluted with DCM. The mixture was washed three times with 1 M HCl followed by aqueous saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude intermediate was then diluted in anhydrous DMF (300 mL, 0.2 M) and KI (12 g, 74 mmol, 1.5 eq.) was added. The reaction was stirred for 10 hours at 70 °C. Upon full conversion was observed (R_f 0.3 (Pentane)), the reaction mixture was concentrated to a fifth of its original volume and diluted with H_2O. The aqueous layer was extracted three times with Et_2O. The organic layer was washed twice with aq. sat. $Na_2S_2O_3$ and subsequently brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (pentane). Obtaining 1-azido-8-iodooctane as a pale-yellow oil (7.4 g, 26 mmol, 53% over two steps).

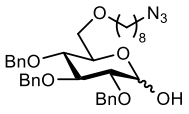
Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(8-azido-octane)-1-thio-β-D-glucopyranose (16).



Compound **15** (0.54 g, 1.0 mmol) was dissolved in anhydrous DMF (10 mL, 0.1 M) and cooled on ice. 1-azido-8-iodooctane (0.42 g, 1.5 mmol, 1.5 eq.) and NaH (60 wt% in mineral oil, 80 mg, 2.0 mmol, 2.0 eq.) were added respectively. The reaction was stirred overnight while allowed to attain to room temperature. Upon full conversion was observed (R_f 0.7 (Et_2O:pentane, 2:8, v:v)), the reaction was diluted with Et_2O and washed with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 Et_2O:pentane → 30:70 Et_2O:pentane) yielded the donor **16** as a colourless oil (0.55 g, 0.8 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.66 – 7.22 (m, 20H, CH_{arom}), 4.98 – 4.83 (m, 4H, C*H*H Bn, C*H*H Bn, CH*H* Bn, H-1), 4.76 (d, *J* = 10.2 Hz, 1H, CH*H* Bn), 4.70 – 4.65 (m, 2H, C*H*H Bn, CH*H* Bn), 3.77 – 3.63 (m, 4H, H-3, H-4, H-6), 3.56 – 3.41 (m, 4H, H-2, H-5, CH_2O spacer), 3.26 (t, *J* = 7.0 Hz, 2H, CH_2N_3 spacer), 1.67 – 1.53 (m, 4H, spacer), 1.44 – 1.29 (m, 8H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 138.5, 138.3, 138.1, 134.1, 131.9 ($C_{q\text{-}arom}$), 128.9, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.4 (CH_{arom}),

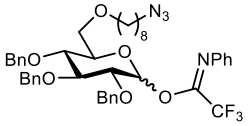
87.6 (C-1), 86.8 (C-3), 80.9 (C-2), 79.2 (C-5), 78.0 (C-4), 76.0, 75.5, 75.1 (CH_2Bn), 71.7 (CH_2O spacer), 69.7 (C-6), 51.5 (CH_2N_3 spacer), 29.9, 29.5, 29.2, 28.9, 26.8, 26.2 (spacer); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{41}H_{49}N_3NaO_5S$ 718.3291; Found 718.3305.

2,3,4-Tri-*O*-benzyl-6-*O*-(8-azido-octane)-α/β-D-glucopyranose (17).



Compound **16** (0.55 g, 0.8 mmol) was dissolved in a mixture of acetone and water (4:1, 10 mL, 0.08M) after which TCCA (0.19 g, 0.8 mmol, 1.0 eq.) was added. The reaction mixture was stirred for 2 hours at room temperature after which TLC confirmed full consumption of the starting material (R_f 0.5 (Et_2O:pentane, 1:1, v:v)). The mixture was diluted with sat. aq. $Na_2S_2O_3$ and Et_2O, the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (40:60 Et_2O:pentane → 50:50 Et_2O:pentane) yielded compound **17** as an anomeric mixture in a 1:1 ratio (0.36 g, 0.59 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.44 – 7.06 (m, 30H, CH_{arom}), 5.24 (dd, *J* = 3.1, 3.1 Hz, 1H, H-1β), 4.99 – 4.61 (m, 13H, CH_2Bn, CH_2Bn, CH_2Bn, CH_2Bn, CH_2Bn, CH_2Bn, H-1α), 4.07 – 3.94 (m, 2H, H-3α, H-3β), 3.72 – 3.56 (m, 6H, H-2α/β, H-4α/β, H-6α, H-6β), 3.55 – 3.47 (m, 6H, 1-OHα, H-4α/β, CH_2N_3 spacer), 3.45 – 3.35 (m, 4H, H-2α/β, H-5α, H-5β), 3.25 (m, 4H, CH_2O spacer), 3.11 – 3.00 (m, 1H, 1-OHβ), 1.68 – 1.52 (m, 8H, spacer), 1.40 – 1.26 (m, 16H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 138.8, 138.6, 138.5, 138.4, 138.3, 137.9 ($C_{q\text{-}arom}$), 128.6, 128.6, 128.5, 128.5, 128.5, 128.2, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7 (CH_{arom}), 97.6 (C-1α), 91.4 (C-1β), 84.7, 83.3 (C-3), 81.9, 80.1 (C-2) , 77.9, 77.8 (C-5), 75.9, 75.8 (C-4), 74.8, 73.0, 71.9, 71.8 (CH_2Bn), 70.8 (CH_2O spacer), 69.7, 68.9 (C-6), 51.5 (CH_2N_3 spacer), 29.6, 29.4, 29.2, 28.9, 27.4, 26.1 (spacer); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{35}H_{45}N_3NaO_6$ 626.3206; Found 626.3212.

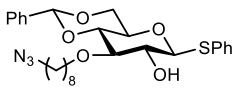
2,2,2-Trifluoro-*N*-phenylacetimido-yl 2,3,4-tri-*O*-benzyl-6-*O*-(8-azido-octane)-α/β-D-glucopyranose (18).



Compound **17** (0.36 g, 0.59 mmol) was dissolved in a mixture of acetone and water (50:1, 6.0 mL, 0.1 M) and cooled on ice. Subsequently, Cs_2CO_3 (0.31 g, 0.95 mmol, 1.6 eq.) and 2,2,2-Trifluoro-*N*-phenylacetimido-yl chloride (0.20 g, 0.95 mmol, 1.6 eq.) were added respectively. The reaction was stirred overnight while allowed to attain to room temperature. Upon full conversion was observed (R_f 0.2 (Et_2O:pentane, 1:9, v:v)), the reaction was diluted with Et_2O and washed with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 Et_2O:pentane → 20:80 Et_2O:pentane) yielded the donor **18** as an anomeric mixture in a 1:1 ratio (0.44 g, 0.56 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.41 – 7.23 (m, 40H, CH_{arom}), 6.54 (bs, 1H, H-1α/β), 5.66 (bs, 1H, H-1α/β), 5.04 – 4.61 (m, 12H, CH_2Bn, CH_2Bn, CH_2Bn, CH_2Bn, CH_2Bn, CH_2Bn), 4.06– 3.62 (m, 12H, H-2α, H-3α, H-4α, H-5α, H-6α, H-2β, H-3β, H-4β, H-5β, H-6β), 3.54 (m, 2H, CH_2O spacer), 3.47 – 3.36 (m, 2H, CH_2O spacer), 3.25 (m, 4H, CH_2N_3 spacer), 1.67 – 1.52 (m, 8H, spacer), 1.35 (m, 16H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 143.6 (C=N), 138.7, 138.5, 138.3, 137.9, 137.8 ($C_{q\text{-}arom}$), 128.8, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7

(CH_{arom}), 81.6, 81.0, 79.4, 77.4, 76.9 (C-2, C-3, C-4, C-5), 75.9, 75.4, 75.3, 73.4, 73.2 (CH_2Bn), 71.8, 71.8 (CH_2O spacer), 69.5, 68.9 (C-6), 51.5 (CH_2N_3 spacer), 29.8, 29.7, 29.4, 29.2, 28.9, 26.8, 26.2 (spacer); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{43}H_{49}F_3N_4NaO_6$ 797.3502; Found 797.3514.

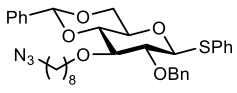
Phenyl 3-*O*-(8-azido-octane)-4,6-*O*-benzylidene-1-thio-β-D-glucopyranose (19).



Compound **13** (18 mmol, 6.4 g) was dissolved in anhydrous toluene (0.1 M, 170 mL) and Bu_2SnO (5.3 g, 21 mmol, 1.2 eq.) was added. The reaction mixture refluxed for 4 hours, equipped with a Dean-Stark apparatus, after which the residual solvent was removed under reduced pressure.

1-azido-8-iodooctane (6.0 g, 21 mmol, 1.2 eq.) was added to the crude intermediate and co-evaporated three times with toluene. The mixture was dissolved in anhydrous DMF (50 mL, 0.4 M) and CsF (27 mmol, 4.1 g, 1.5 eq.) was added. The reaction mixture was stirred for 72 hours at room temperature. While there was still starting material present (R_f 0.3 (EtOAc:pentane, 1:9, v:v)) the reaction mixture was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 twice and the combined organic layers were washed with brine (400 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (5:95 Et_2O:pentane → 50:50 Et_2O:pentane) to obtain the title compound as an off-white solid (5.5 g, 11 mmol, 61% over two steps). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.61 – 7.41 (m, 4H, CH_{arom}), 7.41 – 7.27 (m, 6H, CH_{arom}), 5.54 (s, 1H, CHPh), 4.64 (d, J = 9.1 Hz, 1H, H-1), 4.38 (dd, J = 10.4, 4.3 Hz, 1H, H-4), 3.94 – 3.60 (m, 3H, H-2, H-6), 3.60 – 3.39 (m, 4H, spacer, H-2, H-5), 3.22 (t, J = 6.9 Hz, 2H, N_3-CH_2 spacer), 2.61 (d, J = 1.9 Hz, 1H, 2-OH), 1.57 (m, 4H, spacer), 1.35 (m, 2H, spacer), 1.27 (m, 6H, spacer). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{35}N_3NaO_5S$ 536.2195; Found 536.2208.

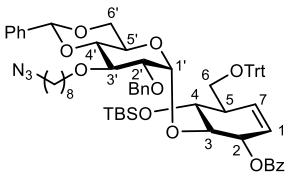
Phenyl 2-*O*-benzyl-3-*O*-(8-azido-octane)-4,6-*O*-benzylidene-1-thio-β-D-glucopyranose (20).



NaH (60 wt% in mineral oil, 0.3 g, 6.1 mmol, 1.8 eq.) was dissolved in anhydrous DMF (17 mL, 0.2 M) under a nitrogen atmosphere and cooled on ice. Subsequently, compound **19** (1.8 g, 3.5 mmol) was dissolved in anhydrous DMF (9.0 mL) and added dropwise to the NaH suspension. The reaction mixture was stirred for 10 min, after which benzyl bromide (0.6 mL, 5.3 mmol, 1.5 eq.) was added dropwise. The reaction was stirred for 2 hours while attaining to room temperature. Upon full conversion (R_f 0.6 (EtOAc:pentane, 1:9, v:v)), the reaction was again cooled to 0 °C and quenched by the addition of MeOH. The solvent was removed under reduced pressure and followed by diluting the reaction mixture with Et_2O and ice-cold water. The solution was transferred to a separation funnel and was further diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O twice, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified using column chromatography (1:99 Et_2O:pentane → 15:85 Et_2O:pentane) and compound **20** was obtained as a pale-yellow oil (1.7 g, 2.8 mmol, 81%). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.56 – 7.27 (m, 15H, CH_{arom}), 5.55 (s, 1H, CHPh), 4.91 – 4.78 (m, 2H, CH_2 Bn), 4.73 (d, J = 9.8 Hz, 1H, H-1), 4.37 (dd, J = 10.5, 5.0 Hz, 1H, H-4), 3.94 – 3.79 (m, 1H, H-2), 3.79 – 3.69 (m, 2H, H-6), 3.69 – 3.53 (m, 2H, H-1, H-5), 3.53 – 3.37 (m, 2H, spacer), 3.21 (t, J = 6.9 Hz, 2H, N_3-CH_2 spacer), 1.56 (m, 4H, spacer), 1.25 (m, 8H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 132.3, 129.0, 128.9 ($C_{q\text{-}arom}$), 128.4, 128.2, 128.1, 127.9, 127.8, 126.0

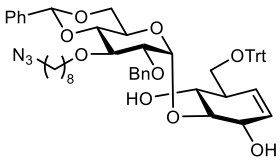
(CH_{arom}), 101.1 (C-7), 88.3 (C-1), 83.3 (C-3), 81.3 (C-2), 80.6 (C-3), 75.8 (CH_2Bn), 73.5 (C-5), 70.3 (C-6), 68.7 (C-4), 51.4, 30.3, 29.3, 29.1, 26.7, 26.1 (spacer). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{34}H_{41}N_3NaO_5S$ 626.2665; Found 626.2678.

2-*O*-Benzoyl-3-*O*-(2-*O*-benzyl-3-*O*-(8-azido-octane)-4,6-*O*-benzylidene-α-D-glucopyranose)-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-cyclophellitol alkene (22).



To compound **20** (0.54 g, 0.89 mmol, 2.0 eq.) was added TTBP (0.87 g, 3.3 mmol, 7.5 eq.) and Ph_2SO (0.23 g, 1.2 mmol, 2.6 eq.) and co-evaporated three times with toluene. The mixture was dissolved in anhydrous DCM (9.0 mL, 0.05 M) and 3 Å molecular rods were added under argon atmosphere. The reaction mixture was cooled down to -78 °C and Tf_2O (0.16 mL, 0.97 mmol, 2.2 eq.) was added. The reaction mixture was warmed-up to -60 °C and was stirred for 15 minutes. Subsequently, the solution was cooled back to -78 °C, and compound **21** (0.28 g 0.44 mmol), dissolved in anhydrous DCM (1.0 mL) was added dropwise. The mixture was stirred for 2 hours, while attaining to -10 °C, after which full conversion (R_f 0.3 (Et_2O:pentane, 2:8, v:v)) was observed. The reaction was quenched by adding sat. aq. $NaHCO_3$ and the mixture were diluted with H_2O and Et_2O. The aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction was purified using flash column chromatography (10:90 Et_2O: pentane → 20:80 Et_2O:pentane), followed by size exclusion chromatography over HW-40 eluted with DCM/MeOH (1:1) to obtain the title compound as a colourless oil (0.28 g, 0.25 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.99 – 7.90 (m, 2H, CH_{arom}), 7.64 – 7.12 (m, 32H, CH_{arom}), 6.24 – 6.18 (m, 1H, H-1), 5.75 (ddd, J = 10.2, 2.9, 2.9 Hz, 1H, H-7), 5.48 (m, 2H, CHPh, H-2), 4.83 (d, J = 3.9 Hz, 1H, H-1'), 4.71 (d, J = 12.5 Hz, 1H, C*H*H Bn), 4.55 (d, J = 12.5 Hz, 1H, CH*H* Bn), 4.30 (dd, J = 10.3, 4.9 Hz, 1H, H-4'), 3.90 (dd, J = 6.0, 3.9 Hz, 1H, H-3), 3.85 – 3.44 (m, 7H, H-4, H-5, H-3', H-4', H-5', H-6'), 3.44 – 3.27 (m, 1H, H-6), 3.22 (t, J = 7.0 Hz, 2H, N_3-CH_2 spacer), 3.14 (d, J = 9.2 Hz, 1H, H-6), 2.59 (s, 1H, H-5), 1.56 (m, 6H, spacer), 1.31 (m, 8H, spacer), 0.74 (s, 9H, $C(CH_3)_3$), 0.01 (s, 3H, $SiCH_3$), -0.16 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 165.9 (C=O Bz), 144.3, 132.8, 131.6, 130.4 ($C_{q\text{-}arom}$), 129.7, 128.7, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.0, 126.1 (C_{arom}), 122.6 (C-1), 101.0 (CHPh), 99.9 (C-1'), 82.0 (C-3') , 81.7 (C-3), 79.2 (C-2'), 78.4 (C-5'), 73.4 (CH_2Bn), 73.1 (C-6'), 69.4 (C-4'), 68.7 (C-2), 65.3 (C-6), 63.3 (C-4), 51.5 (CH_2N_3 spacer), 44.4 (C-5), 29.4, 29.2, 28.8, 26.7, 26.1 (spacer), 25.9 ($C(CH_3)_3$), -3.6, -3.6 ($C(CH_3)_3$); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{67}H_{79}N_3NaO_{10}Si$ 1136.5432; found 1136.5439.

3-*O*-(2-*O*-Benzyl-3-*O*-(8-azido-octane)-4,6-*O*-benzylidene-α-D-glucopyranose)-6-*O*-trityl-cyclophellitol alkene (23).

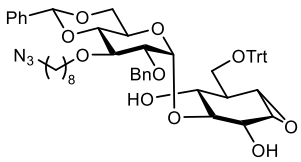


Compound **22** (32 mg, 28 µmol) was dissolved in THF (1.5 mL, 0.02 M) and cooled on ice. TBAF (1 M solution in THF, 56 µL, 56 µmol, 2.0 eq.) was added and the reaction was stirred for 1 hour at room temperature. Upon full conversion was observed (R_f 0.3 (Et_2O:pentane, 3:7, v:v)), the reaction was quenched by the addition of $NaHCO_3$ and diluted with H_2O and Et_2O. The organic layer was separated from the

aqueous layer and the aqueous layer was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated.

The crude was dissolved in a 1:1 mixture of MeOH:DCM (1.1 mL, 0.025 M), and NaOMe (36 mg, 0.56 mmol, 20 eq.) was added. The reaction was stirred for 16 hours at room temperature, after which full conversion was observed (R_f 0.2 (Et_2O: pentane, 1:1, v:v)). The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction was purified using flash column chromatography (30:70 Et_2O:pentane → 60:40 Et_2O:pentane), obtaining compound **23** as a white brittle foam (20 mg, 22 µmol, 77%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.50 – 7.46 (m, 2H, CH_{arom}), 7.45 – 7.41 (m, 6H, CH_{arom}), 7.39 – 7.26 (m, 14H, CH_{arom}), 7.23 – 7.20 (m, 2H, CH_{arom}), 5.69 – 5.55 (m, 2H, H-1, H-7), 5.53 (s, 1H, CHPh), 4.90 – 4.83 (m, 2H, H-1', C*H*H Bn), 4.73 (d, J = 11.8 Hz, 1H, CH*H* Bn), 4.30 – 4.22 (m, 2H, H-4', H-2), 4.06 (ddd, J = 10.0, 10.0, 4.9 Hz, 1H, H-3), 3.93 – 3.83 (m, 3H, H-4, H-3', H-5'), 3.78 – 3.67 (m, 3H, H-6', 2-OH), 3.54 (ddd, J = 9.5, 6.8, 2.9 Hz, 1H, H-2'), 3.40 – 3.30 (m, 2H, H-6), 3.28 – 3.18 (m, 3H, H-4, N_3-CH_2 spacer), 2.94 (s, 1H, 4-OH), 2.55 – 2.46 (m, 1H, H-5), 1.65 – 1.50 (m, 4H, spacer), 1.43 – 1.17 (m, 10H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 144.2, 137.6, 137.4 ($C_{q\text{-}arom}$), 129.1 (CH_{arom}), 128.8 (C-1), 128.7, 128.5, 128.3, 128.3, 127.9 (CH_{arom}), 127.5 (C-7), 127.0, 126.1, 125.6 (CH_{arom}), 101.4 (CHPh), 101.3 (C-1'), 86.5 (CPh_3), 82.0 (C-3'), 78.9 (C-2'), 78.6 (C-5'), 74.5 (CH_2Bn), 73.5 (C-6'), 71.2 (C-2), 69.8 (C-4), 68.8 (C-4'), 63.7 (C-3), 63.3 (C-6), 51.5 (CH_2N_3 spacer), 44.4 (C-5), 30.5, 29.4, 29.2, 28.9, 26.8, 26.1 (spacer); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{54}H_{61}N_3NaO_9$ 918.4306; found 918.4310.

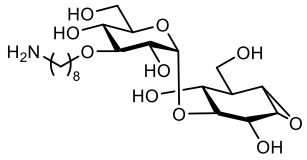
3-*O*-(2-*O*-Benzyl-3-*O*-(8-azido-octane)-4,6-*O*-benzylidene-α-D-glucopyranose)-6-*O*-trityl-1,7-*epi*-cyclophellitol (24).



Compound **23** (24 mg, 27 µmol) was dissolved in anhydrous DCM (1.0 mL, 0.025 M). $NaHCO_3$ (30 mg, 0.35 mmol, 13 eq.) and *m*-CPBA (15 mg, 81 µmol, 3.0 eq.) were added and the reaction mixture was stirred for 36 hours at 5 °C. TLC confirmed full conversion (R_f 0.3 (Et_2O:pentane, 6:4, v:v)). The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ and diluted further with H_2O and DCM. The aqueous layer was extracted twice with DCM, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified using flash column chromatography (40:60 Et_2O:pentane → 60:40 Et_2O:pentane). The title compound was obtained as a colourless oil (24 mg, 26 µmol, 97%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): *δ* 7.48 (m, 2H, CH_{arom}), 7.45 – 7.41 (m, 5H, CH_{arom}), 7.39 – 7.32 (m, 7H, CH_{arom}), 7.32 – 7.26 (m, 7H, CH_{arom}), 7.24 – 7.21 (m, 3H, CH_{arom}), 5.53 (s, 1H, CHPh), 4.91 – 4.79 (m, 1H, C*H*H Bn), 4.77 (d, J = 4.0 Hz, 1H, H-1'), 4.75 – 4.65 (m, 1H, C*H*H Bn), 4.26 (dd, J = 10.3, 6.1 Hz, 1H, H-4'), 4.05 (dd, J = 10.0, 4.9 Hz, 1H, H-3'), 3.98 – 3.80 (m, 4H, H-2, H-7, H-5', 2-OH), 3.80 – 3.63 (m, 3H, H-4, H-6'), 3.58 – 3.29 (m, 4H, H-6, CH_2O spacer), 3.26 – 3.16 (m, 2H, CH_2N_3), 3.15 – 3.08 (m, 1H, H-3), 2.89 (d, J = 4.0 Hz, 1H, 4-OH), 2.22 (ddd, J = 8.9, 5.1, 3.3 Hz, 1H, H-5), 1.66 – 1.50 (m, 6H, spacer), 1.43 (s, 1H, spacer), 1.40 – 1.18 (m, 8H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): *δ* 144.2, 144.0, 137.4 ($C_{q\text{-}arom}$), 129.1, 128.8, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.2, 127.1, 126.1 (CH_{arom}), 101.6 (CHPh), 101.4 (C-1'), 87.6 (CPh_3), 81.9 (C-3'), 79.0 (C-2'), 78.4 (C-5'), 74.7 (CH_2Bn), 73.5 (C-6'), 71.0 (C-2), 69.3 (C-

4), 68.8 (C-4'), 63.6 (C-3), 61.9 (C-6), 56.6 (C-1), 55.1 (C-7), 51.5 (CH_2N_3 spacer), 42.7 (C-5), 30.5, 30.4, 29.4, 29.2, 28.9, 26.8, 26.1 (spacer); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{54}H_{61}N_3NaO_{10}$ 934.4255; found 934.4256.

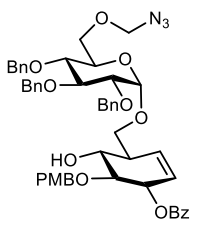
3-*O*-(3-*O*-(8-Azido-octane)-α-D-glucopyranose)-1,7-*epi*-cyclophellitol (26).



Compound **24** (24 mg, 26 µmol,) was co-evaporated two times with anhydrous chloroform and dissolved in anhydrous THF (1.0 mL, 0.025 M). PtO_2 (2.6 mg, 11 µmol, 0.4 eq.) was added and the mixture was purged with N_2, followed by purging with H_2 and kept under a positive H_2 atmosphere for 4 hours. The reaction mixture was filtered over celite, rinsed with THF and concentrated.

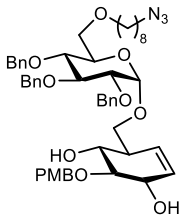
In a separate flask, sodium metal (25 mg, 1.1 mmol, 40 eq.) was dissolved in condensed NH_3 (3.0 mL) at -60 °C. This mixture was stirred for 30 minutes at -60 °C. The crude mixture was dissolved in THF (1.0 mL) and *t*-BuOH (25 µL, 0.26 mmol, 10 eq.) was added. The THF mixture was added dropwise to the liquid NH_3 and was stirred for 1 hour at -60 °C. The reaction was quenched by the addition of 500 µL H_2O and was allowed to attain to room temperature. The mixture was concentrated under reduced pressure and desalted using a C_{18} column chromatography (5:95 MeCN:H_2O → 20:80 MeCN: H_2O), obtaining compound **26** as a colourless oil (12 mg, 25 µmol, 96%).

2-*O*-Benzoyl-3-*O*-(4-methoxybenzyl)-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-(8-azido-octane)-α-D-glucopyranose)-cyclophellitol alkene (29).



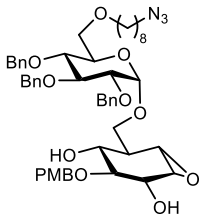
Acceptor **28** (0.14 g, 0.37 mmol) and trifluoro-imidate donor **18** (0.44 g, 0.56 mmol, 1.5 eq.), were combined and co-evaporated twice with toluene. PPh_3O (1.7 g, 5.9 mmol, 16 eq.), activated 3Å molecular rods and anhydrous DCM (7.4 mL, 0.05 M) were added and kept under N_2 atmosphere. Subsequently, TMSI (0.11 mL, 0.74 mmol, 2.0 eq.) was added dropwise and the reaction mixture was stirred overnight at room temperature. Upon full conversion (R_f 0.5 (Et_2O:pentane, 1:1 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (30:70 Et_2O:pentane → 40:60 Et_2O:pentane) to obtain the title compound as a colorless oil (0.24 g, 0.25 mmol, 68%).

3-*O*-(4-Methoxybenzyl)-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-(8-azido-octane)-α-D-glucopyranose)-cyclophellitol alkene (30).



Compound **29** (0.14 g, 0.15 mmol) was dissolved in a 1:1 mixture of DCM and MeOH (4.0 mL, 0.05 M) followed by the addition of NaOMe (98 mg, 1.5 mmol, 10 eq.). The reaction was stirred overnight at room temperature. Upon full conversion (R_f 0.4 (Et_2O:pentane, 8:2 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (60:40 Et_2O:pentane → 80:20 Et_2O:pentane) to obtain the title compound as a colorless oil (0.11 g, 0.13 mmol, 86%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC-GATED): δ 7.45 – 7.26 (m, 17H, CH_{arom}), 6.94 – 6.88 (m, 2H, CH_{arom}), 5.66 (ddd, *J* = 10.1, 2.4, 2.4 Hz, 1H, H-7), 5.48 (ddd, *J* = 10.2, 2.2, 2.2 Hz, 1H, H-1), 4.98 (m, 2H, C*H*H Bn, C*H*H Bn), 4.92 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.87 – 4.75 (m, 4H, C*H*H PMB, CH*H* PMB, CH*H* Bn, H-1'), 4.68 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.64 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.28 – 4.24 (m, 1H, H-2), 3.98 (dd, *J* = 9.2, 9.2 Hz, 1H, H-4'), 3.88 (dd, *J* = 9.5, 5.3 Hz, 1H, H-6), 3.82 (s, 3H, OMe), 3.81 – 3.73 (m, 2H, H-4, 4-OH), 3.70 – 3.57 (m, 5H, H-2', H-3', H-5', H-6'), 3.55 – 3.47 (m, 2H, H-3, CH_2O spacer), 3.41 – 3.34 (m, 2H, H-6, CH_2O spacer), 3.25 (dd, *J* = 7.0, 7.0 Hz, 2H, CH_2N_3 spacer), 2.66 (ddddd, *J* = 8.4, 5.5, 5.5, 2.7, 2.7 Hz, 1H, H-5), 2.20 (d, *J* = 3.5 Hz, 1H, 2-OH), 1.66 – 1.54 (m, 4H, spacer), 1.41 – 1.26 (m, 8H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC, HMBC-GATED): δ 138.8, 138.5, 138.2, 131.2 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.7 (C-7), 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.9, 127.7 (CH_{arom}), 126.0 (C-1), 114.1 (CH_{arom}), 97.9 (C-1'), 84.8 (C-3), 82.2 (C-4'), 80.0, 77.7 (C-2'/C-3'/C-5'/C-6'), 75.8, 75.2, 74.6 (CH_2 Bn/PMB), 74.0 (C-4), 73.5 (CH_2 Bn/PMB), 71.9 (C-2), 71.8 (CH_2O spacer), 71.5 (C-6), 70.6, 69.3 (C-2'/C-3'/C-5'/C-6'), 55.4 (OMe), 51.5 (CH_2N_3 spacer), 44.6 (C-5), 29.7, 29.4, 29.2, 28.9, 26.8, 26.2 (spacer); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{50}H_{63}N_3NaO_{10}$ 888.4411; found 888.4425.

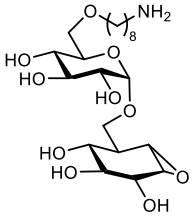
3-*O*-(4-Methoxybenzyl)-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-(8-azido-octane)-α-D-glucopyranose)-1,7-*epi*-cyclophellitol (31).



Compound **30** (55 mg, 64 µmol) was dissolved in anhydrous DCM (1.5 mL, 0.04 M) followed by the addition of $NaHCO_3$ (27 mg, 0.32 mmol, 5.0 eq.). The solution was cooled on ice and *m*-CPBA (33 mg, 0.19 mmol, 3.0 eq.) were added and the reaction was stirred overnight at 4 °C. Upon full conversion (R_f 0.2 (Et_2O:pentane, 8:2 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (70:30 Et_2O:pentane → 90:10 Et_2O:pentane) to obtain the title compound as a colorless oil (49 mg, 56 µmol, 86%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, NOESY): 7.36 – 7.24 (m, 17H, CH_{arom}), 6.90 – 6.85 (m, 2H, CH_{arom}), 4.93 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.88 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.83 – 4.74 (m, 5H, C*H*H Bn, CH*H* Bn, C*H*H PMB, CH*H* PMB, H-1'), 4.64 – 4.57 (m, 2H,

CH*H* Bn, CH*H* Bn), 3.98 – 3.87 (m, 3H, H-2, H-6, H-3'), 3.79 (s, 3H, OMe), 3.69 (ddd, *J* = 10.0, 3.7, 2.0 Hz, 1H, H-5'), 3.65 – 3.54 (m, 4H, H-2', H-4', H-6'), 3.52 – 3.43 (m, 3H, H-4, H-6, CH_2O spacer), 3.42 – 3.30 (m, 3H, H-1, H-3, CH_2O spacer), 3.21 (t, *J* = 7.0 Hz, 2H, CH_2N_3 spacer), 3.10 (d, *J* = 3.9 Hz, 1H, H-7), 3.05 (s, 1H, 4-OH), 2.31 – 2.26 (m, 1H, H-5), 2.25 – 2.20 (bs, 1H, 2-OH), 1.59 – 1.51 (m, 4H, spacer), 1.35 – 1.23 (m, 8H, spacer); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 138.8, 138.4, 138.3, 130.7 ($C_{q\text{-}arom}$), 129.8, 128.6, 128.6, 128.5, 128.1, 128.1, 128.0, 127.9, 127.8, 114.2 (CH_{arom}), 97.7 (C-1'), 82.1, 82.1(C-3, C-3'), 80.2 (C-4'), 77.7 (C-2'), 75.8, 75.3, 75.2 (CH_2 Bn/PMB), 73.4 (C-2), 72.5 (CH_2 Bn/PMB), 71.9 (CH_2O spacer), 71.4 (C-4), 70.7 (C-5'), 69.3 (C-6'), 68.3 (C-6), 56.7 (C-1), 55.4 (OMe), 54.2 (C-7), 51.6 (CH_2N_3 spacer), 42.6 (C-5), 29.7, 29.4, 29.2, 28.9, 26.8, 26.2 (spacer); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{50}H_{63}N_3NaO_{11}$ 904.4360; found 904.4373.

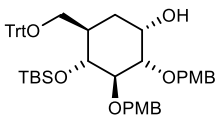
6-*O*-(6-*O*-(8-Azido-octane)-α-D-glucopyranose)-1,7-*epi*-cyclophellitol (S1).



Compound **31** (25 mg, 28 µmol,) was co-evaporated two times with anhydrous chloroform and dissolved in anhydrous THF (1.0 mL, 0.03 M). PtO_2 (2.6 mg, 11 µmol, 0.4 eq.) was added and the mixture was purged with N_2, followed by purging with H_2 and kept under a positive H_2 atmosphere for 4 hours. The reaction mixture was filtered over celite, rinsed with EtOAc and concentrated.

In a separate flask, sodium metal (26 mg, 1.1 mmol, 40 eq.) was dissolved in condensed NH_3 (3.0 mL) at -60 °C. This mixture was stirred for 30 minutes at -60 °C. The crude mixture was dissolved in THF (1.0 mL) and *t*-BuOH (27 µL, 0.28 mmol, 10 eq.) was added. The THF mixture was added dropwise to the liquid NH_3 and was stirred for 1 hour at -60 °C. The reaction was quenched by the addition of 500 µL H_2O and was allowed to attain to room temperature. The mixture was concentrated under reduced pressure and desalted using a C_{18} column chromatography (5:95 MeCN:H_2O → 20:80 MeCN: H_2O), obtaining compound **S1** as a colourless oil (14 mg, 28 µmol, quant.). NMR (500 MHz, D_2O, HH-COSY, HSQC, NOESY): δ 4.82 (d, *J* = 3.7 Hz, 1H, H-1'), 3.85 – 3.80 (m, 2H, H-3, H-6), 3.68 – 3.51 (m, 6H, H-6, H-3', H-4', H-5', H-6'), 3.50 – 3.37 (m, 3H, H-2', CH_2O spacer), 3.36 – 3.20 (m, 5H, H-1, H-2, H-4, H-7), 2.48 (t, *J* = 7.1 Hz, 2H, CH_2N_3 spacer), 2.09 (ddd, *J* = 9.6, 6.5, 3.4 Hz, 1H, H-5), 1.50 – 1.27 (m, 4H, spacer), 1.20 (d, *J* = 5.3 Hz, 8H, spacer); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 98.2 (C-1'), 73.1 (C-2/C-4), 73.0 (C-3'/C-4'/C-5'), 71.9 (CH_2O spacer), 71.2 (C-3), 70.6, 69.8 (C-3'/C-4'/C-5'), 69.5 (C-2/C-4), 69.1 (C-6'), 66.6 (C-6), 57.5 (C-1), 55.1 (C-7), 42.2 (C-5), 40.5 (CH_2N_3 spacer), 31.4, 28.5, 28.4, 28.4, 25.9, 25.1 (spacer); HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{40}NO_{10}$ 466.2652; found 466.2658.

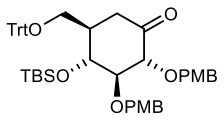
2,3-Di-*O*-(4-methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-carba-α-D-glucose (45).



Compound **44** (1.3 g, 2.0 mmol) was dissolved in anhydrous toluene (30 mL, 0.067 M) and Bu_2SnO (0.56 g, 2.3 mmol, 1.15 eq.) was added. The reaction mixture was stirred at reflux for 4 hours under N_2 atmosphere after which the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The crude was dissolved in anhydrous DMF (20 mL, 0.1 M) followed by the addition of CsF (0.52 g, 3.4 mmol, 1.8 eq.) and PMBCl (0.4 mL, 3.0 mmol, 1.5 eq.). The mixture was continued stirring for 16 hours at room temperature after which TLC confirmed full conversion (R_f 0.3 (Et_2O:pentane, 2:8, v:v)). The reaction was quenched

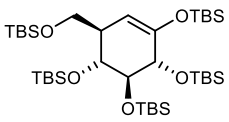
by the addition of sat. aq. $NaHCO_3$ and diluted further with H_2O and Et_2O. The aqueous layer was extracted twice with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude was purified using flash column chromatography (10:90 Et_2O:pentane → 40:60 Et_2O:pentane). The title compound was obtained as a colourless oil (0.59 g, 0.67 mmol, 33%). In addition, starting material was recovered (1.0 g, 1.5 mmol, 67%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.61 – 7.29 (m, 19H, CH_{arom}), 7.01 – 6.94 (m, 4H, CH_{arom}), 4.97 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.79 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.70 (s, 2H, CH*H* PMB, CH*H* PMB), 4.33 – 4.20 (m, 1H, H-1), 3.94 (s, 6H, OMe, OMe), 3.78 – 3.68 (m, 2H, H-3, H-6), 3.49 (dd, *J* = 9.4, 3.1 Hz, 1H, H-2), 3.28 (dd, *J* = 10.2, 8.6 Hz, 1H, H-4), 2.71 – 2.64 (m, 2H, H-6, H-7), 2.59 – 2.48 (m, 1H, H-5), 1.41 (dd, *J* = 7.2, 7.2 Hz, 1H, 1-OH), 1.15 (ddd, *J* = 14.9, 12.5, 2.5 Hz, 1H, H-7), 0.81 (s, 9H, $C(CH_3)_3$), 0.00 (s, 3H, $SiCH_3$), -0.25 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 158.6, 144.4, 131.6, 130.2 ($C_{q\text{-}arom}$), 129.6, 128.8, 128.7, 127.7, 126.8, 113.9, 113.4 (CH_{arom}), 86.4 (CPh_3), 83.6 (C-2), 82.6 (C-3), 74.9 (C-4), 74.8, 72.5 (CH_2 PMB), 66.1 (C-1), 65.9 (C-6), 55.3, 55.2 (OMe), 38.4 (C-5), 30.5 (C-7), 26.0 ($C(CH_3)_3$), 17.9 ($C(CH_3)_3$), -3.4, -4.5 ($SiCH_3$); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{48}H_{58}NaO_7Si$ 797.3850; found 797.3855.

2,3-Di-*O*-(4-methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-D-validone (46).



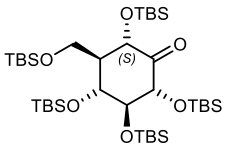
Compound **45** (2.2 g, 2.8 mmol) was dissolved in anhydrous DCM (22 mL, 0.1 M) and cooled on ice. Subsequently, $NaHCO_3$ (1.9 g, 23 mmol, 8.0 eq.) and DMP (2.4 g, 5.7 mmol, 2.0 eq.) were added and the reaction mixture was stirred for 2 hours while attaining to room temperature. Upon full conversion (R_f 0.7 (Et_2O:pentane, 2:8 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (0:100 Et_2O:pentane → 20:80 Et_2O:pentane) to obtain the title compound as a colorless oil (2.2 g, 2.8 mmol, quant.). NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 7.42 – 7.11 (m, 19H, CH_{arom}), 6.87 – 6.77 (m, 4H, CH_{arom}), 4.83 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.76 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.56 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.41 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.00 (d, *J* = 9.2 Hz, 1H, H-2), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.63 (dd, *J* = 8.7, 3.3 Hz, 1H, H-6), 3.57 (dd, *J* = 9.2, 8.0 Hz, 1H, H-4), 3.46 (dd, *J* = 9.3, 8.1 Hz, 1H, H-3), 2.91 (d, *J* = 10.0 Hz, 1H, H-7), 2.73 (dd, *J* = 8.7, 8.7 Hz, 1H, H-6), 2.15 – 2.00 (m, 2H, H-5, H-7), 0.67 (s, 9H, $C(CH_3)_3$), -0.12 (s, 3H, $SiCH_3$), -0.33 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 206.1 (C-1), 159.5, 158.9, 144.1, 131.4, 130.1 ($C_{q\text{-}arom}$), 129.8, 129.1, 128.8, 128.0, 127.2, 113.9, 113.6 (CH_{arom}), 86.9 (CPh_3), 85.7 (C-3), 85.6 (C-2), 74.8 (CH_2 PMB), 73.9 (C-4), 73.1 (CH_2 PMB), 66.4 (C-6), 55.9 (OMe), 41.4 (C-5), 40.2 (C-7), 26.0 ($C(CH_3)_3$), 17.1 ($C(CH_3)_3$), -3.4, -4.5 ($SiCH_3$); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{48}H_{56}NaO_7Si$ 795.3693; found 795.3701.

1,2,3,4,6-Penta-*O-tert*-butyldimethylsilyl-cyclophellitol alk-1-enyl ether (48).



Compound **46** (2.2 g, 2.8 mmol) was dissolved in anhydrous DCM (56 mL, 0.05 M) and cooled on ice. Subsequently, TES (1.4 mL, 8.5 mmol, 3.0 eq.) and TFA (2.6 mL, 34 mmol, 12 eq.) were added and stirring continued for 3.5 hours at this temperature. Upon full conversion (R_f 0.2 (Et_2O:pentane, 1:1 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (30:70 Et_2O:pentane → 70:30 Et_2O:pentane) to obtain the deprotected intermediate as a colorless oil (0.75 g, 2.6 mmol, 93%). The purified intermediate was dissolved in anhydrous DCM (50 mL, 0.05 M) under argon atmosphere and cooled on ice. Subsequently, 2,6-lutidine (3.6 mL, 31 mmol, 12 eq.) was added followed by the dropwise addition of TBSOTf (4.8 mL, 21 mmol, 8.0 eq.). The reaction mixture was allowed to warm to room temperature and stirring continued at this temperature overnight. Upon full conversion was observed (R_f 0.3 (DCM:pentane, 1:9 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (1:99 DCM:pentane → 20:80 DCM:pentane) to obtain the title compound as a colorless oil (1.7 g, 2.3 mmol, 88%). NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 4.88 (dd, *J* = 4.4, 0.7 Hz, 1H, H-7), 3.88 (ddd, *J* = 2.7, 1.8, 0.6 Hz, 1H, H-4), 3.82 (ddd, *J* = 2.6, 1.1, 1.1 Hz, 1H, H-3), 3.75 (dd, *J* = 2.0, 0.9 Hz, 1H, H-2), 3.59 (dd, *J* = 9.3, 7.6 Hz, 1H, H-6), 3.44 (dd, *J* = 9.3, 7.3 Hz, 1H, H-6), 2.47 (ddd, *J* = 7.0, 7.0, 3.8 Hz, 1H, H-5), 0.96 – 0.83 (m, 45H, $C(CH_3)_3$), 0.20 – -0.03 (m, 30H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 149.6 (C-1), 103.9 (C-7), 76.8 (C-4), 73.5 (C-2), 69.6 (C-3), 66.1 (C-6), 46.7 (C-5), 26.4, 26.3, 26.2, 26.1, 25.9 ($C(CH_3)_3$), 18.7, 18.6, 18.5, 18.5, 18.0 ($C(CH_3)_3$), -3.7, -3.7, -4.0, -4.1, -4.3, -4.3, -4.5, -4.6, -5.2 ($SiCH_3$); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{37}H_{82}NaO_5Si_5$ 769.4906; found 769.4912.

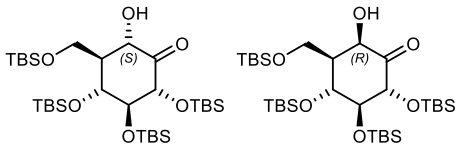
2,3,4,6,7-Penta-*O-tert*-butyldimethylsilyl-D-7-(*S*)-hydroxyvalidone (49).



Compound **48** (0.11 g, 0.15 mmol) was dissolved in anhydrous DCM (7.0 mL, 0.02 M) and cooled on ice. Subsequently, *m*-CPBA (63 mg, 0.37 mmol, 2.5 eq.) was added and the reaction mixture was stirred for 2 hours while kept on ice. TLC confirmed full consumption of the starting material (R_f 0.6 (DCM:pentane, 2:8 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (1:99 DCM:pentane → 20:80 DCM:pentane) to obtain the title compound as a colorless oil (60 mg, 79 µmol, 53%). NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 4.17 (dd, *J* = 8.2, 1.0 Hz, 1H, H-3), 4.12 (dd, *J* = 3.7, 1.5 Hz, 1H, H-6), 4.01 (ddd, *J* = 3.7, 1.3 Hz, 1H, H-6), 3.95 (d, *J* = 1.1 Hz, 1H, H-2), 3.91 – 3.79 (m, 2H, H-4, H-7), 2.12 (dddd, *J* = 9.6, 8.5, 5.6, 1.5 Hz, 1H, H-5), 0.97 – 0.79 (m, 45H, $C(CH_3)_3$), 0.22 – 0.00 (m, 30H, $SiCH_3$);

^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 206.9 (C-1), 82.7 (C-2), 81.0 (C-3), 72.1 (C-4), 68.8 (C-7), 63.9 (C-6), 58.2 (C-5), 26.2, 26.2, 26.1, 25.9 (C(CH_3)$_3$), 18.6, 18.5, 18.1, 18.0 (*C*(CH_3)$_3$), -3.6, -4.0, -4.3, -4.5, -4.9, -5.1, -5.2, -5.7 ($SiCH_3$); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{37}H_{82}NaO_6Si_5$ 785.4855; found 785.4864.

2,3,4,6-Tetra-*O-tert*-butyldimethylsilyl-D-7-(*S*)-hydroxyvalidone (50) and 2,3,4,6-tetra-*O-tert*-butyldimethylsilyl-D-7-(*R*)-hydroxyvalidone (51).



Compound **48** (0.30 g, 0.40 mmol) was dissolved in acetone (15 mL, 0.025 M) followed by the addition of NMO (50 wt% in H_2O, 0.38 mL, 1.6 mmol, 4.0 eq.), OsO_4 (2 wt% in H_2O, 5.1 mL, 0.4 mmol, 1.0 eq.). The reaction mixture was stirred vigorously at 75 °C for 20 hours upon almost full conversion was observed. (R_f 0.5 (DCM:pentane, 3:7 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ followed by diluting the reaction mixture with water and Et_2O. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (5:95 DCM:pentane → 30:70 DCM:pentane) to obtain the title compounds as a mixture of C-7 epimers in a 6.5:1 ratio of *S*:*R* respectively (0.13 g, 0.2 mmol, 50%). In addition, starting material was recovered (87 mg, 0.12 mmol, 29%).

Data of the major isomer **50**: ^{1}H NMR (600 MHz, DMSO, HH-COSY, HSQC): δ 4.90 (d, *J* = 5.6 Hz, 1H, 7-OH), 4.08 (dd, *J* = 3.4, 2.3 Hz, 1H, H-4), 3.96 – 3.94 (m, 1H, H-3), 3.94 – 3.90 (m, 2H, H-2, H-7), 3.85 – 3.79 (m, 2H, H-6), 1.97 – 1.91 (m, 1H, H-5), 0.95 – 0.72 (m, 36H, C(CH_3)$_3$), 0.18 – -0.11 (m, 24H, $SiCH_3$); ^{13}C NMR (151 MHz, DMSO, HSQC): δ 210.0 (C-1), 82.7 (C-3), 80.8 (C-2/C-7), 70.8 (C-2/C-7), 69.9 (C-4), 64.1 (C-6), 57.3 (C-5), 27.1, 27.1, 27.0 (C(*C*H_3)$_3$), 19.5, 19.3, 19.0, 18.9 (*C*(CH_3)$_3$), -2.6, -3.4, -3.6, -3.8, -4.0, -4.1, -4.1, -4.4 ($SiCH_3$).

Data of the minor isomer **51**: ^{1}H NMR (600 MHz, DMSO, HH-COSY, HSQC): δ 5.18 (dd, *J* = 6.8, 5.5 Hz, 1H, H-7), 4.90 (d, *J* = 5.8 Hz, 1H, 7-OH), 4.20 (q, *J* = 2.0 Hz, 1H, H-4), 3.94 – 3.92 (m, 1H, H-3), 3.85 – 3.83 (m, 1H, H-2), 3.75 (dd, *J* = 10.3, 4.9 Hz, 1H, H-6), 3.51 (dd, *J* = 10.7, 10.7 Hz, 1H, H-6), 2.50 – 2.45 (m, 1H, H-5), 0.92 – 0.68 (m, 36H, C(CH_3)$_3$), 0.15 – -0.09 (m, 24H, $SiCH_3$); ^{13}C NMR (151 MHz, DMSO, HSQC): δ 210.3 (C-1), 81.2 (C-2), 81.0 (C-3), 72.4 (C-4), 69.6 (C-7), 60.1 (C-6), 57.1 (C-5), 27.0, 26.9, 26.8 (C(*C*H_3)$_3$), 19.2, 19.2, 19.2, 18.9 (*C*(CH_3)$_3$), -3.3, -3.6, -3.7, -4.0, -4.0 ($SiCH_3$); HRMS (ESI) m/z: [M+Na]+ Calcd for $C_{31}H_{68}NaO_6Si_4$ 671.3991; found 671.4000.

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