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

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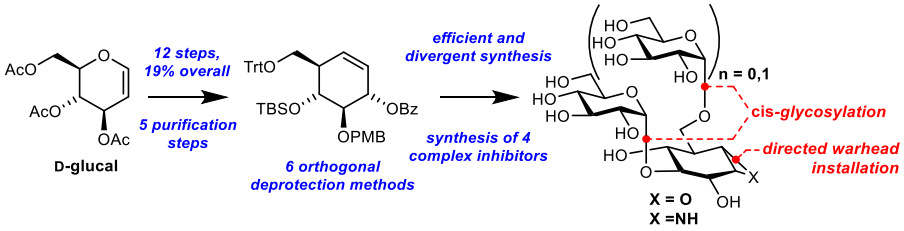
Chapter 2

An orthogonally protected cyclitol for the construction of nigerose- and dextran-mimetic cyclophellitols



ABSTRACT Cyclophellitols are potent inhibitors of *exo*- and *endo*glycosidases. Efficient synthetic methodologies are needed to fully capitalize on this intriguing class of mechanism-based enzyme deactivators. This chapter reports on the synthesis of an orthogonally protected cyclitol from D-glucal (19% yield over 12 steps), and its use in the synthesis of α-(1,3)-linked di- and trisaccharide dextran mimetics. These new glycomimetics may find use as dextranase inhibitors, and the developed chemistries in widening the palette of glycoprocessing enzyme targeting glycomimetics.

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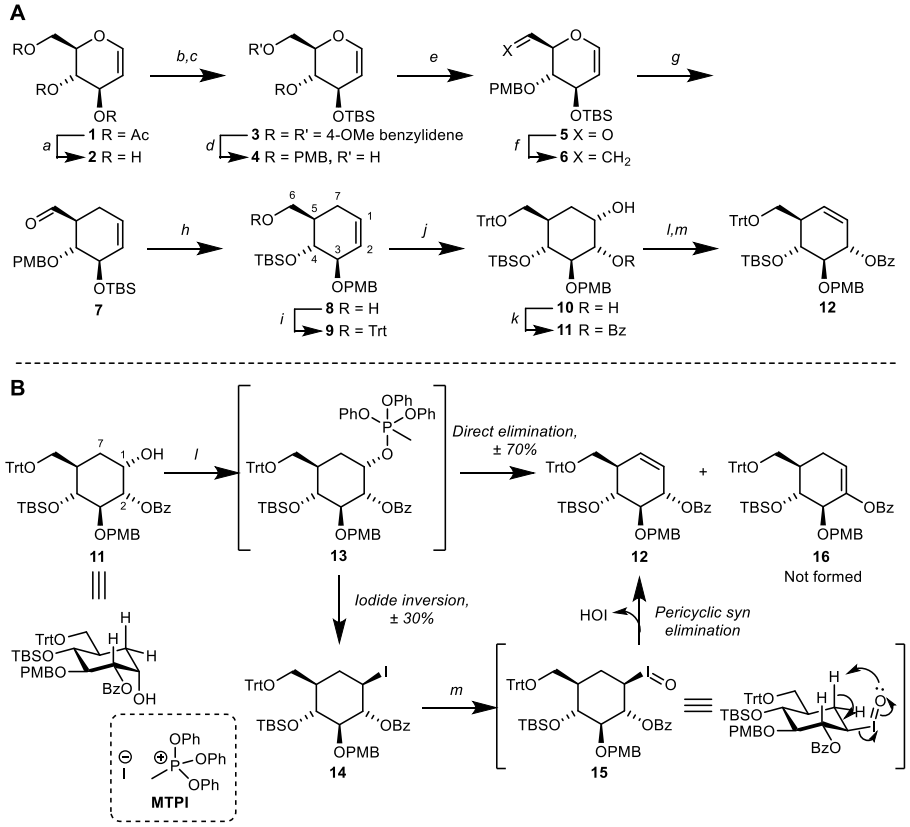
Introduction

Cyclophellitol is a natural product isolated from species of the *Phellinus sp.* mushroom, and is a potent irreversible inhibitor of retaining β-exoglucosidases.[1,2] Since its discovery, a number of syntheses of cyclophellitol have appeared in literature.[3–6] Cyclophellitol is a densely functionalized cyclohexane featuring the β-D-glucopyranose configuration with an epoxide bridging C-1 and C-7.[1,2] The epoxide forces the cyclohexane ring in a $^4H_3$ conformation, which is also the expected conformation of the transition state oxocarbenium ion that emerges during the enzyme-catalyzed hydrolysis of β-glucosidic linkages by retaining β-glucosidase enzymes.[7] Binding in the active site results in a stable ester-linked enzyme-inhibitor adduct, effectively incapacitating the enzyme. This mode of action makes it attractive for use in activity-based protein profiling (ABPP).[7–10] Previous studies revealed that tagging cyclophellitol, and also its nitrogen congener, cyclophellitol aziridine, with a reporter entity (biotin, fluorophore), allows for very sensitive profiling of retaining β-glucosidases.[11] In a follow-up study, it was revealed that the same holds true for 1,7-*epi*-cyclophellitol (or α-cyclophellitol) and the corresponding aziridine in inhibiting and tagging retaining α-glucosidases.[12] ABPP now finds wide use in glycobiology research and a host of configurational and functional cyclophellitol analogues have been reported, each targeting unique retaining exo- and endoglycosidases in the context of drug discovery and bulk polysaccharide processing enzyme discovery.[13–18] However, retaining glycosidase ABPP has not been exploited to the full of its potential yet and this is -at least in part- due to the challenges associated with the synthesis of cyclophellitol-based inhibitors and probes. Challenges that rest in the manipulations of the functionalized cyclohexene/cyclitol epoxide/aziridine cores that are required to create diverse substitution patterns, including glycosidic linkages. With the aim of extending the scope of synthetic cyclophellitol-based glycosidase inhibitors and probes the synthesis strategies towards α-cyclophellitols were revisited, with special focus on the orthogonality of protection group arrays in advanced intermediates. The results of these studies are presented here and entail the synthesis of a fully orthogonal cyclophellitol building block in twelve steps, starting from commercially available 3,4,6-tri-*O*-acetyl-D-glucal, and the demonstration of its versatility in the construction of glycosylated α-cyclophellitols mimicking linear and branched dextran substructures.

Results and discussion

The synthesis of orthogonally protected cyclohexene **12** started from commercially available per-acetylated D-glucal (scheme 1A). Saponification of the acetyl protecting groups (Et_3N, H_2O, MeOH) yielded unprotected D-glucal **2**. Subsequently, a regioselective protection of the 4- and 6-OH followed, using anisaldehyde dimethyl acetal and catalytic amounts of PPTS. Treatment with TBSCl, imidazole and DMAP allowed for the 3-OH to be protected as a TBS ether **3**. Reductive opening of the 4-methoxybenzylidene towards the 4-position was accomplished by treatment with DiBAl-H yielding intermediate **4** in good yield (51% over four steps, >50 gram scale). The primary hydroxyl of compound **4** was oxidized by treatment with Dess-Martin periodinane, resulting into the corresponding aldehyde **5** which was transformed into alkene **6** under Wittig conditions in good yield (80% over two steps, >20 gram scale).[19] The ensuing key thermal [3,3]-sigmatropic Claisen rearrangement by heating of **6** in diphenyl ether to 210 °C yielded intermediate aldehyde **7**, which was directly reduced with $NaBH_4$ to give alcohol **8** (80% over two steps, 20 gram scale) according to literature precedent.[20–22] Tritylation of the primary hydroxyl of compound **8** (TrtCl, Et_3N), followed by dihydroxylation of the alkene using catalytic amounts of OsO_4 and NMO as co-oxidant yielded solely the glucose configured *syn*-diol **10**. Subsequently, the 2-OH could be regioselectively protected as a benzoyl ester under mild conditions (BzCl, pyridine, -15 °C) due to the higher reactivity of the equatorial 2-OH over the axial 1-OH, to yield compound **11** (79% over three steps, >15 gram scale).[23]

Scheme 1. Synthesis of orthogonally protected cyclohexene **12** (A) and the proposed mechanism of the dehydration reaction of compound **11** *via* an iodide intermediate (B).



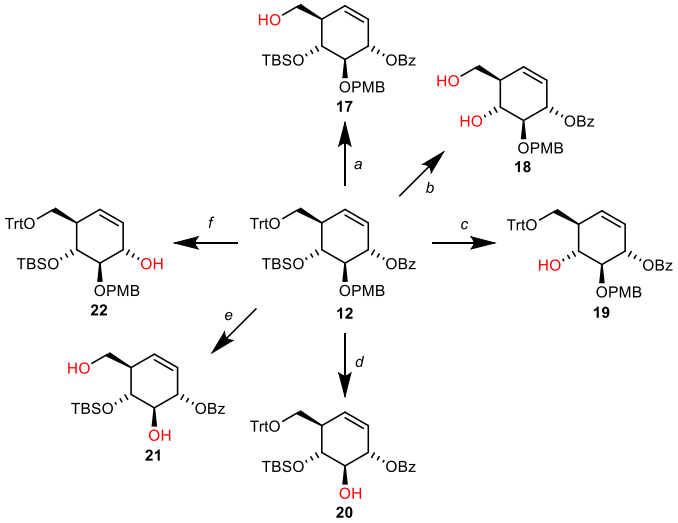
Reagents and conditions: *a*) MeOH, Et_3N, H_2O; 8:1:1, 16 h, rt; *b*) anisaldehyde dimethyl acetal, PPTS, DMF, 1 h, 35 °C; *c*) TBSCl, DMAP, imidazole, DMF, 1 h, 35 °C; *d*) DiBAL-H, DCM, 2 h, -15 °C (51% over four steps); *e*) Dess-Martin periodinane, $NaHCO_3$, DCM, 2 h, rt; *f*) $MePPh_3Br$, *n*-BuLi, THF, 2 h, -78 °C to 0 °C (80% over two steps); *g*) Ph_2O, 2 h, 210 °C; *h*) $NaBH_4$, THF, EtOH, 20 min., 0 °C (80% over two steps); *i*) TrtCl, Et_3N, DMAP, DCM, 16 h, rt; *j*) OsO_4, NMO, acetone, H_2O, 16 h, rt; *k*) BzCl, pyridine, 1.5 h, -15 °C (79% over three steps); *l*) MTPI, 2,6-lutidine, DMF, 1.5 h, 100 °C; *m*) m-CPBA, $NaHCO_3$, 4 h, 0 °C (75%).

With intermediate **11** in hand, attempts were made to regioselectively eliminate the 1-OH to alkene **12**. Compound **11** was subjected to a myriad of dehydration conditions (see Appendix Table S1). The best results were obtained when treating compound **11** with methyl triphenoxyphosphonium iodide (MTPI) and the sterically hindered base 2,6-lutidine, in DMF and at elevated temperature.[24] This procedure gave the desired elimination product **7** together with the corresponding iodide **14**, which formed in a competing substitution reaction, in a ratio of 7:3 of compound **12** to **14** respectively (Scheme 1B). Exposure of this mixture of compounds to *m*-CPBA and $NaHCO_3$ resulted in oxidation and subsequent elimination towards compound **12**. Under these oxidative

conditions, iodide **11** was oxidized to the corresponding iodoso intermediate **15**. This iodoso species quickly undergoes a pericyclic *syn* elimination which, again, solely yields the desired alkene **12**. Due to the high reaction rates, reaction times could be limited to only a few hours and over-oxidation of the relatively electron poor alkene was not observed.[25] Alkene **12** was thus obtained in a total yield of 75%.[26]
It is postulated that the regioselectivity of this reaction sequence results from favoring the Hoffman elimination. This is caused by the use of a mild, sterically hindered base like 2,6-lutidine, but also the steric interactions of the large phosphonate leaving group prevailing the deprotonation of the more acidic H-2 which would have resulted in the more stable Zaitsev product, compound **16**. Instead, the more accessible H-7 is abstracted resulting solely in **12**. Co-elution of the formed methyl diphenoxy phosphonate resulted in troublesome purification of cyclohexene **12**, therefore **12** was directly subjected to the deprotection method of choice.

Attention was then turned to the orthogonal deprotection of **12**, using various conditions (Scheme 2). Treatment of **12** with Lewis acid ($ZnCl_2$) in the presence of a nucleophile (methanol) resulted in the clean removal of the trityl protecting group in high yield (compound **17**, 87%), whereas treatment with a Brønsted acid (*p*-TsOH), under the same conditions resulted in simultaneous removal of the trityl and TBS protecting groups (compound **18**, 84%). Selective, orthogonal removal of the TBS protecting group could be achieved by treatment with TBAF in THF to yield compound **19** (95%). The PMB protecting group was oxidatively removed using DDQ in a biphasic medium consisting of DCM and aqueous phosphate buffer[27], leading to compound **20** (91%). The PMB and trityl protecting groups were removed by subjecting **12** to TFA and TES in anhydrous DCM to yield diol **21** (84%). The TBS protecting group was left untouched due to the absence of a nucleophile. The benzoyl protecting group was removed by saponification with NaOMe in DCM/MeOH, delivering compound **22** (86%). Larger scale deprotections were performed successfully using crude cyclohexene **12**.

Scheme 2. Orthogonal deprotection methods on cyclohexene **12**.

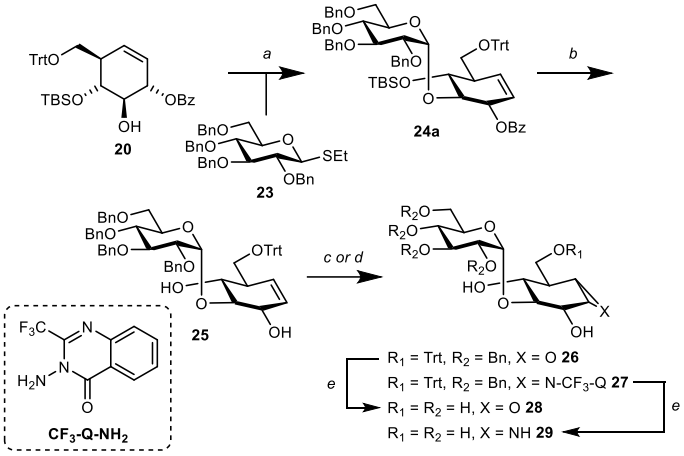


Reagents and conditions: a) $ZnCl_2$, MeOH, DCM, 16 h, rt (87%); *b) p*-TsOH, MeOH, DCM, 16 h, rt (84%); *c)* TBAF, THF, 1 h, rt (95%); *d)* DDQ, DCM, aq. phosphate buffer pH = 7.4[27], 1 h, 0 °C to rt (91%); *e)* TFA, TES, DCM, 1 h, 0 °C to rt (84%); *f)* NaOMe, MeOH, DCM, 16 h, rt (86%).

Having established the full orthogonality of the protective group pattern in cyclohexene **12**, their value was then demonstrated by the synthesis of a set of α(1,3)-linked di- and trisaccharide structures. These structures (**28**/**29** and **36**/**37**; Scheme 3 and 4 respectively) can be regarded as cyclophellitol derivatives of nigerose (α(1,3)-linked glucose) and dextran (α(1,6)-branched α(1,3)-linked glucose), and are thus envisioned as potential inhibitors for the corresponding nigerase and dextranase enzymes.[28,29]

Pre-activation based glycosylation with compound **20** acting as acceptor and glucose donor **23**[30] yielded a separable mixture of stereoisomers (**24a**:**24b**, 4:1, 88%). Removal of both the TBS and benzoyl protecting groups from disaccharide **24a** by standard deprotection procedures gave **25** in 66% yield over two steps. The stereoselective installation of the epoxide and aziridine warheads was achieved making use of the directing effect of the allylic alcohol on the C-2 position. Treatment of **25** with *m*-CPBA and $NaHCO_3$ in anhydrous DCM yielded exclusively α-epoxide **26** in 70% yield. Conversion of precursor **25** to the aziridine was accomplished using 3-amino-2-(trifluoromethyl)quinazolin-4(3*H*)-one (CF_3-Q-NH_2) and BAIB in anhydrous DCM, exclusively yielding α-aziridine **27** in 76% yield.[31] Birch reduction of compounds **26** and **27** resulted in the clean removal of the benzyl, trityl and CF_3-Q protecting groups, yielding compound **28** and **29** in 71% and 86% yield respectively.

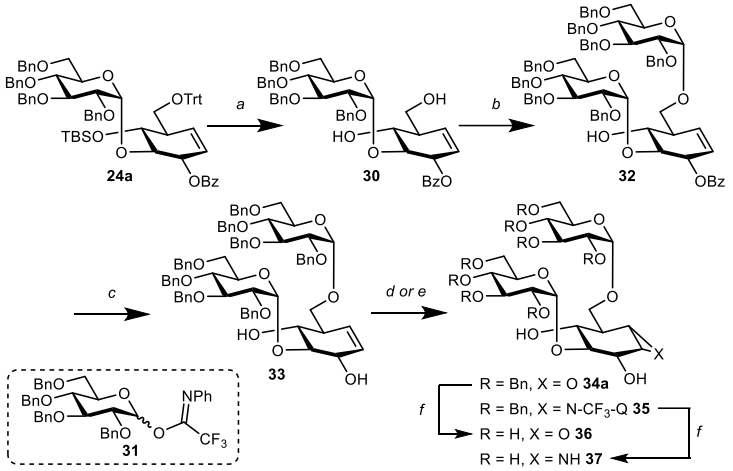
Scheme 3. Assembly of disaccharide target structures **28** and **29**.



Reagents and conditions: a) Tf_2O, TTBP, Ph_2SO, donor **23**[30], 3Å molecular rods, DCM, -78 °C, *then* **20**, 2 h, -78 °C to -10 °C (88%; α:β, 4:1); b) i. TBAF, THF, 1 h, rt; ii. NaOMe, DCM, MeOH, 16 h, rt (66%); *c) m*-CPBA, $NaHCO_3$, DCM, 16 h, rt (70% for **26**); *d)* BAIB, CF_3-Q-NH_2, DCM, 48 h, -40 °C to rt (76% for **27**); *e)* Na, *t*-BuOH, NH_3, 2 h, -60 °C (71% for **28**, 86% for **29**).

The synthesis of dextran-analogues trisaccharidic compounds **36** and **37** (Scheme 4) started by subjecting alkene **24a** to TFA and TES in anhydrous DCM, to selectively remove the trityl protecting group, followed by removal of the TBS protecting group by treatment with TBAF in THF, yielding compound **30** (72% over two steps). Acceptor **30** was treated with an excess of *N*-phenyltrifluoroacetimidate donor **31**[32] in the presence of PPh_3O and TMSI in anhydrous DCM, following literature procedures[33,34], to stereoselectively yield α(1,6)-linked trimer **32** (79%). Saponification of the benzoyl protecting group then liberated the 2-OH to direct the epoxidation/aziridination reactions. Surprisingly, conversion of alkene **33** to the epoxide with *m*-CPBA, $NaHCO_3$ in anhydrous DCM, proceeded with no stereoselectivity to yield a mixture of separable stereo-isomers (**34a** and **34b**), with a combined yield of 69%. The stereochemistry of the two isomers was unequivocally established by NOESY NMR experiments. Conversion of **33** to the aziridine was accomplished by treatment with CF_3-Q-NH_2 and BAIB in anhydrous DCM and this transformation did proceed with complete diastereotopic selection to yield α-aziridine **35** in 76%. Final deprotection of both **34a** and **35** under Birch conditions resulted in the cleavage of all benzyl and CF_3-Q protecting groups to yield trisaccharide **36** and **37** in 91% and 87% respectively.

Scheme 4. Assembly of trisaccharide target structures **36** and **37**.



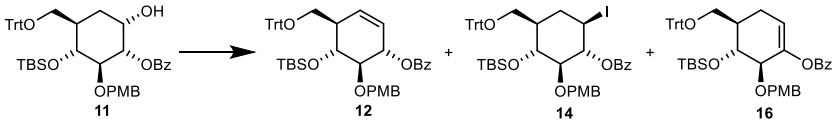
Reagents and conditions: a) i. TES, TFA, DCM, 1 h, 0 °C; *ii.* TBAF, THF, 1 h, rt (72%); *b)* donor **31**, PPh_3O, TMSI, 3Å molecular rods, DCM, 48 h, rt (79%); *c)* NaOMe, MeOH, DCM, 16 h, rt (72%); *d)* *m*-CPBA, $NaHCO_3$, DCM, 48 h, 0 °C (69% for **34a**:**34b**; α:β, 1:1); *e)* BAIB, CF_3-Q-NH_2, DCM, 48 h, -40 °C to rt (62% for **35**); *f)* Na, *t*-BuOH, NH_3, 2 h, -60 °C (91% for **36**, 87% for **37**).

Conclusion

To conclude, this Chapter describes the development of a synthetic route towards a versatile, fully orthogonal cyclophellitol building block, which can be obtained on multi-gram scale with an overall yield of 19% over 12 steps. The synthesis route has been optimized to only require five column purification steps. The key transformation involved the two-step, regioselective elimination of the C1-OH in carbaglucose **11** using MTPI and subsequent treatment with *m*-CPBA, leading to the overall transposition of the initially formed 1,2-alkene to the corresponding 1,7-alkene. Subjection of this building block to several deprotection methods demonstrated the orthogonal nature of the protecting groups. To illustrate its versatility, a number of complex glycomimetics resembling the structures of the natural polysaccharides nigerose and dextran was synthesized. Combined, the methodology as presented here may assist in the generation of complex inhibitors and activity-based probes for use in understanding and modulating carbohydrate-processing enzymes in glycobiology.

Appendix

Table S1. Screened dehydration conditions on compound **11**



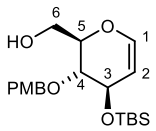
Conditions	Observations
DEAD, PPh_3, Imidazole, THF, reflux, 16 h.	43% (mixture of **12** : **16**, 8:2)
$SOCl_2$, Et_3N, DCM, 0 ˚C, *then* DBU, 16 h.	No conversion, **11** recovered
Martin sulfurane, DCM, 0 ˚C, 16 h.	Degradation of starting material
Burgess reagent, THF, 0 ˚C, 16 h.	Degradation of starting material
NBS, PPh_3, Imidazole, THF, reflux, 16 h.	Small amounts of **12** + Degradation of starting material
TCCA, PPh_3, Imidazole, THF, reflux, 16 h.	Small amounts of **12** + Degradation of starting material
MTPI, 2,6-Lutidine, DMPU, 100 ˚C, 1.5 h.	Full conversion, 68% (mixture of **12** : **14**, 7:3)
MTPI, 2,6-Lutidine, DMF, 100 ˚C, 1.5 h.; *then*: *m*-CPBA, $NaHCO_3$, DCM, 0 ˚C, 3 h.	75%, clean **12**

Experimental

General procedures.

All chemicals were of commercial grade and were used as received unless stated otherwise. Solvents used in synthesis were dried and stored over 4Å molecular sieves. 2,6-Lutidine was stored over KOH pellets. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over P_2O_5 and stored at 3 °C under a nitrogen atmosphere. Deuterated chloroform was stored over activated 3 Å molecular rods (rods, size 1/16 in., Sigma Aldrich) and potassium carbonate. Flash column chromatography was performed on silica gel 60 Å (0.04 – 0.063 mm, Screening Devices B.V.). TLC analysis was performed on TLC Silica gel 60 (Kieselgel 60 F254, Merck) with UV detection (254 nm) and by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% sulfuric acid in water followed by charring at ± 200 °C. TLC-MS analysis was performed on a Camag TLC-MS Interface coupled with an API165 (SCIEX) mass spectrometer (eluted with *tert*-butylmethylether/EtOAc/MeOH, 5/4/1, v/v/v +0.1% formic acid, flow rate 0.12 mL/min). High-resolution mass spectra (HRMS) were recorded on a Waters Synapt G2-Si (TOF) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV) and an internal lock mass LeuEnk ($M+H^+$ = 556.2771). ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 NMR, a Bruker AV-500 NMR or a Bruker AV-850 NMR instrument. All samples were measured in $CDCl_3$, unless stated otherwise. Chemical shifts (δ) are given in ppm relative to tetramethyl silane as internal standard or the residual signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. All given ^{13}C APT spectra are proton decoupled. NMR peak assignment was accomplished using COSY, HSQC. If necessary, additional NOESY, HMBC and HMBC-gated experiments were used to further elucidate structures. Stereochemical product ratios were based on integration of ^1H NMR (crude and purified). Proton and carbon numbering for NMR peak assignment was done as followed: numbering was done similarly to their glucose counterparts and not their respective nomenclature. Numbering starts at the 'anomeric' center and progresses similarly as their glucose counterpart. 'H-7' or 'C-7' is used where the intramolecular oxygen is replaced for the substituted carbon.

3-*O*-*Tert*-butyldimethylsilyl-4-*O*-(4-methoxybenzyl)-D-glucal (4).



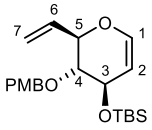
3,4,6-tri-*O*-acetyl-D-glucal (54 g, 0.20 mol) was dissolved in MeOH/Et_3N/H_2O (8:1:1, 1.0 L, 0.2 M) and stirred overnight at room temperature. Upon full conversion (R_f 0.5 (MeOH:DCM, 1:9 v:v)), The reaction mixture was concentrated under reduced pressure and co-evaporated with DMF (50 mL) twice.

The crude was dissolved in anhydrous DMF (0.29 L, 0.70 M). Anisaldehyde dimethyl acetal (44 mL, 0.26 mol, 1.3 eq.) and pyridinium *p*-toluene sulfonate (1.0 g, 4.0 mmol, 0.02 eq.) were added and the mixture was stirred for 1 hour under reduced pressure at 35 °C. Upon full conversion (R_f 0.3 (EtOAc:pentane, 2:8 v:v)), the reaction mixture was quenched by addition of imidazole (27 g, 0.40 mol, 2.0 eq.) and concentrated to 80% of its original volume to secure the removal of any remaining methanol.

The solution was diluted with anhydrous DMF (final concentration: 0.33 L, 0.60 M) followed by the addition of DMAP (2.4 g, 20 mmol, 0.1 eq.) and TBSCl (39 g, 0.26 mol, 1.3 eq.). The mixture was stirred for 1 hour at 35 °C (oil bath) after which full conversion was observed (R_f 0.7 (Toluene)). The reaction was quenched by addition of methanol (10 mL) followed by concentration to a fifth of its original volume. The mixture was diluted with water (1.0 L) and Et_2O (300 mL) and separated in a separation funnel. The aqueous layer was extracted two more times with Et_2O (200 mL), the combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (toluene:pentane, 1:1 v:v) to result in the desired intermediate contaminated with anisaldehyde dimethyl acetal.

This mixture was dissolved in anhydrous DCM (0.33 L, 0.6 M) and cooled to -15 °C. A 1 M solution of DIBAL-H in DCM (0.26 L, 0.26 mol, 1.3 eq.) was slowly added. Subsequently, the reaction mixture was allowed to attain room temperature. Upon stirring for an additional two hours TLC showed full conversion (R_f 0.7 (EtOAc:pentane, 3:7 v:v)). The solution was quenched by the dropwise addition of methanol (10 mL) followed by the addition of a saturated solution of Rochelle's salt (500 mL) and sat. aq. NaOH (100 mL), this was added whilst keeping the solution below 0 °C. Upon full addition, the solution was transferred to a separation funnel followed by separation of the organic layer. The aqueous layer was extracted two more times with EtOAc (200 mL), the combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10:90 EtOAc:pentane → 20:80 EtOAc:pentane) to obtain the title compound as a colorless oil (39 g, 0.1 mol, 51% over four steps). Spectral data was in accordance with literature precedence.[19] ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.28 (d, *J* = 8.6 Hz, 2H, CH_{arom}), 6.89 (d, *J* = 8.7 Hz, 2H, CH_{arom}), 6.33 (dd, *J* = 6.1, 1.4 Hz, 1H, H-1), 4.77 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.67 (dd, *J* = 6.1, 2.9 Hz, 1H, H-2), 4.63 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.34 (dddd, *J* = 5.9, 2.9, 1.4, 0.6 Hz, 1H, H-3), 3.94 (ddd, *J* = 8.2, 4.3, 4.3 Hz, 1H, H-5), 3.81 (s, 5H, OMe, H-6), 3.62 (dd, *J* = 8.0, 5.8 Hz, 1H, H-4), 2.05 (dd, *J* = 6.8, 6.8 Hz, 1H, 6-OH), 0.92 (s, 9H, $C(CH_3)_3$), 0.12 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.1 ($C_{q\text{-}arom}$), 143.6 (C-1), 130.2 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 114.1 (CH_{arom}), 103.7 (C-2), 77.2 (C-5), 76.5 (C-4), 74.1 (CH_2 PMB), 68.7 (C-3), 62.1 (C-6), 55.4 (OMe), 26.0 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), -4.2 ($SiCH_3$), -4.5 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{32}NaO_5Si$ 403.1911; Found 403.1910.

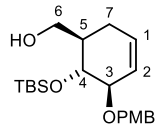
(2*R*,3*R*,4*R*)-3-*O*-(4-Methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-2-vinyl-2,3-dihydro-2*H*-pyran (6).



Compound **4** (25 g, 67 mmol) was dissolved in DCM (0.33 L, 0.2 M) followed by the addition of $NaHCO_3$ (56 g, 0.67 mol, 10 eq.) and consecutively cooled on ice. Dess-Martin periodinane (42 g, 0.10 mol, 1.5 eq.) was added to the mixture after which the reaction was stirred for 2 hours while attaining to room temperature. Upon full conversion (R_f 0.1-0.6 (EtOAc:pentane, 3:7 v:v)), the mixture was quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution (100 mL). The mixture was filtered over celite and rinsed with water (100 mL) and DCM (100 mL) followed by transferring to a separation funnel. Additional 500 mL of water were added and the organic layer was separated. The aqueous layer was extracted two more times with EtOAc after which the combined organic layers were dried over $MgSO_4$, filtered over celite and concentrated under reduced pressure to yield the crude intermediate as a yellow oil. The crude intermediate was co-evaporated twice with toluene and dissolved in THF (70 mL).

Ph_3PCH_3Br (36 g, 0.10 mmol, 1.5 eq.) was dissolved in anhydrous THF (200 mL, 0.5 M) and cooled to -78 °C. *n*-BuLi (2.5 M in hexane, 38 mL, 94 mmol, 1.4 eq.) was added dropwise, stirring continued at 0 °C for 1 hour. Subsequently, the mixture was cooled back to -78 °C and the previously prepared aldehyde solution was added dropwise. This reaction mixture was allowed to attain to 0 °C and stirring continued for another hour. Upon full conversion (R_f 0.5 (toluene:pentane, 1:1 v:v)), the reaction was quenched by addition of sat. aq. $NaHCO_3$ (50 mL) and diluted with 500 mL of water and 100 mL of Et_2O. The organic layer was separated and the aqueous layer was extracted twice with 200 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (30:70 toluene:pentane → 90:10 toluene:pentane) to obtain the title compound as a colorless oil (20 g, 54 mmol, 80% over two steps). Spectral data was in accordance with literature precedence.[19] ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.27 – 7.25 (m, 2H, CH_{arom}), 6.87 (m, 2H, CH_{arom}), 6.33 (dd, *J* = 6.1, 1.5 Hz, 1H, H-1), 6.01 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H, H-6), 5.40 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H, H-7), 5.27 (ddd, *J* = 10.5, 1.6, 1.1 Hz, 1H, H-7), 4.70 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.67 (dd, *J* = 6.1, 2.6 Hz, 1H, H-2), 4.59 (d, *J* = 10.7 Hz, 1H, CH*H* PMB), 4.35 (ddd, *J* = 6.2, 2.6, 1.4 Hz, 1H, H-3), 4.28 (dddd, *J* = 9.2, 6.8, 1.2, 1.2 Hz, 1H, H-5), 3.80 (s, 3H, OMe), 3.42 (dd, *J* = 8.6, 6.2 Hz, 1H, H-4), 0.92 (s, 9H, $C(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4 ($C_{q\text{-}arom}$), 142.7 (C-1), 134.8 (C-6), 131.4 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 118.2 (C-7), 115.3 (CH_{arom}), 104.1 (C-2), 80.2 (C-4), 78.3 (C-5), 74.0 (CH_2 PMB), 69.3 (C-3), 55.4 (OMe), 26.0 ($C(CH_3)_3$), 17.6 ($C(CH_3)_3$), -4.3 ($SiCH_3$), -4.4 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{32}NaO_4Si$ 399.1968; Found 399.1959.

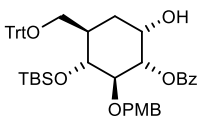
3-*O*-(4-Methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-carba-D-glucal (8).



Compound **6** (20 g, 54 mmol) was dissolved in anhydrous diphenyl ether (2.5 M, 21 mL) under a N_2 atmosphere. The solution was heated to 210 °C (oil bath) and stirred for 2 hours. Upon full conversion (EtOAc:pentane, 1:9 v:v), the reaction mixture was transferred to a second flask containing a solution of $NaBH_4$ (3.0 g, 80 mmol, 1.5 eq.) in a 2:1 mixture of THF:EtOH (0.21 L, 0.25 M) and stirred at 0 °C. After stirring for 20 minutes, full conversion was observed (R_f 0.3 (EtOAc:pentane, 2:8 v:v)) and

the reaction was quenched using sat. aq. $NaHCO_3$ (50 mL), diluted with water (600 mL) and Et_2O (200 mL). The organic layer was separated and the aqueous layer extracted twice with Et_2O (200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (10:90 Et_2O:pentane → 60:40 Et_2O:pentane) to obtain the title compound as a colorless oil (16 g, 43 mmol, 80% over two steps). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.31 – 7.20 (m, 2H, CH_{arom}), 6.87 (m, 2H, CH_{arom}), 5.78 (dddd, *J* = 10.1, 4.2, 3.1, 1.4 Hz, 1H, H-1), 5.68 (dddd, *J* = 10.1, 2.4, 2.4, 1.6 Hz, 1H, H-2), 4.58 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.49 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 3.88 – 3.81 (m, 2H, H-3, H-4), 3.80 (s, 3H, OMe), 3.73 (ddd, *J* = 11.0, 6.7, 4.3 Hz, 1H, H-6), 3.61 (ddd, *J* = 11.0, 7.6, 4.8 Hz, 1H, H-6), 2.42 (dd, *J* = 7.6, 4.4 Hz, 1H, 6-OH), 2.23 (ddddd, *J* = 17.8, 5.8, 3.9, 1.6, 1.6 Hz, 1H, H-7), 1.98 (ddddd, *J* = 7.8, 7.8, 6.2, 4.9, 4.9 Hz, 1H, H-5), 1.89 (dddd, *J* = 18.0, 5.4, 5.4, 2.7 Hz, 1H, H-7), 0.89 (s, 9H, $C(CH_3)_3$), 0.09 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.2, 131.7 ($C_{q\text{-}arom}$), 129.4 (CH_{arom}), 128.5 (C-1), 125.1 (C-2), 113.8 (CH_{arom}), 78.9 (C-3), 73.7 (C-4), 70.8 (CH_2 PMB), 64.9 (C-6), 55.8 (OMe), 41.7 (C-5), 27.2 (C-7), 26.0 ($C(CH_3)_3$), 18.3 ($C(CH_3)_3$), -3.5 ($SiCH_3$), -4.7 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{34}NaO_4Si$ 401.2124; Found 401.2116.

2-*O*-Benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-carba-α-D-glucose (11).



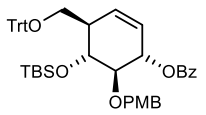
Compound **8** (16 g, 43 mmol) was dissolved in anhydrous DCM (0.22 L, 0.2 M) followed by the addition of Et_3N (30 mL, 0.22 mol, 5.0 eq.), DMAP (0.53 g, 4.3 mmol, 0.1 eq.) and TrtCl (18 g, 65 mmol, 1.5 eq.) and stirred overnight at room temperature. Upon full conversion (R_f 0.7 (Toluene)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ followed by diluting the reaction mixture with 500 mL of water. The organic layer was separated and the aqueous layer was extracted twice with 200 mL of Et_2O. The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated.

The crude was dissolved in an acetone/water mixture (6:1, 0.43 L, 0.1 M) followed by the addition of an aqueous NMO solution (50% w:w, 18 mL, 87 mmol, 2.0 eq.) and an aqueous osmium tetra oxide solution (2.5 % w/w, 18 mL, 1.7 mmol, 0.04 eq.). The reaction mixture was stirred overnight after which full conversion was observed (R_f 0.4 (EtOAc:pentane, 3:7 v:v)). The reaction was quenched by addition of sat. aq. $NaHCO_3$ (50 mL) and sat. aq. $Na_2S_2O_3$ (50 mL), This mixture was transferred to a separation funnel and diluted with water (1.0 L) and EtOAc (300 mL). The organic layer was separated and the aqueous layer was extracted twice with EtOAc (300 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated.

The crude was dissolved in pyridine (0.22 L, 0.2 M) and cooled to -15 °C. Subsequently, BzCl (7.5 mL, 65 mmol, 1.5 eq.) was added dropwise after which the reaction mixture was stirred for another 1.5 hours at this temperature. Upon full conversion (R_f 0.3 (Et_2O:pentane, 3:7 v:v)), the reaction was quenched by the addition of MeOH (10 mL) and allowed to attain to room temperature followed by diluting the reaction mixture with water (1.0 L) and Et_2O (300 mL). The organic layer was separated and the aqueous layer extracted twice with Et_2O (200 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (10:90 Et_2O:pentane → 50:50 Et_2O:pentane) to obtain the title compound as a white foam (26 g, 34 mmol, 79% over three steps).

^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.00 – 7.91 (m, 2H, CH_{arom}), 7.53 (dd, *J* = 7.8, 7.1 Hz, 1H, CH_{arom}), 7.46 – 7.35 (m, 8H, CH_{arom}), 7.28 – 7.18 (m, 9H, CH_{arom}), 7.04 – 6.97 (m, 2H, CH_{arom}), 6.64 – 6.57 (m, 2H, CH_{arom}), 5.10 (dd, *J* = 9.7, 3.0 Hz, 1H, H-2), 4.64 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.61 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.24 (dd, *J* = 3.3, 3.3 Hz, 1H, H-1), 3.91 (dd, *J* = 9.7, 8.3 Hz, 1H, H-3), 3.68 (s, 3H, OMe), 3.62 (dd, *J* = 8.4, 3.9 Hz, 1H, H-6), 3.32 (dd, *J* = 9.7, 8.3 Hz, 1H, H-4), 2.65 (dd, *J* = 9.8, 8.4 Hz, 1H, H-6), 2.52 (ddd, *J* = 14.2, 3.9 , 3.9 Hz, 1H, H-7), 2.49 – 2.42 (m, 1H, H-5), 2.08 (bs, 1H, 1-OH), 1.27 (ddd, *J* = 14.3, 11.9, 2.4 Hz, 1H, H-7), 0.70 (s, 9H, $C(CH_3)_3$), -0.14 (s, 3H, $SiCH_3$), -0.36 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 165.4 (C=O Bz), 158.2, 143.6 ($C_{q\text{-}arom}$), 133.3 (CH_{arom}), 130.8 ($C_{q\text{-}arom}$), 129.9, 129.8, 128.9, 128.5, 127.9, 127.0, 113.5 (CH_{arom}), 86.2 (CPh_3), 81.6 (C-3), 77.7 (C-2), 75.0 (CH_2 PMB), 75.0 (C-4), 67.7 (C-1), 65.8 (C-6), 55.2 (OMe), 38.8 (C-5), 31.1 (C-7), 26.1 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$), -3.5 ($SiCH_3$), -4.4 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{47}H_{54}NaO_7Si$ 781.3537; Found 781.3526.

2-*O*-Benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-cyclophellitol alkene (12).

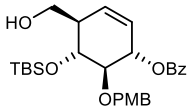


Compound **11** (0.94 g, 1.2 mmol) was dissolved in anhydrous DMF (12 mL, 0.1 M) followed by the addition of 2,6-lutidine (0.71 mL, 6.2 mmol, 5.0 eq.) and subsequently methyl triphenoxy phosphonium iodide (1.1 g, 2.5 mmol, 2.0 eq.). The reaction was kept under N_2 atmosphere while heating to 100 °C (oil bath), after 1.5 hours at this temperature the reaction was cooled to room temperature. Upon full conversion (R_f 0.5 (Et_2O:pentane, 2:8 v:v)), the reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL) followed by diluting the reaction mixture with water (200 mL) and Et_2O (50 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (50 mL). The combined organic layers were washed with sat. aq. NH_4Cl before subsequent drying over $MgSO_4$, filtration over a glass filter and concentration.

The crude mixture was dissolved in anhydrous DCM (12 mL, 0.1 M), cooled on ice, followed by the addition of $NaHCO_3$ (1.0 g, 12 mmol, 10 eq.) and *m*-CPBA (1.4 g, 8.4 mmol, 7.0 eq.). This reaction mixture was stirred on ice for 4 hours after which full conversion was observed (R_f 0.55 (Et_2O:pentane, 2:8 v:v)). The reaction was quenched by addition of sat. aq. $NaHCO_3$ (5.0 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL), The mixture was transferred to a separation funnel and diluted with water (100 mL) and Et_2O (50 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (50 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40:60 DCM:pentane was used to flush off methyl diphenyl phosphonate *then* 10:90 Et_2O:pentane) to obtain the title compound as a colorless oil (0.68 g, 0.92 mmol, 75% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.98 – 7.86 (m, 2H, CH_{arom}), 7.62 – 7.05 (m, 20H, CH_{arom}), 6.73 – 7.55 (m, 2H, CH_{arom}), 6.16 – 6.02 (m, 1H, H-1), 5.67 – 5.62 (m, 2H, H-2, H-7), 4.66 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.61 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 3.79 (dd, *J* = 9.2, 7.3 Hz, 1H, H-3), 3.69 (s, 3H, OMe), 3.61 (dd, *J* = 9.2, 7.9 Hz, 1H, H-4), 3.57 (d, *J* = 3.6 Hz, 1H, H-6), 2.78 – 2.76 (m, 2H, H-5, H-6), 0.72 (s, 9H, $C(CH_3)_3$), -0.08 (s, 3H, $SiCH_3$), -0.31 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.2 (C=O Bz), 158.9, 143.7 ($C_{q\text{-}arom}$), 133.0 (CH_{arom}), 130.8 ($C_{q\text{-}arom}$), 130.6 (C-1), 130.3 ($C_{q\text{-}arom}$), 129.8, 129.4, 128.9, 128.4, 127.9, 127.1 (CH_{arom}), 124.9 (C-7), 114.2 (CH_{arom}), 86.8 (CPh_3), 82.1 (C-

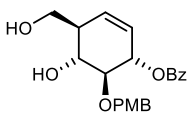
3), 75.6 (C-2), 74.4 (CH_2 PMB), 72.2 (C-4), 64.7 (C-6), 55.2 (OMe), 46.1 (C-5), 26.0 (C(CH_3)$_3$), 18.1 (*C*(CH_3)$_3$), -3.6 ($SiCH_3$), -4.7 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{47}H_{52}NaO_6Si$ 763.3431; Found 763.3423.

2-*O*-Benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-cyclophellitol alkene (17).



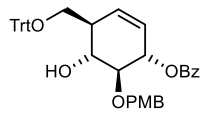
Compound **12** (0.74 g, 1.0 mmol) was dissolved in a 3:1 mixture of DCM and MeOH (5.0 mL, 0.2 M). subsequently, $ZnCl_2$ (1.4 g, 10 mmol, 10.0 eq.) was added and the reaction mixture was stirred overnight at room temperature. Upon full conversion (R_f 0.2 (EtOAc:pentane, 1:9 v:v)), the reaction was diluted with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (20:80 Et_2O:pentane → 30:70 Et_2O:pentane) to obtain the title compound as a colorless oil (0.37 g, 0.74 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.00 – 7.90 (m, 2H, CH_{arom}), 7.63 – 7.49 (m, 1H, CH_{arom}), 7.45 – 7.34 (m, 2H, CH_{arom}), 7.19 – 7.12 (m, 2H, CH_{arom}), 6.74 – 6.67 (m, 2H, CH_{arom}), 5.83 – 5.74 (m, 2H, H-1, H-7), 5.70 – 5.63 (m, 1H, H-2), 4.71 (s, 2H, CH_2 PMB), 3.90 (dd, *J* = 8.2, 6.9 Hz, 1H, H-4), 3.84 – 3.75 (m, 3H, H-3, H-6), 3.72 (s, 3H, OMe), 2.48 (dddd, *J* = 6.7, 4.1, 2.4, 2.4 Hz, 1H, H-5), 1.86 (bs, 1H, 6-OH), 0.88 (s, 9H, C(CH_3)$_3$), 0.06 (s, 3H, $SiCH_3$), -0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 166.2 (C=O Bz), 133.1 (CH_{arom}), 130.9, 130.4 ($C_{q\text{-}arom}$), 130.3 (C-1), 130.1, 129.8, 129.6, 128.4 (CH_{arom}), 126.4 (C-7), 113.7 (CH_{arom}), 80.9 (C-3), 74.1 (CH_2 PMB), 73.9 (C-2), 71.4 (C-4), 62.8 (C-6), 55.3 (OMe), 47.4 (C-5), 26.1 (C(*C*H_3)$_3$), 18.3 (*C*(CH_3)$_3$), -3.7 ($SiCH_3$), -4.9 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{38}NaO_6Si$ 521.2335; Found 521.2328.

2-*O*-Benzoyl-3-*O*-(4-methoxybenzyl)-cyclophellitol alkene (18).



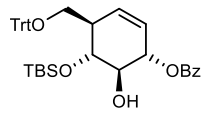
Compound **12** (0.37 g, 0.50 mmol) was dissolved in a 1:1 mixture of DCM and MeOH (10 mL, 0.05 M). subsequently, *p*-TsOH (0.43 g, 2.5 mmol, 5.0 eq.) was added and the reaction mixture was stirred overnight at room temperature. Upon full conversion (R_f 0.3 (EtOAc:pentane, 1:1 v:v)), the reaction was diluted with water (50 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted twice with EtOAc (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40:60 EtOAc:pentane → 60:40 EtOAc:pentane) to obtain the title compound as a colorless oil (0.12 g, 0.32 mmol, 84%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.08 – 7.97 (m, 2H, CH_{arom}), 7.64 – 7.52 (m, 1H, CH_{arom}), 7.50 – 7.41 (m, 2H, CH_{arom}), 7.23 – 7.12 (m, 2H, CH_{arom}), 6.85 – 6.66 (m, 2H, CH_{arom}), 5.77 – 5.71 (m, 1H, H-2), 5.67 (ddd, *J* = 10.1, 2.9, 2.2 Hz, 1H, H-7), 5.60 (ddd, *J* = 10.1, 1.9, 1.7 Hz, 1H, H-1), 4.75 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.63 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 3.90 – 3.69 (m, 7H, H-3, H-4, H-6, OMe), 3.23 (d, *J* = 1.7 Hz, 1H, 4-OH), 2.74 (s, 1H, 6-OH), 2.61 – 2.52 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.1 (C=O Bz), 159.5 ($C_{q\text{-}arom}$), 133.3 (CH_{arom}), 130.0 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 128.9 (C-1), 128.6 (CH_{arom}), 126.7 (C-7), 114.0 (CH_{arom}), 82.1 (C-3), 75.8 (C-2), 74.5 (CH_2 PMB), 72.7 (C-4), 65.1 (C-6), 55.3 (OMe), 45.3 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{24}NaO_6$ 407.1471; Found 407.1464.

2-*O*-Benzoyl-3-*O*-(4-methoxybenzyl)-6-*O*-trityl-cyclophellitol alkene (19).



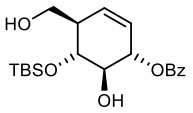
Compound **12** (0.37 g, 0.50 mmol) was dissolved in THF (2.5 mL, 0.2 M) followed by the addition of a 1 M solution of TBAF in THF (4.0 mL, 4.0 mmol, 8.0 eq.). The reaction was stirred for 1 hour at room temperature. Upon full conversion (R_f 0.3 (Et_2O:pentane, 3:7 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (5:95 Et_2O:pentane → 10:90 Et_2O:pentane) to obtain the title compound as a colorless oil (0.20 g, 0.32 mmol, 95%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.07 – 8.01 (m, 2H, CH_{arom}), 7.59 – 7.52 (m, 1H, CH_{arom}), 7.47 – 7.40 (m, 9H, CH_{arom}), 7.32 – 7.26 (m, 6H, CH_{arom}), 7.26 – 7.15 (m, 4H, CH_{arom}), 6.80 – 6.72 (m, 2H, CH_{arom}), 5.78 (dd, *J* = 7.9, 3.2 Hz, 1H, H-2), 5.69 – 5.60 (m, 2H, H-1, H-7), 4.76 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.67 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 3.92 (dd, *J* = 9.5, 9.5 Hz, 1H, H-4), 3.84 (dd, *J* = 10.1, 7.8 Hz, 1H, H-3), 3.71 (s, 3H, OMe), 3.34 (dd, *J* = 8.8, 5.2 Hz, 1H, H-6), 3.28 (dd, *J* = 8.8, 5.0 Hz, 1H, H-6), 2.92 (bs, 1H, 4-OH), 2.59 (dddd, *J* = 9.3, 4.5, 4.5, 4.5 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.1 (C=O Bz), 159.4, 144.0 ($C_{q\text{-}arom}$), 133.2 (CH_{arom}), 130.3 ($C_{q\text{-}arom}$), 130.2 (C-1), 130.2 ($C_{q\text{-}arom}$), 129.8, 129.8, 128.8, 128.5, 128.0, 127.1 (CH_{arom}), 125.7 (C-7), 113.8 (CH_{arom}), 86.8 (CPh_3), 82.4 (C-3), 75.8 (C-2), 74.6 (CH_2 PMB), 71.3 (C-4), 63.9 (C-6), 55.3 (OMe), 44.2 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{41}H_{38}NaO_6$ 649.2566; Found 649.2562.

2-*O*-Benzoyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-cyclophellitol alkene (20).



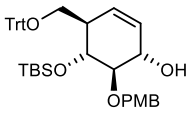
Compound **12** (0.37 g, 0.50 mmol) was dissolved in DCM (10 mL, 0.05 M) followed by the addition of a pH 7.4 aq. phosphate buffer (5.0 mL, 0.1 M). The solution was cooled on ice and subsequently DDQ (0.68 g, 3.0 mmol, 6.0 eq.) was added. The reaction was stirred for 1 hour while attaining to room temperature. Upon full conversion (R_f 0.6 (Et_2O:pentane, 2:8 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (20:80 Et_2O:pentane → 50:50 Et_2O:pentane) to obtain the title compound as a colorless oil (0.21 g, 0.35 mmol, 91%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.30 – 8.20 (m, 2H, CH_{arom}), 7.76 – 7.67 (m, 1H, CH_{arom}), 7.66 – 7.56 (m, 9H, CH_{arom}), 7.52 – 7.37 (m, 8H, CH_{arom}), 6.26 (ddd, *J* = 10.2, 2.1, 2.1 Hz, 1H, H-1), 5.86 (ddd, *J* = 10.2, 2.5, 2.5 Hz, 1H, H-7), 5.80 (ddd, *J* = 8.1, 3.5, 2.0 Hz, 1H, H-2), 4.15 – 4.05 (m, 1H, H-3), 3.80 – 3.71 (m, 2H, H-4, H-6), 3.14 – 3.01 (m, 1H, H-6), 2.86 (dddd, *J* = 10.4, 7.5, 3.6, 3.6 Hz, 1H, H-5), 2.74 (d, *J* = 2.8 Hz, 1H, 3-OH), 0.91 (s, 9H, $C(CH_3)_3$), 0.20 (s, 3H, $SiCH_3$), -0.08 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.9 (C=O Bz), 144.1 ($C_{q\text{-}arom}$), 133.2 (CH_{arom}), 130.9 (C-1), 130.1 ($C_{q\text{-}arom}$), 129.9, 128.8, 128.5, 128.0, 128.0, 127.9, 127.3, 127.2 (CH_{arom}), 124.8 (C-7), 86.8 (CPh_3), 75.8 (C-2), 75.6 (C-3), 73.1 (C-4), 64.3 (C-6), 45.4 (C-5), 26.0 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), -3.7 ($SiCH_3$), -4.7 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{39}H_{44}NaO_5Si$ 643.2856; Found 643.2847.

2-*O*-Benzoyl-4-*O*-*tert*-butyldimethylsilyl-cyclophellitol alkene (21).



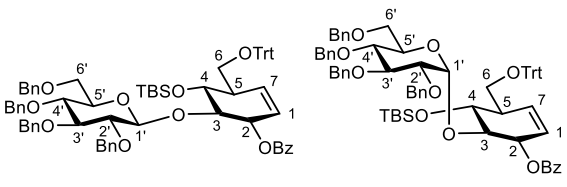
Compound **12** (0.37 g, 0.50 mmol) was dissolved in anhydrous DCM (10 mL, 0.05 M) followed by the addition of TES (0.24 mL, 1.5 mmol, 3.0 eq.). The mixture was cooled on ice after which TFA (0.62 mL, 8.0 mmol, 16 eq.) was added, the solution was stirred for 1 hour while attaining to room temperature. Upon full conversion (R_f 0.5 (Et_2O:pentane, 6:4 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (20:80 Et_2O:pentane → 40:60 Et_2O:pentane) to obtain the title compound as a colorless oil (0.13 g, 0.35 mmol, 84%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.10 – 8.03 (m, 2H, CH_{arom}), 7.59 – 7.52 (m, 1H, CH_{arom}), 7.46 – 7.40 (m, 2H, CH_{arom}), 5.77 (ddd, *J* = 10.2, 1.5, 1.4 Hz, 1H, H-1/H-7), 5.73 (ddd, *J* = 10.2, 2.0, 1.8 Hz, 1H, H-1/H-7), 5.61 (dddd, *J* = 7.7, 2.9, 1.6, 1.5 Hz, 1H, H-2), 3.93 (dd, *J* = 9.5, 7.7 Hz, 1H, H-3), 3.88 – 3.81 (m, 2H, H-4, H-6), 3.75 (dd, *J* = 10.5, 4.8 Hz, 1H, H-6), 2.76 (s, 1H, 3-OH/6-OH), 2.43 (dddd, *J* = 9.8, 4.9, 2.3, 1.0 Hz, 1H, H-5), 1.86 (s, 1H, 3-OH/6-OH), 0.92 (s, 9H, $C(CH_3)_3$), 0.17 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.9 (C=O Bz), 133.3 (CH_{arom}), 130.3 (C-1/C-7), 130.1 ($C_{q\text{-}arom}$), 129.9, 128.5 (CH_{arom}), 126.6 (C-1/C-7), 75.8 (C-2), 75.4 (C-3), 72.1 (C-4), 62.3 (C-6), 46.9 (C-5), 26.1 ($C(CH_3)_3$), 18.4 ($C(CH_3)_3$), -3.7 ($SiCH_3$), -4.6 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{30}NaO_5Si$ 401.1760; Found 401.1752.

3-*O*-(4-Methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-cyclophellitol alkene (22).



Compound **12** (2.2 g, 3.0 mmol) was dissolved in a 1:1 mixture of DCM and MeOH (60 mL, 0.05 M) followed by the addition of NaOMe (0.78 g, 12 mmol, 4.0 eq.). The reaction was stirred overnight at room temperature. Upon full conversion (R_f 0.3 (EtOAc:pentane, 1:9 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (200 mL) and Et_2O (50 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (50 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (10:90 Et_2O:pentane → 30:70 Et_2O:pentane) to obtain the title compound as a colorless oil (1.2 g, 1.9 mmol, 86%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.50 – 7.34 (m, 6H, CH_{arom}), 7.33 – 7.07 (m, 11H, CH_{arom}), 6.86 – 6.79 (m, 2H, CH_{arom}), 5.84 (ddd, *J* = 10.2, 3.3, 1.2 Hz, 1H, H-7), 5.77 (ddd, *J* = 10.2, 3.5, 2.1 Hz, 1H, H-1), 4.50 (d, *J* = 12.0 Hz, 1H, C*H*H PMB), 4.41 (d, *J* = 12.0 Hz, 1H, CH*H* PMB), 4.05 – 3.89 (m, 2H, H-2, H-4), 3.80 (s, 3H, OMe), 3.53 (dd, *J* = 6.5, 4.6 Hz, 1H, H-3), 3.35 (dd, *J* = 8.6, 6.9 Hz, 1H, H-6), 2.99 (dd, *J* = 8.6, 7.7 Hz, 1H, H-6), 2.67 – 2.57 (m, 1H, H-5), 2.46 (d, *J* = 7.9 Hz, 1H, 2-OH), 0.80 (s, 9H, $C(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), -0.09 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 144.3, 130.7 ($C_{q\text{-}arom}$), 129.4, 128.9, 127.9 (CH_{arom}), 127.8 (C-1), 127.8 (C-7), 127.1, 114.0 (CH_{arom}), 86.8 (CPh_3), 81.1 (C-3), 73.0 (CH_2 PMB), 70.1 (C-4), 68.9 (C-2), 65.0 (C-6), 55.4 (OMe), 45.4 (C-5), 26.0 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), -4.3 ($SiCH_3$), -4.7 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{40}H_{48}NaO_5Si$ 659.3169; Found 659.3157.

3-*O*-(Perbenzyl-α-D-glucopyranosyl)-2-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-cyclophellitol alkene (24a) and 3-*O*-(perbenzyl-β-D-glucopyranosyl)-2-*O*-benzoyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-trityl-cyclophellitol alkene (24b).



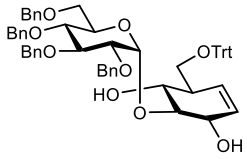
To perbenzylated donor **23** (1.2 g, 2.1 mmol, 2.0 eq.), synthesized according to literature precedence [30], was added TTBP (2.0 g, 8.0 mmol, 7.5 eq.) and Ph_2SO (0.56 g, 2.8 mmol, 2.6 eq.) and co-evaporated twice with toluene. This mixture was subsequently dissolved in anhydrous DCM (20 mL, 0.05 M) followed by the addition of activated 3Å molecular rods and stirred under inert atmosphere. The solution was cooled to -78 °C after which Tf_2O (0.39 mL, 2.3 mmol, 2.2 eq.) was added, the reaction mixture was allowed to warm to -60 °C and stirring continued at this temperature for 15 minutes. Subsequently, the solution was cooled back to -78 °C and compound **20** (0.66 g, 1.1 mmol, 1.0 eq.) dissolved in 2 mL of anhydrous DCM was added dropwise. The reaction was allowed to warm to -10 °C over the course of 2 hours after which full conversion was observed (R_f 0.3 and 0.5 for **24a** and **24b** respectively (Et_2O:pentane, 2:8 v:v)). The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (200 mL) and Et_2O (50 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (50 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (10:90 Et_2O:pentane → 20:80 Et_2O:pentane) to obtain the title compounds as colorless oils (0.85 g, 0.74 mmol for **24a** and 0.21 g, 0.19 mmol for **24b**, α:β ratio; 4:1 with an overall yield of 88%).

Analytical data for **24a**: NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.05 – 7.92 (m, 2H, CH_{arom}), 7.55 – 7.08 (m, 38H, CH_{arom}), 6.22 (dd, *J* = 10.1, 3.8 Hz, 1H, H-7), 5.79 (ddd, *J* = 9.9, 3.7, 1.8 Hz, 1H, H-1), 5.49 (ddd, *J* = 3.2, 3.0, 1.6 Hz, 1H, H-2), 4.93 (d, *J* = 3.7 Hz, 1H, H-1'), 4.76 (d, *J* = 10.8 Hz, 1H, C*H*H Bn), 4.72 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.61 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.58 (d, *J* = 11.0 Hz, 1H, C*H*H Bn), 4.56-4.43 (m, 2H, CH*H* Bn, CH*H* Bn), 4.47 (d, *J* = 10.8 Hz, 1H, CH*H* Bn), 4.34 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 3.92 (dd, *J* = 4.9, 2.9 Hz, 1H, H-3), 3.79 (dd, *J* = 4.9, 3.4 Hz, 1H, H-4), 3.77 – 3.59 (m, 5H, H-3', H-4', H-5', H-6'), 3.48 (dd, *J* = 14.0, 7.0 Hz, 1H, H-6), 3.41 (dd, *J* = 9.7, 3.7 Hz, 1H, H-2'), 3.31 (dd, *J* = 9.3, 9.1 Hz, 1H, H-6), 2.54 (dddd, *J* = 7.4, 6.0, 3.6, 1.4 Hz, 1H, H-5), 0.75 (s, 9H, $C(CH_3)_3$), -0.03 (s, 3H, $SiCH_3$), -0.11 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.1 (C=O Bz), 144.5, 139.2, 138.7, 138.4 ($C_{q\text{-}arom}$), 132.9 (CH_{arom}), 132.0 (C-7), 130.6 ($C_{q\text{-}arom}$), 129.9, 128.9, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.1 ($C_{q\text{-}arom}$), 122.4 (C-1), 99.0 (C-1'), 87.0 (CPh_3), 82.2 (C-3'/C-4'/C-5'), 80.5 (C-3), 79.7 (C-2'), 77.4 (C-3'/C-4'/C-5'), 75.6, 75.2, 74.0, 73.1 (CH_2 Bn), 71.5 (C-3'/C-4'/C-5'), 70.5 (C-2), 69.2 (C-4), 68.3 (C-6'), 65.7 (C-6), 44.4 (C-5), 26.0 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), -3.9 ($SiCH_3$), -4.7 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{73}H_{78}NaO_{10}Si$ 1165.5262; Found 1164.5253.

Analytical data for **24b**: NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.03 (d, *J* = 8.4 Hz, 1H, CH_{arom}), 7.63 – 7.07 (m, 39H, CH_{arom}), 6.16 (ddd, *J* = 10.3, 3.1, 1.4 Hz, 1H, H-7), 5.74 (ddd, *J* = 10.3, 2.8, 2.1 Hz, 1H, H-1), 5.57 (ddd, *J* = 5.4, 3.5, 1.7 Hz, 1H, H-2), 4.84 – 4.76 (m, 2H, H-1', C*H*H Bn), 4.71 (d, *J* = 11.0 Hz, 1H, C*H*H Bn), 4.67 – 4.60 (m, 2H, C*H*H Bn, C*H*H Bn), 4.59 – 4.51 (m, 3H, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.38 (d, *J* = 11.2, Hz, 1H, CH*H* Bn), 4.22 (ddd, *J* = 7.1, 5.5, 1.4 Hz, 1H, H-3), 3.84 (ddd, *J* =

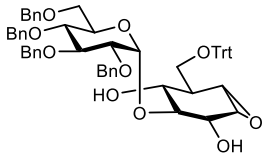
7.3, 5.8, 1.4 Hz, 1H, H-4), 3.78 (ddd, *J* = 10.8, 1.6, 1.6 Hz, 1H, H-6'), 3.68 (ddd, *J* = 10.7, 5.0, 1.2 Hz, 1H, H-6'), 3.58 – 3.40 (m, 4H, H-6, H-3', H-4', H-5'), 3.23 (ddd, *J* = 9.2, 7.9, 1.3 Hz, 1H, H-2'), 2.93 (ddd, *J* = 8.7, 8.7, 1.4 Hz, 1H, H-6), 2.83 – 2.76 (m, 1H, H-5), 0.76 (s, 9H, $C(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), -0.13 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.1 (C=O Bz), 144.2, 138.8, 138.7, 138.5, 138.3 ($C_{q\text{-}arom}$), 133.0 (CH_{arom}), 131.1 (C-7), 130.4 ($C_{q\text{-}arom}$), 129.8, 128.9, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 127.9, 127.7, 127.6, 127.5, 127.1 (CH_{arom}), 123.7 (C-1), 102.8 (C-1'), 86.8 (CPh_3), 84.9 (C-3'), 82.2 (C-2'), 78.2 (C-4'), 78.0 (C-3), 75.7, 75.1 (CH_2 Bn), 75.1 (C-5'), 74.8 (CH_2 Bn), 73.6 (C-2), 73.6 (CH_2 Bn), 69.9 (C-4), 69.5 (C-6'), 65.1 (C-6), 45.4 (C-5), 26.1 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), -3.3 ($SiCH_3$), -5.2 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{73}H_{78}NaO_{10}Si$ 1165.5262; Found 1164.5254.

3-*O*-(Perbenzyl-α-D-glucopyranosyl)-6-*O*-trityl-cyclophellitol alkene (25).



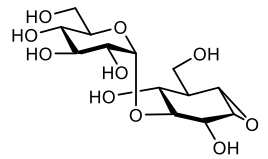
Compound **24a** (0.23 g, 0.20 mmol) was dissolved in THF (4.0 mL, 0.05 M) after which a 1 M TBAF solution in THF (0.60 mL, 0.60 mmol, 3.0 eq.) was added. The reaction mixture was stirred for 1 hour at room temperature. Upon full conversion (R_f 0.2 (Et_2O:pentane, 3:7 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in a 1:1 mixture of DCM and MeOH (4.0 mL, 0.05 M) followed by the addition of NaOMe (0.26 g, 4.0 mmol, 20 eq.). The reaction was stirred overnight at room temperature. Upon full conversion (R_f 0.2 (Et_2O:pentane, 4:6 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). 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 (0.12 g, 0.13 mmol, 66% over two steps). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.49 – 7.41 (m, 6H, CH_{arom}), 7.36 – 7.18 (m, 27H, CH_{arom}), 7.18 – 7.09 (m, 2H, CH_{arom}), 5.67 (ddd, *J* = 10.2, 2.0, 2.0 Hz, 1H, H-1), 5.60 (ddd, *J* = 10.2, 2.6, 2.6 Hz, 1H, H-7), 4.93 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.87 – 4.80 (m, 3H, H-1', C*H*H Bn, C*H*H Bn), 4.77 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.68 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.56 (d, *J* = 12.4 Hz, 1H, CH*H* Bn), 4.50 (d, *J* = 12.4 Hz, 1H, CH*H* Bn), 4.46 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.26 – 4.19 (m, 1H, H-2), 4.07 (ddd, *J* = 10.2, 6.5, 1.9 Hz, 1H, H-5'), 4.04 – 3.98 (m, 1H, H-3'), 3.83 (dd, *J* = 9.9, 9.7 Hz, 1H, H-4), 3.75 – 3.71 (m, 2H, 2-OH, 4-OH), 3.64 (dd, *J* = 10.1, 2.0 Hz, 1H, H-6'), 3.58 (dd, *J* = 9.6, 3.8 Hz, 1H, H-2'), 3.50 (dd, *J* = 10.1, 6.6 Hz, 1H, H-6'), 3.44 (dd, *J* = 10.2, 8.9 Hz, 1H, H-4'), 3.40 – 3.34 (m, 2H, H-3, H-6), 3.25 (dd, *J* = 8.7, 6.0 Hz, 1H, H-6), 2.52 (dddd, *J* = 5.7, 5.7, 5.7, 2.6 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 144.3, 138.6, 137.9, 137.5 ($C_{q\text{-}arom}$), 129.0 (CH_{arom}), 128.9 (C-1), 128.7, 128.6, 128.5, 128.3, 128.1, 128.0 (CH_{arom}), 127.9 (C-7), 127.9, 127.0 (CH_{arom}), 100.1 (C-1'), 91.6 (C-3), 86.5 (CPh_3), 82.3 (C-3'), 79.7 (C-2'), 78.1 (C-4'), 75.9, 75.2, 74.1, 73.6 (CH_2 Bn), 71.4 (C-5'), 71.1 (C-2), 69.7 (C-4), 68.7 (C-6'), 63.4 (C-6), 44.2 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{60}H_{60}NaO_9$ 947.4135; Found 947.4130.

3-*O*-(Perbenzyl-α-D-glucopyranosyl)-6-*O*-trityl-1,7-*epi*-cyclophellitol (26).



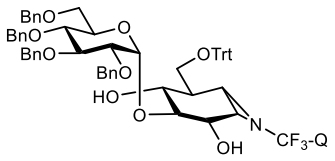
Compound **25** (58 mg, 56 µmol) was dissolved in anhydrous DCM (1.2 mL, 0.05 M). $NaHCO_3$ (24 mg, 0.28 mmol, 5.0 eq.) and *m*-CPBA (29 mg, 0.17 mmol, 3.0 eq.) were subsequently added. The mixture was stirred overnight at room temperature. Upon full conversion (R_f 0.4 (Et_2O:pentane, 6:4 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL) followed by diluting the reaction mixture with water (25 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (50:50 Et_2O:pentane → 70:30 Et_2O:pentane) to obtain the title compound as a colorless oil (42 mg, 39 µmol, 70%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.48 – 7.40 (m, 6H, CH_{arom}), 7.36 – 7.21 (m, 27H, CH_{arom}), 7.16 – 7.10 (m, 2H, CH_{arom}), 4.92 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.85 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.81 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.76 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.76 (d, *J* = 3.9 Hz, 1H, H-1'), 4.66 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.57 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.51 (d, *J* = 12.4 Hz, 1H, CH*H* Bn), 4.47 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.05 (ddd, *J* = 10.3, 6.1, 2.0 Hz, 1H, H-5'), 3.98 (dd, *J* = 9.7, 8.9 Hz, 1H, H-3'), 3.90 (ddd, *J* = 8.1, 3.7, 2.0 Hz, 1H, H-2), 3.81 (s, 1H, 2-OH), 3.70 – 3.60 (m, 3H, H-4, 4-OH, H-6'), 3.56 (dd, *J* = 9.7, 3.8 Hz, 1H, H-6'), 3.52 (dd, *J* = 10.2, 6.1 Hz, 1H, H-2'), 3.46 (dd, *J* = 10.1, 8.9 Hz, 1H, H-4'), 3.42 – 3.34 (m, 4H, H-1, H-3, H-6), 3.10 (d, *J* = 3.9 Hz, 1H, H-7), 2.24 (ddd, *J* = 9.4, 4.3, 4.1 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 144.1, 138.6, 138.0, 137.6, 137.4 ($C_{q\text{-}arom}$), 128.8, 128.8, 128.6, 128.6, 128.6, 128.4, 128.1, 128.0, 128.0, 127.9, 127.2 (CH_{arom}), 100.5 (C-1'), 88.2 (C-3), 86.8 (CPh_3), 82.4 (C-3'), 79.5 (C-2'), 78.0 (C-4'), 75.9, 75.3, 74.3, 73.7 (CH_2 Bn), 71.5 (C-5'), 71.0 (C-2), 69.3 (C-4), 68.6 (C-6'), 62.1 (C-6), 56.7 (C-1), 54.8 (C-7), 42.7 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{60}H_{60}NaO_{10}$ 963.4084; Found 963.4079.

3-*O*-(α-D-Glucopyranosyl)-1,7-*epi*-cyclophellitol (28).



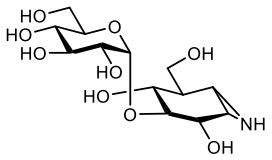
To liquid ammonia (3 mL) at -60 °C, sodium metal (51 mg, 2.2 mmol, 50 eq.) was added. This mixture was stirred for 30 minutes while maintaining a temperature of -60 °C. Subsequently, Compound **26** (42 mg, 44 µmol) was dissolved in THF (1.0 mL) followed by the addition *t*-BuOH (42 µL, 0.44 mmol, 10 eq.). This solution was added dropwise to the flask containing ammonia. The solution was stirred for 1 hour while maintaining a temperature of -60 °C. The reaction was quenched by addition of water (500 µL) and let to attain to room temperature. Upon concentration under reduced pressure, the residue was purified by size exclusion chromatography over HW-40 eluted with water to obtain the title compound as a colorless oil (11 mg, 31 µmol, 71%). NMR (500 MHz, MeOD, HH-COSY, HSQC, HMBC, NOESY): δ 4.99 (d, *J* = 3.9 Hz, 1H, H-1'), 3.93 – 3.79 (m, 4H, H-2, H-6, H-3', H-6'), 3.71 (dd, *J* = 10.9, 6.2 Hz, 1H, H-6), 3.69 – 3.60 (m, 2H, H-4', H-6'), 3.51 – 3.39 (m, 3H, H-3, H-4, H-2'), 3.32 – 3.28 (m, 2H, H-1, H-5'), 3.20 (d, *J* = 4.0 Hz, 1H, H-7), 1.98 (ddd, *J* = 9.6, 6.2, 3.4 Hz, 1H, H-5); ^{13}C NMR (126 MHz, MeOD, HSQC, HMBC): δ 102.7 (C-1'), 86.1 (C-3), 75.3 (C-4'), 74.1 (C-3'), 74.0 (C-2'), 71.8 (C-2), 71.5 (C-5'), 71.2 (C-4), 62.5 (C-6'), 61.8 (C-6), 58.5 (C-1), 55.4 (C-7), 46.0 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{22}NaO_{10}$ 361.1111; Found 361.1104.

3-*O*-(Perbenzyl-α-D-glucopyranosyl)-6-*O*-trityl-1,7-*epi*-cyclophellitol CF_3-Q-aziridine (27).



BAIB (81 mg, 0.25 mmol, 5.0 eq.) was dissolved in anhydrous DCM (1.5 mL, 0.17 M) and cooled to -80 °C. To this, a solution of 2-trifluoromethyl-3-aminoquinazolin-4-one (57 mg, 0.25 mmol, 5.0 eq.) in anhydrous DCM (3 mL, 0.086 M) was added dropwise over the course of 30 minutes. Afterwards, the solution was allowed to warm to -40 °C followed by the dropwise addition of a solution of compound **25** (47 mg, 50 µmol) in DCM (1.0 mL, 0.05 M) over the course of 15 minutes. The reaction was allowed to attain to room temperature and stirred for another 48 hours. Upon full conversion (R_f 0.6 (Et_2O:pentane, 1:1 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). 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 (44 mg, 38 µmol, 76%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, NOESY): δ 8.26 – 7.14 (m, 1H, CH_{arom}), 7.86 – 7.74 (m, 2H, CH_{arom}), 7.59 (dd, *J* = 8.2, 4.8 Hz, 1H, CH_{arom}), 7.50 – 7.09 (m, 35H, CH_{arom}), 4.95 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.89 (d, *J* = 10.9 Hz, 1H, CH*H* Bn), 4.85 – 4.79 (m, 3H, H-1', C*H*H Bn, C*H*H Bn), 4.68 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.58 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.51 – 4.44 (m, 2H, CH*H* Bn, CH*H* Bn), 4.32 (dd, *J* = 7.4, 3.7 Hz, 1H, H-1), 4.13 (ddd, *J* = 10.2, 4.2, 2.8 Hz, 1H, H-5'), 4.03 (dd, *J* = 9.3, 9.3 Hz, 1H, H-3'), 3.95 – 3.89 (m, 2H, H-2, 2-OH/4-OH), 3.88 – 3.83 (m, 2H, H-7, 2-OH/4-OH), 3.71 (dd, *J* = 10.0, 9.8 Hz, 1H, H-4), 3.66 – 3.62 (m, 2H, H-6'), 3.62 – 3.55 (m, 2H, H-2', H-4'), 3.52 (dd, *J* = 9.2, 4.7 Hz, 1H, H-6), 3.46 (dd, *J* = 10.0, 8.5 Hz, 1H, H-3), 3.36 (dd, *J* = 9.2, 3.3 Hz, 1H, H-6), 2.31 (dd, *J* = 9.4, 4.5 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 161.0 (C=O Bz), 144.1, 138.7, 138.2, 137.8, 137.5 ($C_{q\text{-}arom}$), 135.0, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.9, 127.8, 127.1, 126.7 (CH_{arom}), 123.2 ($C_{q\text{-}arom}$), 100.7 (C-1'), 87.6 (C-3), 86.8 (CPh_3), 82.4 (C-3'), 79.7 (C-2'), 78.0 (C-4'), 75.8, 75.2, 74.5, 73.6 (CH_2 Bn), 71.3 (C-5'), 70.1 (C-2), 69.9 (C-4), 68.5 (C-6'), 62.6 (C-6), 43.6 (C-1), 42.5 (C-5), 41.9 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{69}H_{64}F_3N_3NaO_{10}$ 1174.4441; Found 1174.4435.

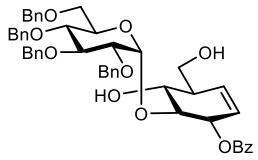
3-*O*-(α-D-Glucopyranosyl)-1,7-*epi*-cyclophellitol aziridine (29).



To liquid ammonia (3 mL) at -60 °C, sodium metal (52 mg, 2.2 mmol, 80 eq.) was added. This mixture was stirred for 30 minutes while maintaining a temperature of -60 °C. Subsequently, Compound **27** (32 mg, 28 µmol) was dissolved in THF (1.0 mL) followed by the addition *t*-BuOH (27 µL, 0.28 mmol, 10 eq.). This solution was added dropwise to the flask containing ammonia. The solution was stirred for 1 hour while maintaining a temperature of -60 °C. The reaction was quenched by addition of water (500 µL) and let to attain to room temperature. Upon concentration under reduced pressure, the residue was purified by size exclusion chromatography over HW-40 eluted with water to obtain the title compound as a colorless oil (8.0 mg, 24 µmol, 86%). NMR (500 MHz, D_2O, HH-COSY, HSQC, HMBC, NOESY): δ 4.99 (d, *J* = 3.9 Hz, 1H, H-1'), 3.88 (dd, *J* = 8.5, 3.7 Hz, 1H, H-2), 3.83 (ddd, *J* = 10.1, 5.0, 2.5 Hz, 1H, H-5'), 3.78 (dd, *J* = 11.1, 3.5 Hz, 1H, H-6), 3.74 (dd, *J* = 12.3, 2.5 Hz, 1H, H-

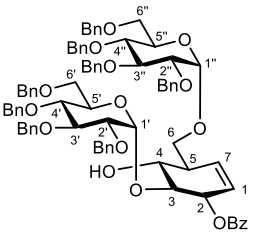
6'), 3.71– 3.62 (m, 2H, H-6, H-6'), 3.58 (dd, *J* = 9.3, 9.1 Hz, 1H, H-3), 3.41 (dd, *J* = 9.6, 3.9 Hz, 1H, H-2'), 3.35 (dd, *J* = 10.0, 9.7 Hz, 1H, H-4), 3.32 – 3.25 (m, 2H, H-3, H-4'), 2.50 (dd, *J* = 6.4, 3.7 Hz, 1H, H-1), 2.26 (dd, *J* = 6.4, 0.8 Hz, 1H, H-7), 1.78 (ddd, *J* = 10.0, 6.4, 3.7 Hz, 1H, H-5); ^{13}C NMR (126 MHz, D_2O, HSQC, HMBC): δ 102.1 (C-1'), 84.6 (C-3), 74.7 (C-3'), 72.9 (C-2'), 72.6 (C-5'), 70.8 (C-4), 70.0 (C-2/C-4), 70.0 (C-2/C-4), 61.9 (C-6), 60.8 (C-6'), 44.7 (C-5), 35.9 (C-1), 31.7 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{23}NNaO_9$ 360.1271; Found 360.1263.

3-*O*-(Perbenzyl-α-D-glucopyranosyl)-2-*O*-benzoyl-cyclophellitol alkene (30).



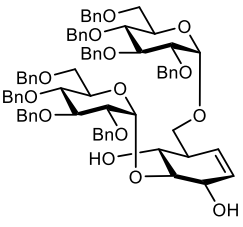
Compound **24a** (0.14 g, 0.12 mmol) was dissolved in anhydrous DCM (2.4 mL, 0.05 M) and cooled on ice. Subsequently, TES (38 µL, 0.24 mmol, 2.0 eq.) and TFA (27 µL, 0.24 mmol, 2.0 eq.) were added respectively. The solution was kept stirring for 1 hour while attaining a temperature of 0 °C. Upon full conversion (R_f 0.3 (Et_2O:pentane, 3:7 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (25 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The crude was dissolved in THF (1.2 mL, 0.05 M) after which a 1 M TBAF solution in THF (0.24 mL, 0.24 mmol, 4.0 eq.) was added. The reaction mixture was stirred for 1 hour at room 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. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (25 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). 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 (68 mg, 86 µmol, 72%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.15– 8.01 (m, 2H, CH_{arom}), 7.61 – 7.53 (m, 1H, CH_{arom}), 7.48 – 7.41 (m, 2H, CH_{arom}), 7.37 – 7.27 (m, 10H, CH_{arom}), 7.27 – 7.18 (m, 6H, CH_{arom}), 7.14 – 7.06 (m, 2H, CH_{arom}), 7.05 – 6.96 (m, 2H, CH_{arom}), 5.68 – 5.60 (m, 2H, H-2, H-7), 5.56 (ddd, *J* = 10.5, 2.0, 1.7 Hz, 1H, H-1), 5.04 (s, 1H, 4-OH), 4.96 (d, *J* = 3.7 Hz, 1H, H-1), 4.90 – 4.83 (m, 3H, C*H*H Bn, C*H*H Bn, C*H*H Bn), 4.75 – 4.67 (m, 2H, CH*H* Bn, CH*H* Bn), 4.35 (d, *J* = 10.7 Hz, 1H, CH*H* Bn), 4.22 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 3.97 (dd, *J* = 9.4, 6.6 Hz, 1H, H-3'), 3.91 – 3.71 (m, 5H, CH*H* Bn, H-3, H-4, H-6), 3.68 – 3.63 (m, 2H, H-4', H-5'), 3.58 (dd, *J* = 9.7, 3.7 Hz, 1H, H-2'), 3.34 (dd, *J* = 10.9, 1.5 Hz, 1H, H-6), 2.85 (d, *J* = 8.2 Hz, 1H, 6-OH), 2.68 (dd, *J* = 10.9, 1.4 Hz, 1H, H-6), 2.65 – 2.59 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 166.1 (C=O Bz), 138.6, 138.3, 137.8, 137.0 ($C_{q\text{-}arom}$), 133.3, 130.1, 128.9, 128.8 (C-1), 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.1, 127.8, 127.8, 127.8, 127.7 (CH_{arom}), 126.3 (C-7), 101.7 (C-1'), 86.6 (C-3), 82.4 (C-3'), 79.6 (C-2'), 77.5 (C-4'/C-5'), 75.7 (CH_2 Bn), 75.0 (CH_2 Bn), 74.7 (CH_2 Bn), 74.3 (C-4), 74.0 (C-2), 73.4 (CH_2 Bn), 71.3 (C-4'/C-5'), 67.8 (C-6'), 65.6 (C-6), 44.9 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{48}H_{50}NaO_{10}$ 809.3302; Found 809.3292.

3,6-Di-*O*-(perbenzyl-α-D-glucopyranosyl)-2-*O*-benzoyl-cyclophellitol alkene (32).



Acceptor **30** (89 mg, 0.11 mmol) and perbenzyl-D-glucopyranosyl N-phenyltrifluoroacetimidate donor **31** (0.20 g, 0.28 mmol, 2.5 eq.), synthesized according to literature precedence[32], were combined and co-evaporated twice with toluene. PPh_3O (0.50 g, 1.8 mmol, 16 eq.), activated 3Å molecular rods and anhydrous DCM (2.3 mL, 0.05 M) were added and kept under N_2 atmosphere. Subsequently, TMSI (40 µL, 0.28 mmol, 2.5 eq.) was added dropwise and the reaction mixture was stirred for 48 hours at room temperature. Upon full conversion (R_f 0.4 (Et_2O:pentane, 1:1 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40:60 Et_2O:pentane → 60:40 Et_2O:pentane) to obtain the title compound as a colorless oil (0.12 g, 89 µmol, 79%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC-GATED): δ 8.11 – 8.07 (m, 2H, CH_{arom}), 7.60 – 7.49 (m, 1H, CH_{arom}), 7.46 – 7.40 (m, 2H, CH_{arom}), 7.38 – 6.97 (m, 40H, CH_{arom}), 5.86 (ddd, *J* = 10.2, 2.0, 1.8 Hz, 1H, H-1), 5.67 (dddd, *J* = 7.8, 4.0, 1.6, 1.5 Hz, 1H, H-2), 5.58 (ddd, *J* = 10.2, 2.6, 2.5 Hz, 1H, H-7), 5.00 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.96 (d, *J* = 3.7 Hz, 1H, H-1'), 4.91 – 4.81 (m, 6H, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn, H-1''), 4.78 – 4.60 (m, 5H, C*H*H Bn, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn), 4.52 – 4.44 (m, 2H, C*H*H Bn, CH*H* Bn), 4.34 (d, *J* = 10.8 Hz, 1H, C*H*H Bn), 4.21 (d, *J* = 12.1 Hz, 1H, CH*H* Bn), 3.99 (m, 2H, H-3', H-3''), 3.86 – 3.72 (m, 7H, CH*H* Bn, H-3, H-5', H-5'', H-6'', 4-OH), 3.72 – 3.62 (m, 5H, H-4, H-6, H-4', H-4''), 3.59 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2'/H-2''), 3.55 (dd, *J* = 9.7, 3.6 Hz, 1H, H-2'/H-2''), 3.35 (dd, *J* = 10.8, 1.6 Hz, 1H, H-6'), 2.77 – 2.68 (m, 2H, H-5, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC, HMBC-GATED): δ 166.1 (C=O Bz), 139.0, 138.7, 138.4, 138.4, 138.3, 138.0, 137.8, 137.4 ($C_{q\text{-}arom}$), 133.2 (CH_{arom}), 130.3 ($C_{q\text{-}arom}$), 130.2 (C-1), 130.1, 128.7, 128.6, 128.5, 128.5, 128.5, 128.3, 128.3, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6 (CH_{arom}), 125.2 (C-7), 101.6 (C-1'), 97.4 (C-1''), 86.8 (C-3), 82.4, 82.1 (C-3', C-3''), 80.2, 79.4 (C-2', C-2''), 77.8, 77.4 (C-4', C-4''), 75.8, 75.7, 75.3, 74.9, 74.2 (CH_2 Bn), 74.2 (C-2), 73.6, 73.3, 73.1 (CH_2 Bn), 71.3 (C-4), 70.9, 70.4 (C-5', C-5''), 68.5 (C-6, C-6''), 67.3 (C-6'), 43.5 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{82}H_{84}NaO_{15}$ 1331.5708; Found 1331.5702.

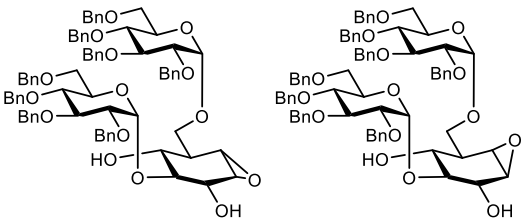
3,6-Di-*O*-(perbenzyl-α-D-glucopyranosyl)-cyclophellitol alkene (33).



Compound **32** (94 mg, 72 µmol) was dissolved in a 1:1 mixture of DCM and MeOH (1.5 mL, 0.05 M) followed by the addition of NaOMe (94 mg, 1.4 mmol, 20 eq.). The reaction was stirred overnight at room temperature. Upon full conversion (R_f 0.2 (Et_2O:pentane, 7:3 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). 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 (62 mg, 51

µmol, 72%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.41 – 7.19 (m, 36H, CH_{arom}), 7.18 – 7.10 (m, 4H, CH_{arom}), 5.73 (ddd, *J* = 10.2, 2.2, 2.0 Hz, 1H, H-1), 5.58 (ddd, *J* = 10.2, 2.5, 2.2 Hz, 1H, H-7), 4.99 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.93 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.87 – 4.77 (m, 7H, H-1', H-1'', C*H*H Bn, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn), 4.73 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.69 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.67 – 4.60 (m, 2H, C*H*H Bn, CH*H* Bn), 4.55 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.52 – 4.44 (m, 4H, CH*H* Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.16 (dd, *J* = 6.6, 3.6 Hz, 1H, H-2), 4.05 (ddd, *J* = 10.1, 6.6, 2.0 Hz, 1H, H-5'/H-5''), 4.03 – 3.95 (m, 2H, H-3',H-3''), 3.85 (s, 1H, 4-OH), 3.79 – 3.72 (m, 2H, H-5'/H-5'', H-6/H-6'/H-6''), 3.72 – 3.60 (m, 7H, H-4, H-4'/H-4'', H-6/H-6'/H-6'', H-6/H-6'/H-6'', H-6/H-6'/H-6'', H-6/H-6'/H-6''), 3.60 – 3.56 (m, 2H, H-2', H-2''), 3.48 (dd, *J* = 10.1, 6.7 Hz, 1H, H-6/H-6'/H-6''), 3.42 (dd, *J* = 10.2, 9.0 Hz, 1H, H-4'/H-4''), 3.37 (dd, *J* = 9.9, 7.4 Hz, 1H, H-3), 2.71 – 2.59 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 139.1, 138.6, 138.5, 138.3, 138.1, 138.0, 137.6, 137.6 ($C_{q\text{-}arom}$), 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7 (CH_{arom}), 100.3, 97.2 (C-1', C-1''), 91.5 (C-3), 82.4, 82.1 (C-3', C-3''), 80.3, 79.6 (C-2', C-2''), 78.1, 77.4 (C-4', C-4''), 75.9, 75.8, 75.4, 75.2, 74.1, 73.6, 73.6, 73.0 (CH_2 Bn), 71.4 (C-5'/C-5''), 71.1 (C-2), 70.4 (C-5'/C-5''), 69.8 (C-4), 68.7, 68.6, 68.5 (C-6, C-6', C-6''), 43.5 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{75}H_{80}NaO_{14}$ 1227.5446; Found 1227.5440.

3,6-Di-*O*-(perbenzyl-α-D-glucopyranosyl)-cyclophellitol (34a) and 3,6-di-*O*-(perbenzyl-α-D-glucopyranosyl)-1,7-*epi*-cyclophellitol (34b).

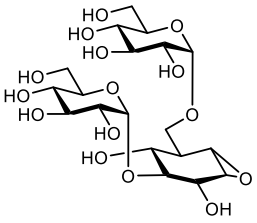


Compound **33** (20 mg, 16 µmol) was dissolved in anhydrous DCM (1.6 mL, 0.01 M) followed by the addition of $NaHCO_3$ (6.7 mg, 80 µmol, 5.0 eq.). The solution was cooled on ice and *m*-CPBA (8.4 mg, 49 µmol, 3.0 eq.) was added. The reaction was stirred for 48 hours at 4 °C. Upon full conversion (R_f 0.2 and 0.3 for **34a** and **34b** respectively (Et_2O:pentane, 7:3 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were subsequently dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (50:50 Et_2O:pentane → 80:20 Et_2O:pentane) to obtain the title compounds as colorless oils (7.0 mg, 5.7 µmol, 35% for **34a** and 6.8 mg, 5.6 µmol, 34% for **34b**). Analytical data for **34a**: NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, NOESY): δ 7.39 – 7.23 (m, 35H, CH_{arom}), 7.15 – 7.10 (m, 5H, CH_{arom}), 4.98 (d, *J* = 10.8 Hz, 1H, C*H*H Bn), 4.90 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.85 – 4.77 (m, 7H, H-1'/H-1'', C*H*H Bn, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.72 (d, *J* = 3.9 Hz, 1H, H-1'/H-1''), 4.70 – 4.62 (m, 3H, C*H*H Bn, C*H*H Bn, CH*H* Bn), 4.57 – 4.42 (m, 5H, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.03 – 3.88 (m, 4H, 2-OH/4-OH, H-3', H-3'', H-5'/H-5''), 3.88 – 3.74 (m, 5H, H-2, H-6, H-5'/H-5'', H-6'/H-6''), 3.72 – 3.58 (m, 5H, 2-OH/4-OH, H-2'/H-2'', H-4'/H-4'', H-6', H-6''), 3.55 (dd, *J* = 9.7, 3.8 Hz, 1H, H-2'/H-2''), 3.49 – 3.42 (m, 2H, H-7, H-6'/H-6''), 3.38 (dd, *J* = 10.2, 8.9 Hz, 1H, H-4'/H-4''), 3.31 (dd, *J* = 9.8, 9.6 Hz, 1H, H-4), 3.15 – 3.10 (m, 2H, H-1, H-3), 2.44 – 2.35 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 139.1, 138.5, 138.4, 138.4,

138.1, 137.8, 137.5, 137.4 ($C_{q\text{-}arom}$), 128.8, 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (CH_{arom}), 100.5, 97.3 (C-1', C-1''), 91.4 (C-3), 82.3, 82.3 (C-3', C-3''), 80.2, 79.5 (C-2', C-2''), 78.2, 77.8 (C-4', C-4''), 75.9, 75.8, 75.3, 75.3, 74.3, 73.7, 73.6, 73.4 (CH_2 Bn), 71.5, 70.3 (C-5', C-5''), 70.2 (C-2), 68.7, 68.5 (C-6', C-6''), 67.0 (C-6), 66.5 (C-4), 56.1 (C-1), 54.7 (C-7), 41.6 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{75}H_{80}NaO_{15}$ 1243.5395; Found 1243.5389.

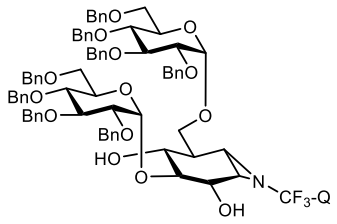
Analytical data for **34b**: NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, NOESY): δ 7.39 – 7.20 (m, 36H, CH_{arom}), 7.18 – 7.10 (m, 4H, CH_{arom}), 4.99 (d, *J* = 11.0 Hz, 1H, C*H*H Bn), 4.91 (d, *J* = 10.9 Hz, 1H, C*H*H Bn), 4.86 – 4.72 (m, 8H, H-1', H-1'', C*H*H Bn, C*H*H Bn, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn), 4.68 – 4.60 (m, 3H, C*H*H Bn, CH*H* Bn, CH*H* Bn), 4.55 (d, *J* = 12.4 Hz, 1H, CH*H* Bn), 4.51 – 4.44 (m, 4H, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.05 – 3.88 (m, 5H, 2-OH/4-OH, H-3', H-3'', H-5'/H-5'', H-6), 3.84 (d, *J* = 7.8 Hz, 1H, H-2), 3.78 – 3.72 (m, 2H, H-5'/H-5'', H-6'/H-6''), 3.70 – 3.58 (m, 6H, H-6, H-2'/H-2'', H-4'/H-4'', H-6'/H-6'', H-6'/H-6''), 3.55 (dd, *J* = 9.7, 3.8 Hz, 1H, H-2'/H-2''), 3.52 – 3.41 (m, 3H, H-4, H-4'/H-4'', H-6'/H-6''), 3.34 (dd, *J* = 9.9, 8.0 Hz, 1H, H-3), 3.29 (dd, *J* = 3.9, 2.0 Hz, 1H, H-1), 3.22 (d, *J* = 3.9 Hz, 1H, H-7), 2.31 (ddd, *J* = 9.6, 5.9, 3.3 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 139.0, 138.6, 138.5, 138.2, 138.1, 138.0, 137.6, 137.4 ($C_{q\text{-}arom}$), 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 127.7, 125.7 (CH_{arom}), 100.6, 97.6 (C-1', C-1''), 88.2 (C-3), 82.4, 82.0 (C-3', C-3''), 80.4, 79.4 (C-2', C-2''), 78.0, 77.4 (C-4', C-4''), 76.0, 75.8, 75.5, 75.2, 74.2, 73.7, 73.6, 73.2 (CH_2 Bn), 71.5 (C-5'/C-5''), 70.9 (C-2), 70.6 (C-5'/C-5''), 69.0 (C-4), 68.6, 68.5 (C-6', C-6''), 67.4 (C-6), 56.7 (C-1), 54.4 (C-7), 42.2 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{75}H_{80}NaO_{15}$ 1243.5395; Found 1243.5389.

3,6-Di-*O*-(α-D-glucopyranosyl)-1,7-*epi*-cyclophellitol (36).



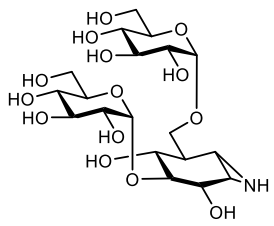
To liquid ammonia (3 mL) at -60 °C, sodium metal (20 mg, 0.88 mmol, 80 eq.) was added. This mixture was stirred for 30 minutes while maintaining a temperature of -60 °C. Subsequently, Compound **34a** (13 mg, 11 µmol) was dissolved in THF (1.0 mL) followed by the addition *t*-BuOH (10 µL, 0.11 mmol, 10 eq.). This solution was added dropwise to the flask containing ammonia. The solution was stirred for 1 hour while maintaining a temperature of -60 °C. The reaction was quenched by addition of water (500 µL) and let to attain to room temperature. Upon concentration under reduced pressure, the residue was purified by size exclusion chromatography over HW-40 eluted with water to obtain the title compound as a colorless oil (5.0 mg, 10 µmol, 91%). NMR (850 MHz, D_2O HH-COSY, HSQC, NOESY): δ 5.15 (d, *J* = 3.9 Hz, 1H, H-1'/H-1''), 4.93 (d, *J* = 3.8 Hz, 1H, H-1'/H-1''), 4.02 (dd, *J* = 8.5, 2.1 Hz, 1H, H-2), 3.97 – 3.93 (m, 2H, H-5'/H-5'', H-6), 3.81 (dd, *J* = 12.4, 2.3 Hz, 1H, H-6''), 3.77 – 3.76 (m, 2H, H-6'), 3.74 – 3.66 (m, 4H, H-6, H-3', H-3'', H-6''), 3.63 – 3.58 (m, 2H, H-5'/H-5'', H-4), 3.54 (m, 2H, H-2', H-2''), 3.47 (dd, *J* = 10.1, 8.5 Hz, 1H, H-3), 3.44 (dd, *J* = 4.1, 2.1 Hz, 1H, H-1), 3.42 (dd, *J* = 9.7, 9.5 Hz, 1H, H-4'/H-4''), 3.40 – 3.36 (m, 2H, H-7, H-4'/H-4''), 2.20 (ddd, *J* = 9.7, 5.9, 3.2 Hz, 1H, H-5); ^{13}C NMR (214 MHz, D_2O, HSQC): δ 100.9, 99.1 (C-1', C-1''), 82.6 (C-3), 73.9 (C-3', C-3''), 72.9, 72.7 (C-5', C-5''), 72.6, 72.2 (C-2', C-2''), 70.9 (C-2), 70.7 (C-4), 70.4, 70.1 (C-4', C-4''), 67.0 (C-6), 61.4, 61.0 (C-6', C-6''), 58.9 (C-1), 56.3 (C-7), 43.0 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{32}NaO_{15}$ 523.1639; Found 523.1633.

3,6-Di-*O*-(perbenzyl-α-D-glucopyranosyl)-1,7-*epi*-cyclophellitol CF_3-Q-aziridine (35).



BAIB (28 mg, 86 µmol, 5.0 eq.) was dissolved in anhydrous DCM (0.5 mL, 0.17 M) and cooled to -80 °C. To this, a solution of 2-trifluoromethyl-3-aminoquinazolin-4-one (20 mg, 86 µmol, 5.0 eq.) in anhydrous DCM (1 mL, 0.086 M) was added dropwise over the course of 30 minutes. Afterwards, the solution was allowed to warm to -40 °C followed by the addition of a solution of compound **33** (21 mg, 17 µmol) in DCM (0.5 mL, 0.034 M) over the course of 15 minutes. The reaction was allowed to attain to room temperature and stirred for another 48 hours. Upon full conversion (R_f 0.7 (Et_2O:pentane, 7:3 v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5.0 mL) and sat. aq. $Na_2S_2O_3$ (5.0 mL) followed by diluting the reaction mixture with water (50 mL) and Et_2O (25 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (25 mL). 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 → 50:50 Et_2O:pentane) to obtain the title compound as a colorless oil (15 mg, 11 µmol, 62%). NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, NOESY): δ 8.24 – 8.09 (m, 1H, CH Q), 7.82 – 7.79 (m, 2H, CH Q), 7.58 – 7.53 (m, 1H, CH Q), 7.36 – 7.19 (m, 32H, CH_{arom}), 7.18 – 7.03 (m, 8H, CH_{arom}), 4.94 (d, *J* = 11.0 Hz, 1H, C*H*H Bn), 4.88 – 4.74 (m, 8H, H-1', H-1'', C*H*H Bn, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.73 – 4.59 (m, 4H, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn), 4.57 (d, *J* = 12.3 Hz, 1H, C*H*H Bn), 4.50 – 4.43 (m, 4H, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 4.13 – 4.07 (m, 2H, H-1, H-5'/H-5''), 4.06 – 4.01 (m, 3H, H-6, H-3'/H-3''), 4.00 (s, 1H, 4-OH), 3.95 – 3.89 (m, 2H, H-7, H-3'/H-3''), 3.89 – 3.82 (m, 2H, H-2, 2-OH), 3.77 (m, 2H, H-5'/H-5'', H-6'/H-6''), 3.71 – 3.38 (m, 9H, H-3, H-4, H-2', H-2'', H-4', H-4'', H-6'/H-6'', H-6'/H-6'', H-6'/H-6''), 2.37 (ddd, *J* = 9.4, 3.8, 3.6 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC, HMBC): δ 160.9 (C=O Q), 144.1, 139.0, 138.8, 138.5, 138.3, 138.3, 138.1, 137.8, 137.5, 135.7, 135.0 ($C_{q\text{-}arom}$), 129.5, 129.4, 128.9, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.1, 126.7, 125.7, 123.2 (CH_{arom}), 100.8, 97.9 (C-1', C-1''), 87.7 (C-3), 82.5, 82.0 (C-3', C-3''), 80.3, 79.5 (C-2', C-2''), 78.0, 77.4 (C-4', C-4''), 75.9, 75.7, 75.4, 75.1, 74.4, 73.6, 72.9 (CH_2 Bn), 71.3, 70.5 (C-5', C-5''), 69.9 (C-2), 69.5 (C-4), 68.5 (C-6', C-6''), 67.9 (C-6), 43.9 (C-1), 42.2 (C-5), 42.0 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{84}H_{84}F_3N_3NaO_{15}$ 1454.5752; Found 1454.5747.

3,6-Di-*O*-(α-D-glucopyranosyl)-1,7-*epi*-cyclophellitol aziridine (37).



To liquid ammonia (3 mL) at -60 °C sodium metal (20 mg, 0.85 mmol, 80 eq.) was added. This mixture was stirred for 30 minutes while maintaining a temperature of -60 °C. Subsequently, Compound **35** (15 mg, 11 µmol) was dissolved in THF (1.0 mL) followed by the addition *t*-BuOH (10 µL, 0.11 mmol, 10 eq.). This solution was added dropwise to the flask containing ammonia. The solution was stirred for 1 hour while maintaining a temperature of -60 °C. The reaction was quenched by addition of water (500 µL) and let to attain to room temperature. Upon concentration under reduced pressure, the residue was purified by size exclusion chromatography over HW-40 eluted with water to obtain the title compound as a

colorless oil (4.8 mg, 9.6 µmol, 87%). ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC, HMBC, NOESY): δ 5.14 (d, *J* = 4.0 Hz, 1H, H-1'), 4.94 (d, *J* = 3.7 Hz, 1H, H-1''), 3.98 – 3.94 (m, 2H, H-2, H-5'/H-5''), 3.92 – 3.85 (m, 1H, H-6), 3.84 – 3.67 (m, 7H, H-3', H-3'', H-6, H-6', H-6''), 3.66 – 3.62 (m, 1H, H-5'/H-5''), 3.55 (dd, *J* = 3.8, 1.2 Hz, 1H, H-2'/H-2''), 3.54 – 3.48 (m, 2H, H-4, H-2'/H-2''), 3.44 – 3.35 (m, 3H, H-3, H-4', H-4''), 2.57 (dd, *J* = 6.4, 3.7 Hz, 1H, H-1), 2.41 (d, *J* = 6.4 Hz, 1H, H-7), 2.03 (ddd, *J* = 10.2, 6.7, 3.4 Hz, 1H, H-5); ^{13}C NMR (126 MHz, D_2O, HSQC, HMBC): δ 100.0 (C-1'), 98.2 (C-1''), 82.8 (C-3), 73.1, 73.0 (C-3', C-3''), 72.0, 72.0 (C-5', C-5''), 71.8, 71.4 (C-2', C-2''), 70.7 (C-4), 70.2 (C-2), 69.6, 69.3 (C-4', C-4''), 67.6 (C-6), 60.5, 60.3 (C-6', C-6''), 42.5 (C-5), 35.9 (C-1), 31.9 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{34}NNaO_{14}$ 500.1979; Found 500.1975.

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