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

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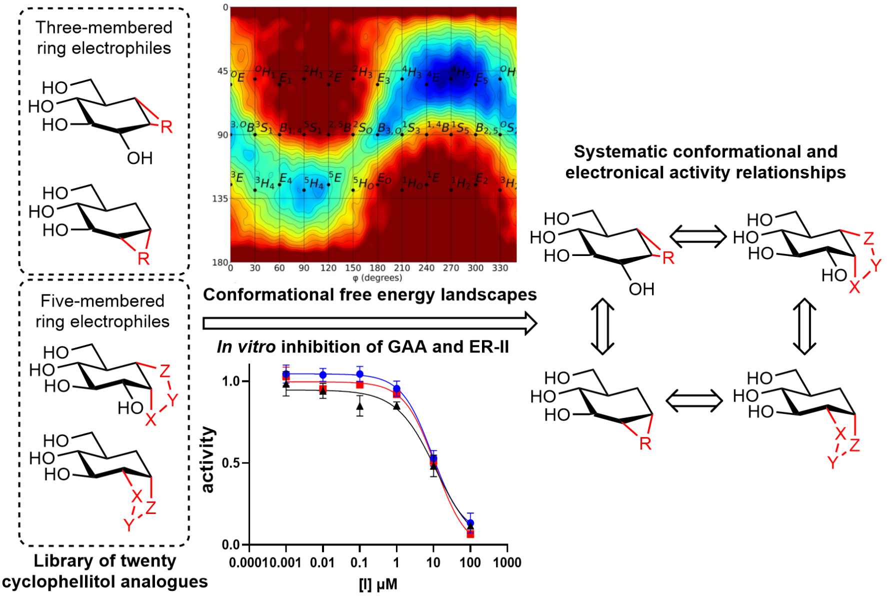
Chapter 3

Conformational and electronic differences of 1,2- and 1,7-cyclophellitols and their impact on α-glucosidase inhibition



ABSTRACT Twenty configurational and functional cyclophellitol analogues, featuring a systematic array of electrophiles were synthesized and evaluated as putative retaining α-glucosidase inhibitors. The inhibitory properties of the focused library of compounds were determined on human α-glucosidases after which the conformational free energy landscapes of the most active compounds were mapped. Our results add to the growing list of competitive and covalent α-glucosidase inhibitors and may help in the design of new therapeutics targeting these enzymes.

Introduction

Carbohydrates are found abundantly in nature and are essential in numerous biological processes.[1–4] The huge structural diversity of carbohydrates, oligosaccharides and glycoconjugates (glycoproteins, glycolipids) is reflected in the large variety of hydrolytic enzymes that have evolved and that are responsible for their processing and degradation. This large family of glycoside hydrolases is categorized in over 170 subfamilies, based on their primary sequence, tertiary structure and function.[5] Understanding their mode of action and reaction itineraries is an important stepping stone in the rational design of compounds that can selectively and efficiently inhibit specific glycoside hydrolases.

Retaining glycoside hydrolases, which comprise a large number of the known glycosidases and that encompass the human retaining α-glucosidases subject of the here-presented studies, employ a Koshland double displacement mechanism (Figure 1A).[6] Two carboxylic acid residues residing in the enzyme active site are positioned in such a way that one residue can act as a nucleophile and the other as a catalytic acid/base. Upon enzyme active site binding of the substrate, a Michaelis complex is formed with the substrate adopting a $^4C_1$-conformation. In this way, the leaving group is positioned in a (pseudo) axial fashion, allowing protonation by the catalytic acid-base and subsequent nucleophilic displacement of the aglycon by the nucleophilic acid residue. This process proceeds through a glucosyl $^4H_3$ oxocarbenium ion-like transition state and results in the formation of a covalent intermediate, with the bound glucose adopting a $^1S_3$-conformation. Next and following expulsion of the aglycon, water enters the active site. Following a reversed conformational itinerary ($^1S_3$-$^4H_3$-$^4C_1$), α-glucose is released and the enzyme returned to its resting phase ready for another catalytic cycle. [7–10]

In the past decades, a vast array of α- and β-retaining glycosidase inhibitors have been identified, many of which are based on the natural product, cyclophellitol (**1**). Cyclophellitol is a potent inhibitor of retaining β-glucosidases found in the *Phellinus sp*. Mushroom.[11] Cyclophellitol is the carbocyclic analogue of the natural retaining β-glucosidase substrates (β-glucopyranosides), bearing an epoxide bridging the C1 and C7 position.[12,13] This epoxide effectively constrains the cyclohexane into a $^4H_3$ conformation thereby mimicking the transition state (TS) during hydrolysis of β-glucopyranoses by retaining β-glucosidases. Not long after the discovery of cyclophellitol and fueled by its unique mode of action, the 1,7-epimer of cyclophellitol was constructed and shown to be a mechanism-based inhibitor of retaining α-glucosidases.[14] As soon as 1,7-*epi*-cyclophellitol (**2**) enters the active site of a retaining α-glucosidase, the nucleophilic carboxylate opens the epoxide in a trans diaxial fashion forming an irreversible, covalent ester linkage with the inhibitor, thereby incapacitating the enzyme (Figure 1B). This *modus operandi* has been well-appreciated in the design of activity-based protein profiling (ABPP) as tools in chemical glycobiology.[15–19]

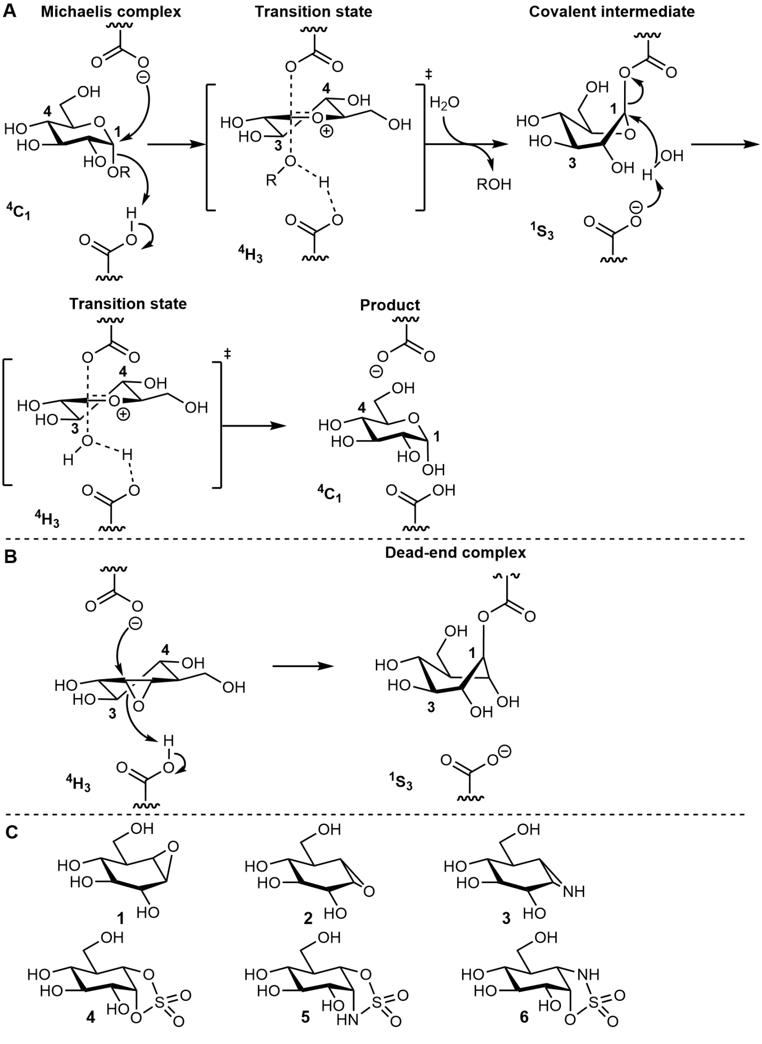


Figure 1. (A) Mechanistic itinerary of retaining α-glucosidases, (B) mechanism of inhibition by 1,7-*epi*-cyclophellitol **2** and (C) a selection of established covalent and non-covalent inhibitors of retaining β-glucosidases (**1**) and α-glucosidases (**2** – **6**).

Previously, the 1,7-epimer of cyclophellitol (**2**) and its nitrogen congener (**3**) were shown to be effective irreversible inhibitors and probes with micromolar to nanomolar affinities for human acid α-glucosidase (GAA) and endoplasmic reticulum glucosidase II (ER-II, Figure 1C).[18,20] As well, it was found that replacing the epoxide by a cyclic sulfate (as in **4**) gave an inhibitor with excellent potency and selectivity for α-glucosidases (1,7-

epi-cyclophellitol has retaining β-glucosidases as off-target).[21] Conformationally, these inhibitors do not exhibit $^4H_3$ character since the ring is not distorted by a strained three-membered ring. Rather, a $^4C_1$ conformation is adopted mimicking the structure of the α-glucosyl substrate in the Michaelis complex instead. As a follow up study, the corresponding cyclic sulfamidates (**5** and **6**) were revealed to be, due to their reduced electrophilicity, competitive retaining α-glucosidase inhibitors.[22]. Due to this reversible binding mode, **6** could be further developed into an enzyme stabilizer and thereby as pharmacological chaperone for the possible treatment of Pompe disease, in which the lysosomal α-glucosidase GAA is genetically impaired.[23–25] These results invite for a more in-depth study of modified cyclophellitol analogues as mechanism-based inhibitors. Here, the synthesis and inhibitory potential of α-1,2-cyclophellitol (**12** – **21**, Figure 2) in comparison with α-1,7-*epi*-cyclophellitols (**2** – **11**) is described. The inhibitory potencies and mode of action of the focused library of cyclophellitols on GAA and ER-II was studied in comparison to their parent α-1,7-*epi*-cyclophellitol. Although no improved inhibitors were found, low micromolar affinities were observed for some.

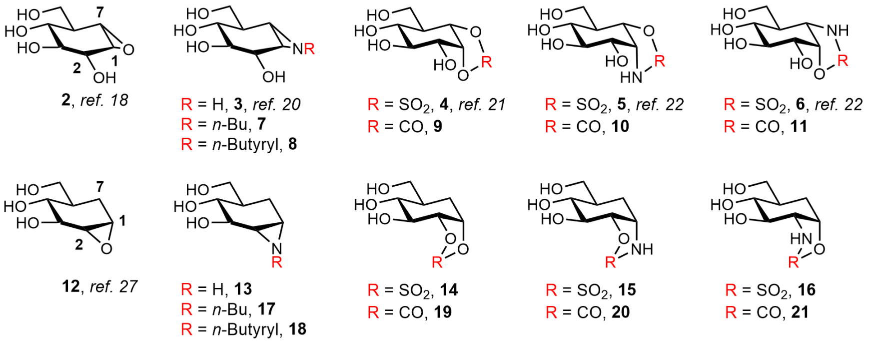


Figure 2. Twenty cyclophellitol analogues studied in this chapter for their inhibitory potencies against human retaining α-glucosidases.

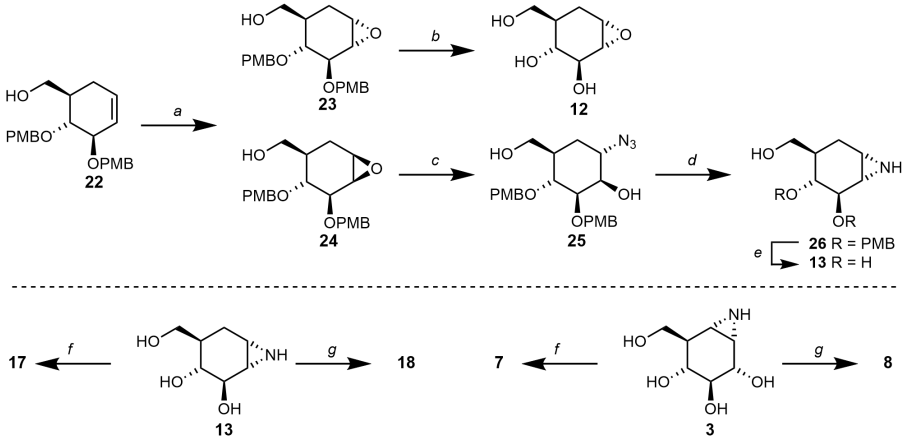
In all, the work presented here comprises expansion of the cyclophellitol scaffold in the design of both covalent and competitive retaining glycosidase inhibitors, including chemistries that can be readily adapted to differently configured carbohydrate mimetics and that would target glycosidases other than the α-glucosidase ones studied here.

Results and discussion

Compound synthesis. Compound **22** (Scheme 1), the key intermediate from which all 1,2-cyclophellitols were derived, was synthesized in eight steps according to procedures of Crotti and co-workers (See experimental, Scheme S1).[26] Epoxidation of the double bond in **22** under the *aegis* of *m*-CPBA yielded a separable mixture of epoxides **23** and **24** in 53% and 26% yield, respectively. Reductive deprotection (Pd/C, H_2) of α-epoxide

23 yielded **12** (83%) as the first target compound, of which all spectroscopic data were in full agreement with those reported in literature.[27] Following established procedures[28], opening of the β-epoxide with sodium azide under elevated temperatures yielded **25** (60%) which was subsequently treated with triphenylphosphine to undergo an intramolecular Staudinger cyclisation to yield α-aziridine **26** as the single regioisomer (43%). Removal of the 4-methoxybenzyl protecting groups in **26** was accomplished using Birch conditions (Na, NH_3) yielding target compound **13** (92%). Treatment of the α-aziridine with either butyl iodide or butyryl chloride yielded the butylated aziridine **17** and butyrylated aziridine **18** in 84% and 50% respectively.

Scheme 1. Synthesis of compounds **7**, **8**, **12**, **13**, **17** and **18**[a]

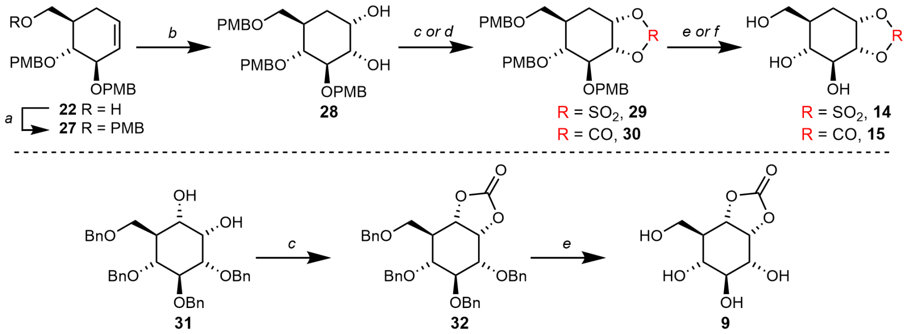


[a]Reagents and conditions: *a)* *m*-CPBA, DCM, 18 h, rt, 53% (**23**), 26% (**24**); *b)* Pd/C, H_2, MeOH, 1 h, rt (83%); *c)* NaN_3, DMF, 18 h, 130 °C (60%); *d)* TPP, CH_3CN, 18 h, 60 °C (43%); *e)* Na, NH_3, 1 h, -60 °C (92%); *f)* butyl iodide, K_2CO_3, DMF, 18 h, 80 °C, 84% (**17**), 24% (**7**); *g)* butyryl chloride, Et_3N, MeOH, 30 min, 0 °C, 50% (**18**), 64% (**8**).

The butylated and butyrylated 1,7-α-aziridine (**7** and **8**) were obtained *via* identical conditions starting from 1,7-α-aziridine **3**, which was in turn synthesized according to procedures optimized as published previously.[20,29]

Cyclic sulfate **14** and carbonate **15** were constructed starting with protection of the primary hydroxyl in **22** as the 4-methoxybenzyl ether under Williamson etherification conditions (NaH, PMBCl) to yield compound **27** in 85% (Scheme 2). Subsequent dihydroxylation of the alkene ($RuCl_3$, $NaIO_4$) yielded solely α-*cis*-diol **28** (85%) which was either sulfurylated ($SOCl_2$, Et_3N, *then* $RuCl_3$, $NaIO_4$) or carbonylated (triphosgene, Et_3N) to yield cyclic sulfate **29** (46%) and cyclic carbonate **30** (86%) respectively. Global deprotection proceeded smoothly *via* hydrogenation yielding the final compounds **14** and **15** in 83% and 68% respectively. In addition, the 1,7-α-carbonate **9** was obtained *via* identical conditions starting from 1,7-α-*cis*-diol **31**, which was in turn synthesized according to procedures published previously.[21]

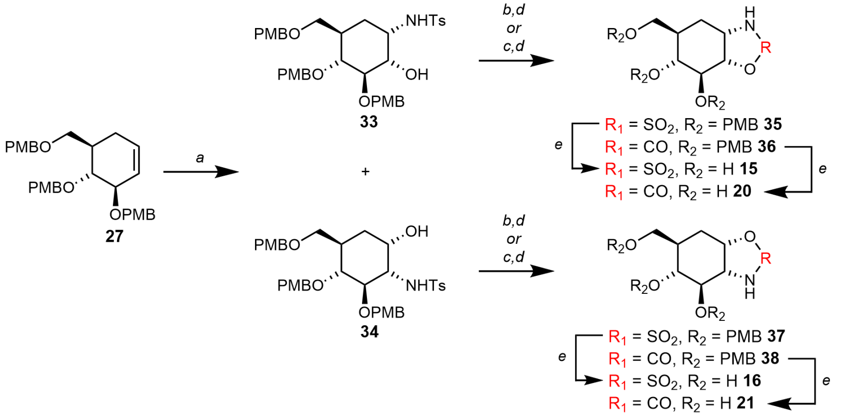
Scheme 2. Synthesis of **9**, **14** and **15**[a]



[a] Reagents and conditions: *a)* PMBCl, NaH, DMF, 16 h, rt (85%); *b)* $RuCl_3$, $NaIO_4$, 1:4:4 H_2O:CH_3CN:EtOAc, 1 h, 0 °C (85%); *c)* triphosgene, pyridine, DCM, 1.5 h, rt, 86% (**29**), 90% (**32**); *d)* (i) $SOCl_2$, Et_3N, DCM, 1 h, rt; (ii) $RuCl_3$, $NaIO_4$, 1:1 H_2O, CH_3CN, 15 min, 0 °C, (46%); *e)* $Pd(OH)_2/C$, H_2, MeOH, 18 h, rt, 68% (**15**), quant. (**9**); *f)* Pd/C, H_2, MeOH, 18 h, rt, 83% (**14**).

Cyclic sulfamidates **15** and **16** and carbamates **20** and **21** were constructed *via* a stereoselective Sharpless aminohydroxylation on alkene **27** ($K_2[OsO_2(OH)_4]$, chloramine-T, TEBACl) to give a separable, regioisomeric mixture of α-*cis*-amino alcohols **33** and **34** in 54% and 31% respectively (Scheme 3). Both α-*cis*-amino alcohols could be transformed into their corresponding cyclic sulfamidates by treatment with sulfuryl chloride and Et_3N at low temperatures (-78 °C) in quantitative yields. Subsequent removal of the *N*-tosyl functionality under reductive conditions (Na, naphthalene) gave rise to cyclic sulfamidates **35** and **38** in 75% and 85% yield, respectively. Alternatively, treatment of the individual amino alcohols **33** and **34** with triphosgene and pyridine followed by subsequent reductive detosylation (Na, naphthalene) yielded cyclic carbamates **36** and **38** (71% and 79% respectively, yield over two steps).

Scheme 3. Synthesis of cyclic sulfamidates **15** and **16** and carbamates **20** and **21**[a]

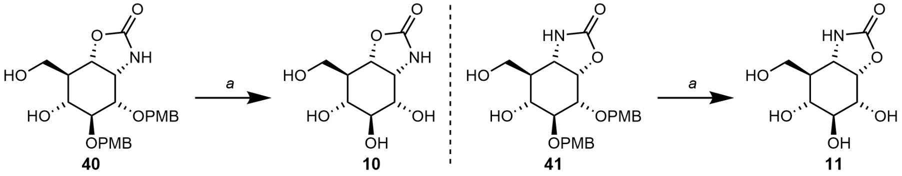


[a]Reagents and conditions: *a)* Chloramine-T, TEBACl, $K_2[OsO_2(OH)_4]$, 1:1 $CHCl_3$:H_2O, 18 h, 60 °C, 54% (**33**), 31% (**34**); *b)* SO_2Cl_2, Et_3N, DCM, 2 h, -78 °C, quant. (**S4**), quant. (**S5**); *c)* triphosgene, pyridine, DCM, 3 h, rt; *d)* naphthalene, Na, THF, 30 min, -78 °C, 75% (**35**), 71% (**36**), 85% (**37**), 79% (**38**); *e)* TFA, TES, DCM, 1 h, 0 °C, 94% (**15**), 67% (**20**), 81% (**16**), 32% (**21**).

Global deprotection with TFA and triethylsilane as cation scavenger afforded target sulfamidates **15** and **16** and carbamates **20** and **21** in 94%, 81%, 67% and 32% respectively.

Cyclic carbamates **10** and **11** were constructed *via* global deprotection of intermediates **40** and **41**. The synthesis of **40** and **41**, prepared *via* modified literature procedures,[29,30] is part of the research described in chapter 7. Deprotection proceeded smoothly by treating compounds **40** and **41** with TFA and triethylsilane (Scheme 4). This afforded the target structures **10** and **11** in 74% and 86% yield respectively.

Scheme 4. Synthesis of cyclic carbamates **10** and **11**[a]



[a]Reagents and conditions: *a)* TFA, TES, DCM, 1 h, 0 °C, 74% (**10**), 86% (**11**).

***In vitro* inhibition of human acid α-glucosidase and ER α-glucosidase II**. With inhibitors **2** – **21** in hand, attention was turned to evaluating their inhibitory potencies as inhibitors against human acid α-glucosidase (GAA) and ER α-glucosidase II (ER-II, Table 1). Apparent IC_{50} values were determined by measuring hydrolysis of the fluorogenic substrate, 4-methylulbelliferyl-α-D-glucose, where release of fluorescent product (4-methylumbelliferonate) is determined in terms of relative absorption (see SI).

Epoxide **12** proved to be a micromolar inhibitor of GAA (IC_{50} = 47 µM) making it slightly less potent than its 1,7-counterpart **2** (IC_{50} = 24 µM). In contrast, superior inhibitory potency was observed for **12** (IC_{50} = 13 µM) when screened against ER-II.[21] Aziridine **13** showed to be inactive on GAA, while inhibiting ER-II in the micromolar range (IC_{50} = 80 µM), whilst its 1,7-counterpart **3** tested to be a sub-micromolar inhibitor of GAA (IC_{50} = 0.37 µM) and ER-II (IC_{50} = 0.98 µM).[21] *n*-Butyl- and *n*-butyryl 1,2-aziridines **17** and **18** proved inactive as inhibitors of GAA and ER-II. Their 1,7-analogues, compounds **7** and **8**, however, yielded micromolar inhibitors. Slightly reduced inhibitory potency was observed for compound **7** and **8** (IC_{50} = 1.7 µM and 1.0 µM respectively) in comparison to unfunctionalized aziridine **3**. Turning to ER-II, compound **7** was shown to be a 3-fold more potent inhibitor (IC_{50} = 0.27 µM) whilst compound **8** showed a 3-fold reduction in inhibitory potency (IC_{50} = 4.1 µM) compared to aziridine **3**.

Table 1. Apparent IC_{50} values for *in vitro* inhibition of GAA and ER-II[a]

Compound	GAA IC_{50} (µM)	ER-II IC_{50} (µM)	Compound	GAA IC_{50} (µM)	ER-II IC_{50} (µM)
2	24[b]	>100[b]	**12**	47	13
3	0.37[b]	0.98[b]	**13**	>100	80
4	0.051[b]	0.035[b]	**14**	2.5	48
5	3.4[c]	>100[c]	**15**	>100	>100
6	40[c]	1.2[c]	**16**	>100	>100
7	1.7	0.27	**17**	>100	>100
8	1.0	4.1	**18**	>100	>100
9	>100	>100	**19**	>100	>100
10	10	>100	**20**	>100	>100
11	>100	>100	**21**	>100	>100

[a]All apparent IC_{50} values are determined from three technical triplicates. [b]Values in accordance to literature data[21]. [c]Values in accordance to literature data[22].

Cyclic sulfate **14** appeared to be a low-micromolar inhibitor of GAA (IC_{50} = 2.5 µM), in contrast to its somewhat weaker inhibition of ER-II (IC_{50} = 48 µM), giving compound **14** a roughly 20-fold selectivity against GAA over ER-II. Its 1,7-counterpart **4** proved to be a 100-fold more active towards both GAA and ER-II (IC_{50} = 0.051 µM and 0.035 µM respectively).[21] Both the 1,2-cyclic sulfamidates **15** and **16**, lacked the ability to reduce enzyme activities of both GAA as ER-II up to concentrations of 100 µM, demonstrating that migration of the sulfamidate from 1,7- to 1,2-position does not lead to effective inhibitors. In regards to the cyclic carbamates **10**, **11**, **20** and **21**, only compound **10** appeared to be an active inhibitor of GAA (IC_{50} = 10 µM), which is in line with the structural relationship observed for the cyclic sulfamidates. Again, the 1,2-modified constructs are not accepted by the binding pocket. In addition, superior inhibitory potencies are observed for the 1,7-(*N*,*O*)-regioisomers (**5** and **10**), which are over an order of magnitude more potent inhibitors when compared to the 1,7-(*O*,*N*)-regioisomers (**6** and **11**). Both cyclic carbonates **9** and **19** did not show a reduction of enzyme activities in both GAA as ER-II.

Having identified the inhibitory potencies of compounds **2** – **21**, focus was shifted to determining the kinetic parameters and the mode of binding of some of the most active inhibitors on recombinant human GAA (rhGAA). For this, rhGAA was incubated with a fixed substrate concentration and various inhibitor concentrations. Subsequently, apparent IC_{50} values were measured under varying incubation times. Compounds **2**, **3**, **4**, **6**, **7**, **8**, **12** and **14** showed a gradual decrease in enzyme activity indicating these compounds to be covalent and irreversible binders (Table 2). In contrast, both compound **5** and **10** appeared to be competitive inhibitors of rhGAA, as indicated by the observed lack of time dependency of the enzyme activity. Compounds **12** and **14** display pseudo first order kinetics due to fast inhibition against GAA, limiting measurement of a combined k_{inact}/K_I ratio.

Table 2. Inhibitor kinetic constants for recombinant human α-glucosidase (rhGAA)[a]

Compound	k_{inact}/K_I (min^{-1} mM^{-1})	Mode of binding	Compound	k_{inact}/K_I (min^{-1} mM^{-1})	Mode of binding
2	0.1511[b]	Covalent[b]	**12**	0.1526	Covalent
3	N.D.	Covalent[b]	**13**	N.D.	N.D.
4	62.41[b]	Covalent[b]	**14**	1.389	Covalent
5	0.06169[c]	Non-covalent[c]	**15**	N.D.	N.D.
6	N.D.	Covalent	**16**	N.D.	N.D.
7	N.D.	Covalent	**17**	N.D.	N.D.
8	N.D.	Covalent	**18**	N.D.	N.D.
9	N.D.	N.D.	**19**	N.D.	N.D.
10	N.D.	Non-covalent	**20**	N.D.	N.D.
11	N.D.	N.D.	**21**	N.D.	N.D.

[a]All apparent IC_{50} values are determined from two technical triplicates. [b]Values in accordance to literature data[21]. [c]Values in accordance to literature data[22]. N.D.: not determined due to low inhibitory potency.

Conformational free energy landscapes. The conformational energy landscapes of the most potent 1,2-cyclophellitol inhibitors (**12** – **14**) were mapped next. Free energy landscapes (FELs) were computed by means of metadynamics simulations based on density functional theory (DFT). For compounds **12** and **13**, the lowest energy conformation calculated is centered at $^4H_5$, with relative energies quickly inclining around this energy minimum (Figure 3D,E, respectively). This suggests compounds **12** and **13** to be relatively rigid and to mainly occupy this $^4H_5$ conformation. In contrast, their 1,7-counterparts, **2** and **3**, exhibit local energy minima around the $^3H_4$ conformation, related to a 60° displacement along the φ-axis (Figure 3A, B, respectively). The lack of flexibility exhibited by compounds **12** and **13** prevents adoption of the $^3H_4$ conformation, required for suitable mimicry of the transition state. This could, at least partly, explain the observed reduced inhibitory potencies of compounds **12** and **13** relative to their parent structures **2** and **3**. The energy minimum of cyclic sulfate **14** is located around $^4C_1$, with a relatively wide minimum expanding toward the $^4H_3$–^4E–$^4H_5$ region, with even an additional energy minimum extending toward the $B_{3,0}$–$^1S_3$ region (Figure 3F).

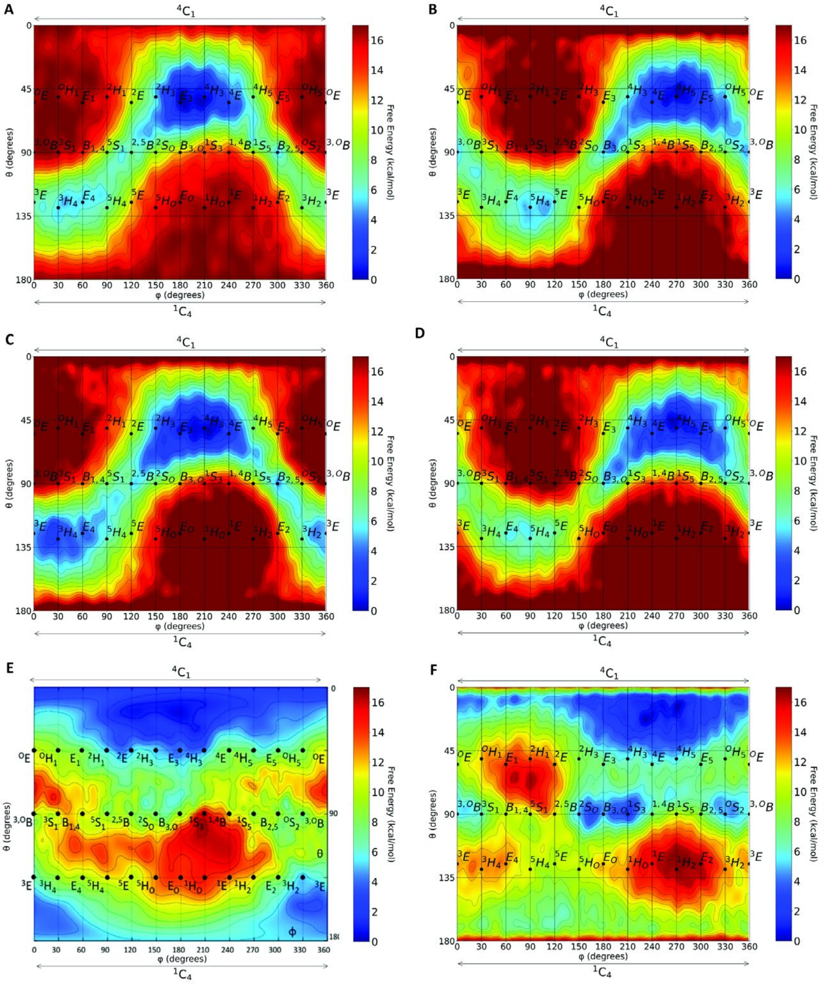


Figure 3. Computational free energy landscapes of 1,7-*epi*-cyclophellitol **2** (A), 1,7-aziridine **3** (B), cyclic 1,7-sulfate **4** (adapted from Artola *et al.*[21]) (C), 1,2-epoxide **12** (D), 1,2-aziridine **13** (E) and cyclic 1,2-sulfate **14** (F). Isolines are 1 kcal/mol with the x and y axis representing the angle (in degrees) in Cremer-Pople puckering coordinates (φ and θ respectively).

Again a 60° shift along the φ-axis is observed when compared to **4** (Figure 3C).[21] Interestingly, here an additional energy minimum is observed around the $B_{3,O}$–$^1S_3$ region not observed in parent structure **4**. These many low-energy conformations suggest **14** not only to adopt a $^4C_1$ conformation, but to be flexible enough to reach the $^4H_3$ transition state conformation. Thus, compound **14** should, as observed during *in vitro* assays, inhibit α-glucosidases with higher potencies in comparison to compounds **12** and **13**.

Conclusion

In this study, cyclophellitol based inhibitors of α-glucosidases were investigated, bearing a warhead over the 1,2-position of the cyclitol backbone. In addition to the preparation of 1,2-analogues (**12** – **16**) of the most prominent 1,7-*epi*-cyclophellitols known to date (**2** – **6**), additional warheads were proposed (**7** – **11**, **17** – **21**) and studied in *in vitro* assays for their inhibitory potencies against human acid α-glucosidase (GAA) and ER α-glucosidase II (ER-II). *N*-alkyl-1,7-aziridine **7** has improved inhibitory potency for ER-II compared to its non-alkylated counterpart **3**, resulting in a nanomolar IC_{50} against ER-II with a 6-fold selectivity over GAA. Additionally, 1,7-(*N*,*O*)-carbamate **10** revealed to be a non-covalent, low-micromolar inhibitor of GAA. Here, a strong structural relationship can be drawn with 1,7-(*N*,*O*)-sulfamidate **5**, suggesting identical enzyme interactions are at play. Therefore, compound **10** may be an interesting candidate for further study as enzyme stabilizer that can be potentially used in treatment of Pompe disease. All 1,2-analogues (**12** – **21**) revealed reduced inhibitory potencies in comparison to their 1,7-counterpart, with only compounds **12** – **14** exhibiting inhibitory potencies below 100 µM. Free energy landscapes revealed the ground state of compounds **12** – **14** to have undergone a shift in lowest energy conformation in comparison to their parent structures (**2** – **4**). As a result of this shift, the conformation does not resemble the conformation of either the Michaelis complex or transition state during hydrolysis. This conformational shift may explain the overall reduction in observed inhibitory potencies of the 1,2-cyclophellitols in contrast to their 1,7-counterparts. Overall, this study into structure-activity relationships of cyclophellitol analogues as human α-glucosidase inhibitors may fuel future design of constructs to effectively act on glycoside hydrolases of various sources and acting on various substrate glycosides.

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Biochemical methods

Cell culture/lysates

Fibroblast cell lines were cultured in HAMF12-DMEM medium (manufactor) supplied with 10% (v/v) FCS, 0.1% (w/v) penicillin/streptomycin, and 0.5% (w/v) sodium pyruvate, under 7% CO_2 at 37 °C. Confluent fibroblasts were cultured 1:3 each week. Cell pellets were stored at -80 °C until lysates were prepared. Cell lysates were prepared in potassium phosphate (KPi) lysis buffer (25 mM K_2HPO_4/KH_2PO_4, pH 6.5, supplemented with protease inhibitor cocktail (EDTA-free, Roche, Basel, Switzerland) and 0.1 % (v/v) triton X-100) *via* one Freeze-thaw cycle, followed by sonication on ice. Protein concentration was determined with the BCA Protein Assay Kit (ThermoFisher Pierce^{TM}) with 10x lysate dilution in KPi buffer (without protease inhibitor). Lysates were stored in aliquots at -80 °C until use.

IC_{50} determination

Enzymes used for IC_{50} were obtained as follows: recombinant human GAA (Myozyme) were obtained from Genzyme, USA and fibroblast cell lysates were used for ER-II α-glucosidase. Apparent IC_{50} values were determined throughout pre-incubation of 12.5 µL enzyme-mixture with 12.5 µL inhibitor for 30 minutes at 37 °C. GAA activity was measured with 47 nM enzyme (Myozyme) and 100 µL 3 mM 4-MU-α-D-glucopyranoside for 30 minutes at 37 °C. ER-II activity was measured using fibroblast cell lysates containing 10 µg protein (concentration was determined with BCA protein assay kit; Thermo Fisher) and 100 µL, 3 mM 4-MU α-D-glucopyranoside for 1 hour at 37 °C. After incubation with substrate mixture, the enzymatic reactions were quenched with 200 µL 1 M NaOH-Glycine (pH 10.3) and hydrolyzed 4-MU fluorescence is measured with a LS55 fluorescence spectrophotometer (Perkin Elmer: λ_{EX} 366 nm, λ_{EM} 445 nm). Background fluorescence (enzyme-mixture without substrate) is subtracted from the mean value and normalized with maximal activity (without inhibitor). GAA is diluted in 150 mM McIlvain buffer pH 4.0 supplemented with 0.1% bovine serum albumin (BSA, w/v%) and 0.01% NaN_3 as bacteriostatic. ER-II is diluted in 150 mM McIlvain buffer pH 7.0 supplemented with 0.1% bovine serum albumin (BSA, w/v%) and 0.01% NaN_3 as bacteriostatic. Values plotted for concentration inhibitor are those in the final reaction mixture containing enzyme, inhibitor and substrate (125 µL total). The IC_{50} value is the average of two-/triplicates from technical triplicates.

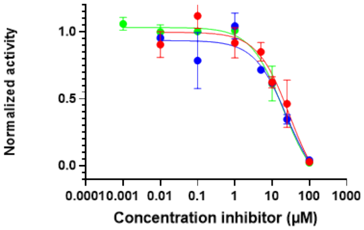
Time dependent inhibition

To study the type of inhibition, GAA and fibroblast cell lysates were pre-incubated for 5, 10, 15, 30, and 60 minutes with inhibitor (2x IC_{50} value) at 37 °C. Thereafter, 100 µL of substrate mixture (3 mM 4-MU α-D-glucopyranoside pH 4.0 for GAA, pH 7.0 for ER-II α-glucosidase) is added and incubated for 30 minutes (GAA) or 60 minutes (ER-II α-glucosidase). Finally, stop buffer (1 M glycine-NaOH pH 10.3) was added to stop the reaction and hydrolyzed 4-MU fluorescence was measured. Background fluorescence (enzyme-mixture without substrate) is subtracted from the mean value and normalized with maximal activity (without inhibitor). Time was plotted *vs* residual enzyme activity. either a straight line was observed or decreased activity over time, relating to non-covalent or covalent inhibition, respectively.

Kinetics

Kinetic parameters for inhibitor of GAA were determined using a continuous fluorescence assay involving simultaneous incubation of the enzyme with substrate and inhibitor. In the assay, the concentration of enzyme (GAA) and substrate (4-MU α-D-glucopyranoside) were 47 nM and 3 mM, respectively. For each inhibitor, sets of eight 2 mL Eppendorf tubes were prepared. Each Eppendorf tube contained 8.13 µL of various inhibitor concentration (diluted in DMSO, 200x assay concentration) or, 8.13 µL DMSO as control, and 154.4 µL McIlvain buffer (150 mM, pH 4.0, 0.1% BSA, 0.01% NaN_3) and 1300 µL substrate mixture. The Eppendorf tubes were pre-warmed on a thermoshaker at 37 °C for 5 minutes, together with a separate Eppendorf tube with 1250 µL enzyme dilution in McIlvain buffer pH 4.0 and enzyme blank (only McIlvain buffer pH 4.0). Prior to the start of the assay, 200 µL stop buffer (1 M glycine-NaOH, pH 10.3) was added to each well of a black 96-well plate. The t = 0 samples were prepared by adding 12.5 µL enzyme solution/blank into the first two columns of the plate and 112.6 µL of inhibitor/substrate mixture per row in duplicates. The reaction was starting by adding 137.6 µL aliquots of the pre-warmed enzyme/blank solution to the pre-warmed tubes containing the inhibitor/substrate mixture, with a time interval of 20 seconds between samples. The reaction tubes were incubated under constant shaking at 800 rpm at 37 °C. At depicted timepoints, 125 µL aliquots from each reaction tube was transferred to the 96-well plate in duplicates, with a 20-second interval between each tube. The 4-MU fluorescence was measured and for each timepoint the blank signal is subtracted and all values are normalized with the maximal activity of the latest timepoint without inhibitor. The observed pseudo-first order rates (k_{obs}) was determined for each concentration inhibitor by fitting the date with the one-phase exponential association function of GraphPad Prism. The obtained k_{obs} values are plotted *vs* the concentration inhibitor and the resulting plots were fitted using a linear function that gives the combined apparent inhibitor parameter k_{inact}/K'_I as the slope.

Fluorescent IC_{50} assays on recombinant human GAA (Myozyme) and ER-II for compounds 2 – 21.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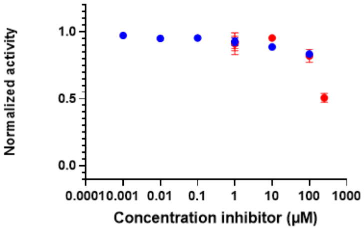
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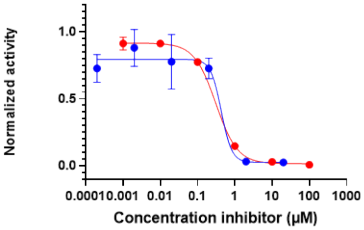
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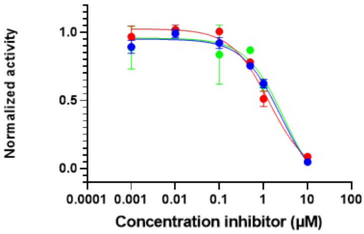
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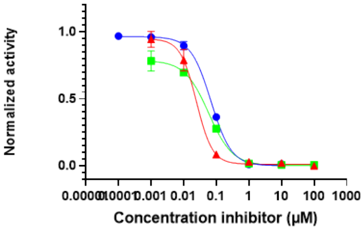
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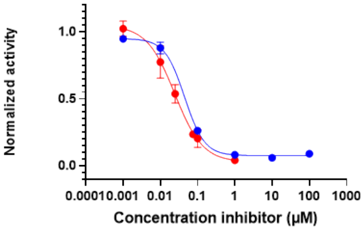
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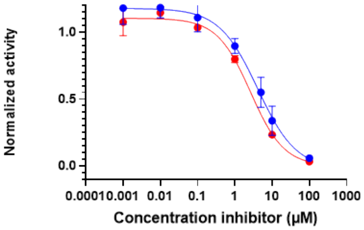
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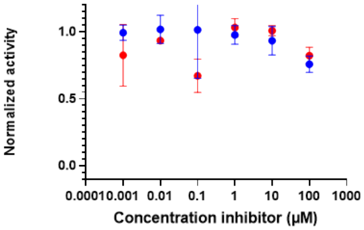
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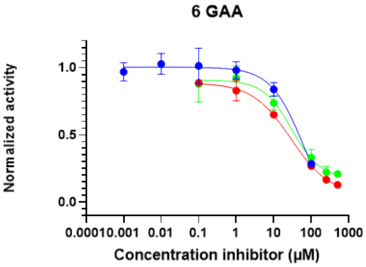
6 GAA
Normalized activity
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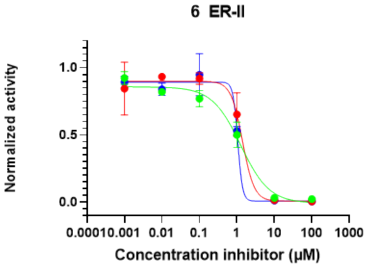
0.0
0.00010.001
0.01
0.1
1
10
100
1000
Concentration inhibitor (µM)


6 ER-II
Normalized activity
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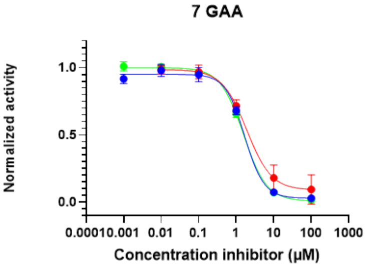
0.0
0.00010.001
0.01
0.1
1
10
100
1000
Concentration inhibitor (µM)


7 GAA
Normalized activity
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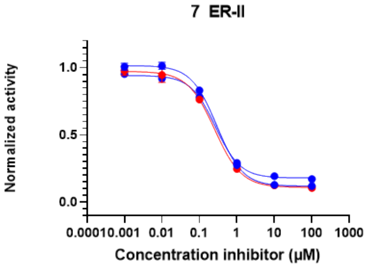
0.5
0.0
0.00010.001
0.01
0.1
1
10
100
1000
Concentration inhibitor (µM)


7 ER-II
Normalized activity
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0.01
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1
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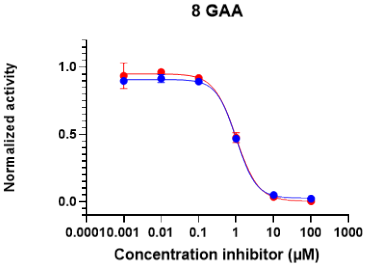
100
1000
Concentration inhibitor (µM)


8 GAA
Normalized activity
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0.1
1
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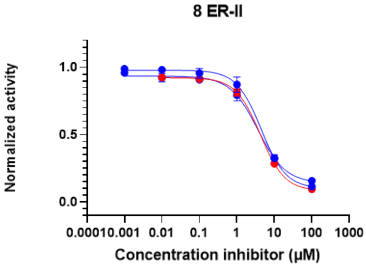
100
1000
Concentration inhibitor (µM)


8 ER-II
Normalized activity
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1
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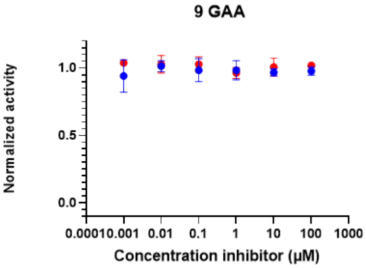
100
1000
Concentration inhibitor (µM)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Normalized activity
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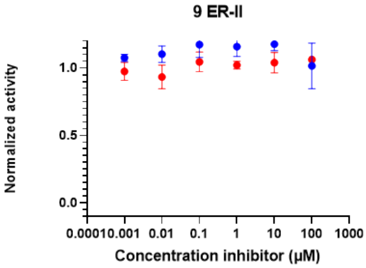
1
10
100
1000
Concentration inhibitor (µM)


9 ER-II
Normalized activity
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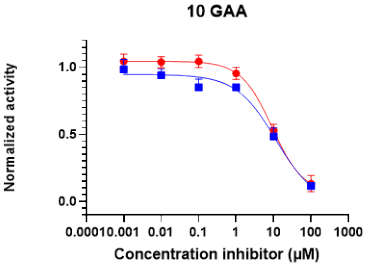
0.00010.001
0.01
0.1
1
10
100
1000
Concentration inhibitor (µM)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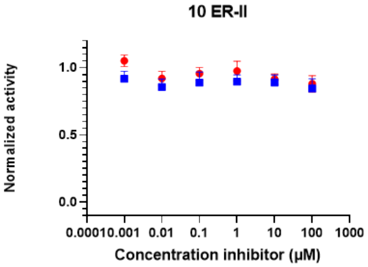
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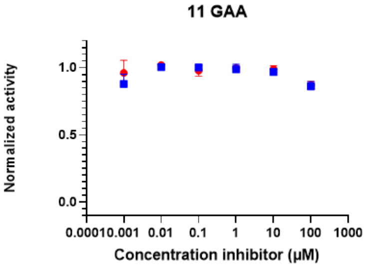
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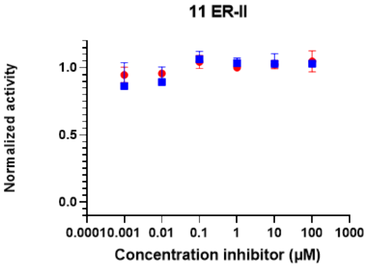
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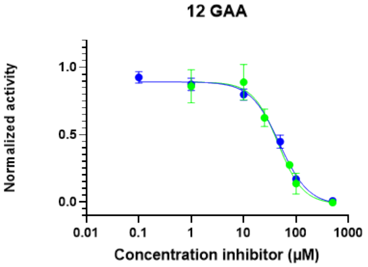
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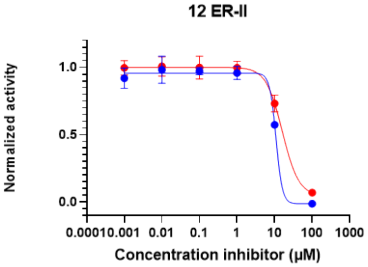
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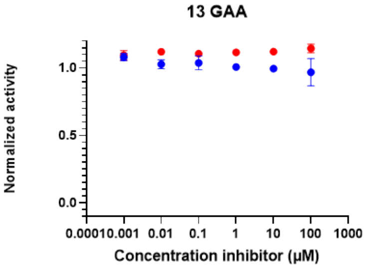
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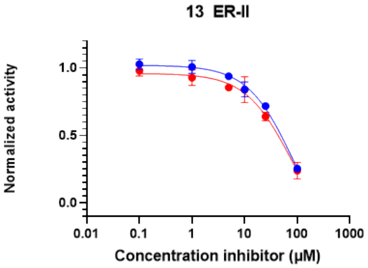
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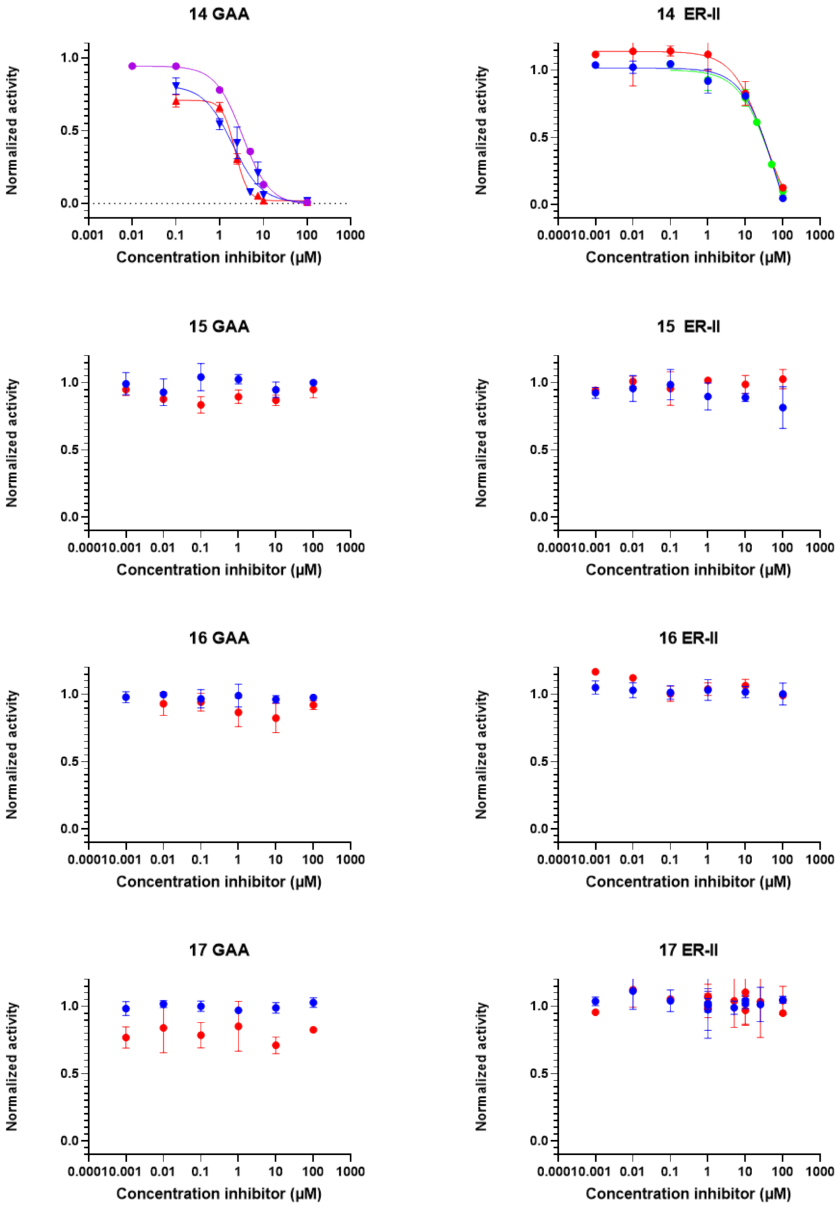
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14 ER-II
15 GAA
15 ER-II
16 GAA
16 ER-II
17 GAA
17 ER-II
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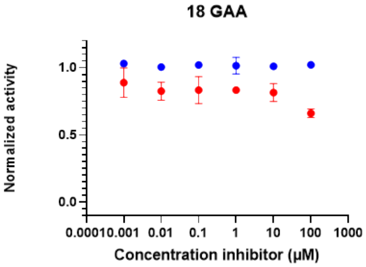
0.001
0.0001
0.001
0.01
0.1
1
10
100
1000
Concentration inhibitor (µM)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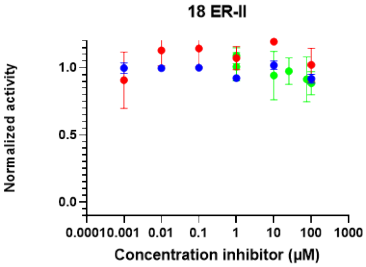
Concentration inhibitor (μM)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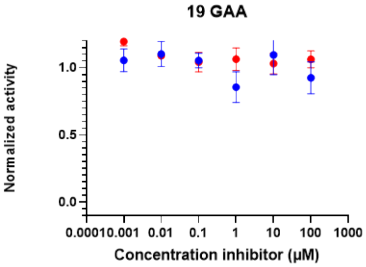
Concentration inhibitor (μM)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Normalized activity
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100
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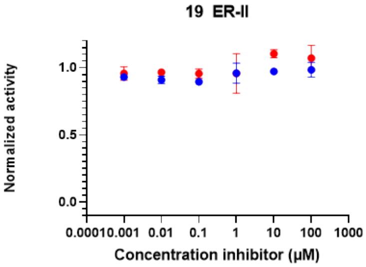
Concentration inhibitor (μM)


19 ER-II
Normalized activity
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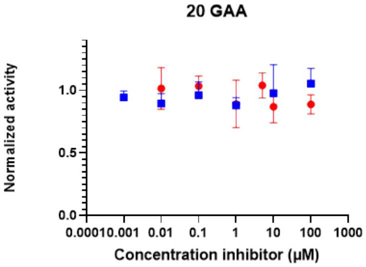
10
100
1000
Concentration inhibitor (μM)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Normalized activity
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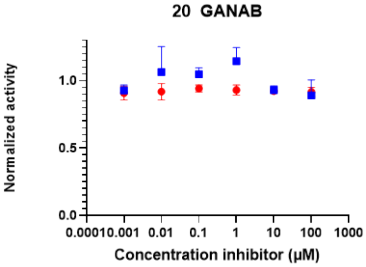
1
10
100
1000
Concentration inhibitor (μM)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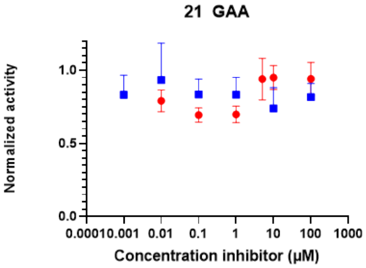
10
100
1000
Concentration inhibitor (μM)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Normalized activity
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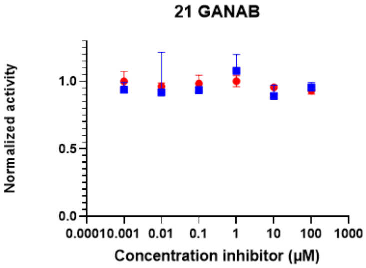
10
100
1000
Concentration inhibitor (μM)


21 GANAB
Normalized activity
1.0
0.5
0.0
0.0001
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0.01
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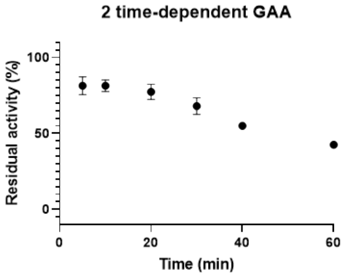
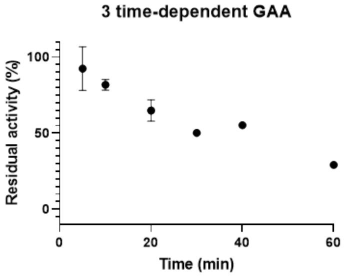
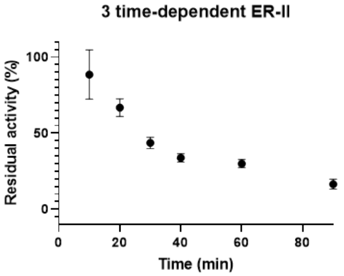
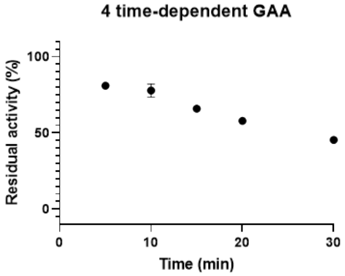
1
10
100
1000
Concentration inhibitor (μM)

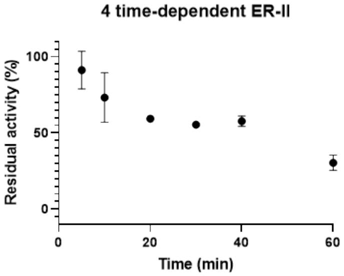
Time dependent inhibition relating to covalent or non-covalent inhibition

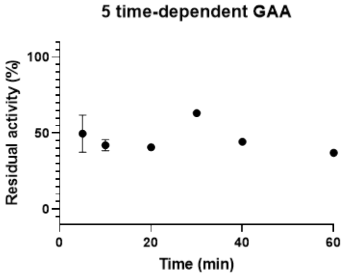


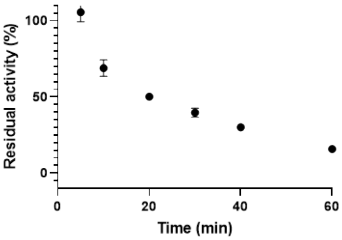


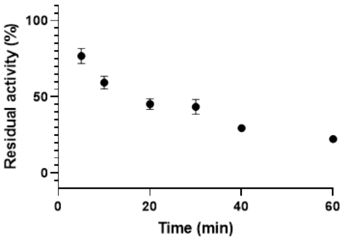


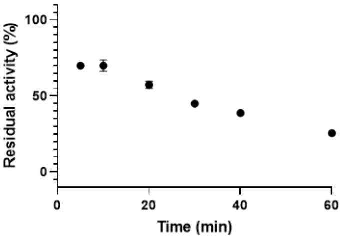







6 time-dependent GAA


6 time-dependent ER-II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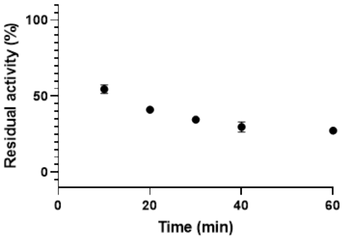
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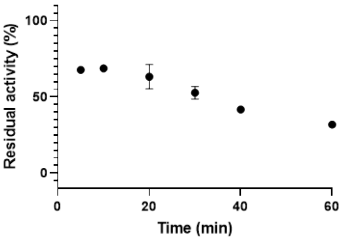
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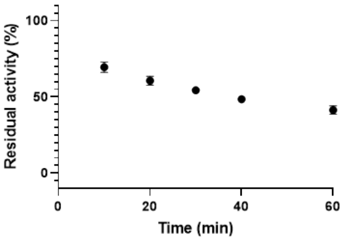
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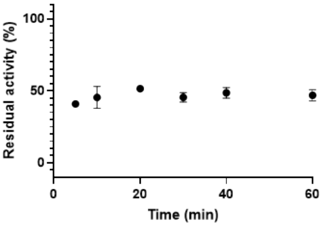
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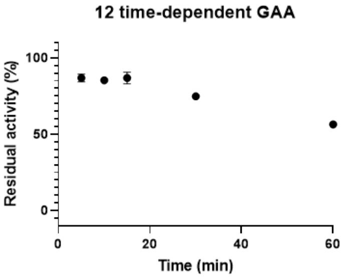
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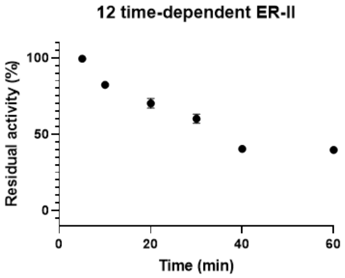
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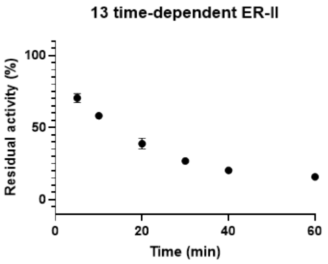
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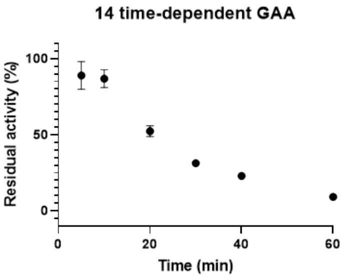
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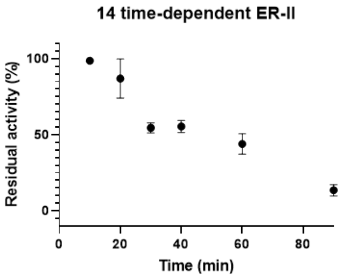
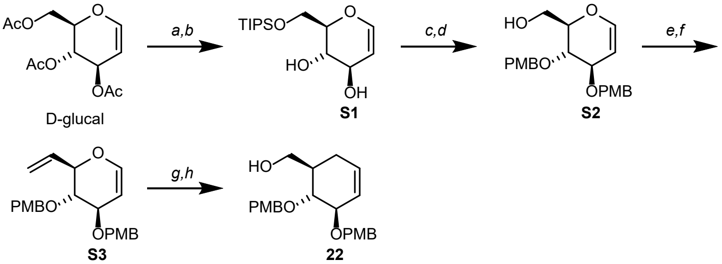

14 time-dependent ER-II

Molecular modeling

The conformational free energy landscapes of the best cyclophellitol inhibitors (1,2-epoxide **12**, 1,2-aziridine **13** and 1,2-cyclic sulfate **14**) were computed by means of quantum mechanical calculations, with the Car-Parrinello approach,[32] based on the density functional theory (DFT),[33,34] using the CPMD 3.15.1 program.[35] The epoxide, aziridine and cyclic sulfate derivatives were enclosed in orthorhombic boxes of size 12.44Å x 14.57Å x 11.26Å, 13.81Å x 13.12Å x 12.90Å and 12.78Å x 13.53Å x 10.28Å, respectively. The electronic structure was computed using the Perdew, Burke and Ernzerhoff generalized gradient-corrected approximation (PBE)[36] which has been proven to give a good performance in previous works on GHs and glycosyltransferases,[37] besides being proved that it is the cheapest computational method which reaches chemical accuracy. [38] Kohn-Sham orbitals were expanded in a plane wave basis set with a kinetic energy cutoff of 70 Ry. Norm-conserving Trouiller-Martins pseudopotentials[39] were employed. The fictitious electronic mass and time step were set to 700 and 5 a.u. The conformational free energy landscape were calculated *via* the enhanced sampling method called metadynamics[40]; using the CPMD program and the Plumed driver.[41] The collective variables (CVs) used are the Cremer-Pople puckering coordinates[42] θ and ϕ. Initially, the height of these Gaussian terms was set at 0.6 kcal·mol^{-1} and a new Gaussian-like potential was added every 500 molecular dynamics steps. Once the whole free energy space was explored, the height of the Gaussian terms was reduced to 0.35 kcal·mol^{-1}. The width of the Gaussian terms was set to 0.10 Å. The number of deposited gaussians were 12000, 6448 and 12000 corresponding to 720, 387 and 720ps for aziridine **12**, epoxide **13** and cyclic sulfate **14**, respectively. The statistical error calculated with the free energy estimator developed by Tiwary[42] was below 1 kcal·mol^{-1}.

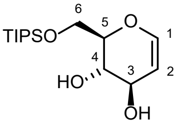
Synthetic procedures.

Scheme S5. Synthesis of key intermediate **22** according to procedures of crotti and co-workers.[26]



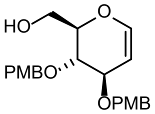
^{a}Reagents and conditions: *a)* K_2CO_3, MeOH, 3 h, 40 °C; *b)* TIPSCl, imidazole, DMF, 16 h, rt, (85%); *c)* PMBCl, NaH, DMF, 16 h, rt; *d)* TBAF, THF, 1 h, rt (89%); *e)* Dess-Martin periodinane, $NaHCO_3$, DCM, 3 h, rt; *f)* Ph_3PCH_3Br, *n*-BuLi, THF, 16 h, -78 °C to rt (62%); *g)* diphenyl ether, 3 h, 225 °C; *h)* $NaBH_4$, THF:EtOH (2:1, v:v), 30 min., 0 °C (97%).

6-*O*-Triisopropylsilyl-D-glucal (S1).



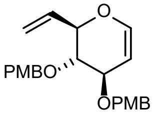
3,4,6-Tri-*O*-acetyl-D-glucal (109 g, 400 mmol) was dissolved in MeOH (400 mL, 1.0 M). K_2CO_3 (16.6 g, 120 mmol, 0.3 eq.) was added and the reaction mixture was stirred for 3 hours at 40 °C. Upon full conversion was observed (R_f 0.4 (MeOH:DCM, 2:8 v:v)), the product was concentrated, co-evaporated twice using DMF and dissolved in DMF (800 mL, 0.5 M). Imidazole (81.6 g, 1.2 mol, 3.0 eq.) was added and the reaction mixture was cooled on ice. Triisoproylsilyl chloride (TIPSCl; 112 mL, 520 mmol, 1.3 eq.) was added and the solution was stirred overnight at room temperature. Upon full conversion (R_f 0.6 (EtOAc:pentane, 1:1 v:v)), the reaction was quenched by addition of MeOH (10 mL) and subsequently concentrated to dryness. The concentrated product was extracted with EtOAc (3x) and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (20:80 EtOAc:pentane → 60:40 EtOAc:pentane) yielded title compound **S1** (103 g, 340 mmol, 85% over 2 steps). Spectral data was in accordance with literature precedence.[26] ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 6.26 (dd, *J* = 6.0, 1.8 Hz, 1H, H-1), 4.68 (dd, *J* = 6.1, 2.2 Hz, 1H, H-2), 4.28 – 4.21 (m, 1H, H-3), 4.05 – 3.95 (m, 3H, 3-OH, H-6), 3.81 – 3.74 (m, 2H, H-4, H-5), 3.56 (d, *J* = 5.3 Hz, 1H, 4-OH), 1.17 – 1.00 (m, 21H, $Si(CH(CH_3)_2)$, $Si(CH(CH_3)_2)$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 144.1 (C-1), 102.6 (C-2), 76.8 (C-5), 72.4 (C-4), 69.5 (C-3), 64.4 (C-6), 18.0, 18.0 ($Si(CH(CH_3)_2)$), 11.9 ($Si(CH(CH_3)_2)$); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{15}H_{30}O_4SiNa$ 325.1811, found 325.1806.

3,4-Di-*O*-(4-methoxybenzyl)-D-glucal (S2).



To an ice-cooled solution of **S1** (103 g, 341 mmol) in DMF (560 mL, 0.6 M) was added PMBCl (140 mL, 1.0 mol, 3.1 eq.) followed by the portion-wise addition of NaH (60 wt% dispersion in mineral oil; 47.6 g, 1.2 mol, 3.5 eq.). The reaction mixture was slowly warmed to room temperature and stirred overnight. Upon full conversion was observed (R_f 0.5 (EtOAc:pentane 1:9 v:v)), the reaction was quenched on ice by addition of water (25 mL) and concentrated to a fifth of its original volume. The crude product was extracted with Et_2O (3x), and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was dissolved in THF (120 mL) and TBAF (1.0 M in THF; 360 mL, 360 mmol, 1.05 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. Upon full conversion (R_f 0.2 (EtOAc:pentane, 3:7 v:v)), the product was concentrated and extracted with Et_2O (3x), after which the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Recrystallization from EtOAc/pentane yielded title compound **S2** (86.5 g, 224 mmol) as a pale-yellow solid. Flash column chromatography of the mother liquor (20:80 EtOAc:pentane → 70:30 EtOAc:pentane) yielded additional **S2**, giving and overall yield of 116.5 g, 302 mmol, 89% over 2 steps. Spectral data was in accordance with literature precedence.[26] ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.29 – 7.22 (m, 4H, CH_{arom}), 6.91 – 6.84 (m, 4H, CH_{arom}), 6.39 (dd, *J* = 6.1, 1.4 Hz, 1H, H-1), 4.87 (dd, *J* = 6.2, 2.7 Hz, 1H, H-2), 4.78 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.65 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.60 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.51 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.19 (ddd, *J* = 6.2, 2.8, 1.4 Hz, 1H, H-3), 3.92 (ddd, *J* = 8.5, 4.2, 4.2 Hz, 1H, H-5), 3.83 (d, *J* = 4.2 Hz, 2H, H-6), 3.81 (s, 3H, OMe PMB), 3.80 (s, 3H, OMe, PMB), 3.76 (dd, *J* = 8.6, 6.2 Hz, 1H, H-4), 2.05 (bs, 1H, 6-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 159.4 ($C_{q\text{-}arom}$), 144.6 (C-1), 130.4, 130.2 ($C_{q\text{-}arom}$), 129.8, 129.5 (CH_{arom}), 114.0, 114.0, (CH_{arom}), 100.4 (C-2), 77.4 (C-5), 75.3 (C-3), 74.3 (C-4), 73.5, 70.4 (CH_2 PMB), 62.0 (C-6), 55.4 (OMe PMB); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{22}H_{26}O_6Na$ 409.1627, found 409.1622.

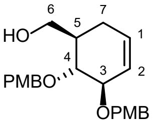
2-Vinyl-3,4-di-*O*-(4-methoxybenzyl)-3,4-dihydro-2*H*-pyran (S3).



Compound **S2** (7.7 g, 20 mmol) was co-evaporated with toluene, dissolved in dry DCM (100 mL, 0.2 M) and kept under a N_2 atmosphere. $NaHCO_3$ (33.6 g, 400 mmol, 20 eq.) was added and the suspension was cooled on ice. Dess-Martin periodinane (12.7 g, 30 mmol, 1.5 eq.) was added, after which the ice bath was removed, and the reaction mixture was stirred at room temperature for 3 hours. Upon full conversion to the aldehyde (R_f 0.5 (EtOAc:pentane, 3:7 v:v)), the reaction was quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$, after which the mixture was filtered over Celite. The product was then extracted with DCM (3x), after which the organic layer was dried over $MgSO_4$, filtered over Celite, and concentrated *in vacuo* to obtain the crude aldehyde as a yellow oil. Wittig reagent Ph_3PCH_3Br (10.7 gr, 30 mmol, 1.5 eq.) was dissolved in dry THF (60 mL) and cooled to –78 °C. *n*-BuLi (11.6 mL, 2.5 M in hexane, 29 mmol, 1.45 eq.) was added over a period of 5 minutes. The reaction mixture was then transferred to an ice bath and stirred for 1 hour. The mixture was cooled back to –78 °C, during which the crude aldehyde was co-evaporated with toluene 3x and dissolved in dry THF (40 mL), followed by the addition to the cooled phosphorus ylide over a period of 10 minutes. The resulting reaction mixture was transferred to an ice bath and stirred overnight while allowing for the reaction to attain to room temperature. Upon full conversion was observed (R_f 0.7 (EtOAc:pentane, 3:7 v:v)), the reaction was quenched with sat. aq. $NaHCO_3$, extracted with

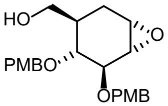
EtOAc (3x) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (dry loading on Celite; 5:95 Et$_2$O:pentane → 50:50 Et$_2$O:pentane) yielded title compound **S3** as a yellow oil, which solidified upon standing (4.7 g, 12.3 mmol, 62% over 2 steps). Spectral data was in accordance with literature precedence.[26] ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30 – 7.23 (m, 4H, CH$_{\text{arom}}$), 6.90 – 6.85 (m, 4H, CH$_{\text{arom}}$), 6.41 (dd, *J* = 6.1, 1.4 Hz, 1H, H-1), 6.05 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H, H-6), 5.43 (ddd, *J* = 17.3, 1.4, 1.4 Hz, 1H, H-7), 5.31 (ddd, *J* = 10.6, 1.4, 1.4 Hz, 1H, H-7), 4.87 (dd, *J* = 6.2, 2.7 Hz, 1H, H-2), 4.71 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.62 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.58 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.53 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.31 (dddd, *J* = 8.0, 6.5, 1.3, 1.3 Hz, 1H, H-5), 4.17 (ddd, *J* = 6.2, 2.9, 1.5 Hz, 1H, H-3), 3.81 (s, 3H, OMe PMB), 3.81 (s, 3H, OMe PMB), 3.57 (dd, *J* = 8.6, 6.2 Hz, 1H, H-4); ^{13}C NMR (101 MHz, CDCl$_3$, HSQC): δ 159.4, 159.3 (C$_{\text{q-arom}}$), 144.5 (C-1), 134.5 (C-6), 130.6, 130.3 (C$_{\text{q-arom}}$), 129.8, 129.5 (CH$_{\text{arom}}$), 118.4 (C-7), 113.9, 113.9 (CH$_{\text{arom}}$), 100.6 (C-2), 78.2 (C-5), 78.0 (C-4), 75.3 (C-3), 73.6, 70.5 (CH$_2$ PMB), 55.4 (OMe PMB); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{23}H_{26}O_5Na$ 405.1678, found 405.1673.

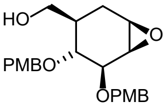
3,4-Di-*O*-(4-methoxybenzyl)-carba-D-glucal (22).



Compound **S3** (4.7 g, 12.3 mmol) was co-evaporated with toluene and dissolved in anhydrous diphenyl ether (48 mL, 0.25 M). The resulting solution was transferred to microwave reaction vials which were subsequently purged with N$_2$ and placed in an aluminum heating block and heated to 225 °C for 3 hours. After full conversion to the aldehyde was observed (R$_f$ 0.5 (EtOAc:pentane, 3:7 v:v)), the yellow solution was directly poured into a stirring suspension of NaBH$_4$ (705 mg, 18.6 mmol, 1.5 eq.) in a mixture of THF:EtOH (2:1 v:v, 120 mL, 0.1 M). The reaction mixture was stirred at room temperature for 30 minutes. Upon full conversion (R$_f$ 0.2 (EtOAc:pentane, 3:7 v:v)), the reaction was quenched with sat. aq. NaHCO$_3$. The mixture was extracted with EtOAc (3x), after which the combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (30:70 EtOAc:pentane → 40:60 EtOAc:pentane) yielded title compound **22** (4.6 g, 11.9 mmol, 97% over 2 steps) as a yellow oil which solidified upon standing. Spectral data was in accordance with literature precedence.[26] ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HSQC): δ 7.32 – 7.20 (m, 4H, CH$_{\text{arom}}$), 6.90 – 6.81 (m, 4H, CH$_{\text{arom}}$), 5.71 (dddd, *J* = 10.2, 4.0, 1.8, 1.8 Hz, 1H, H-1), 5.68 – 5.63 (m, 1H, H-2), 4.88 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.66 – 4.61 (m, 2H, CH*H* PMB, C*H*H PMB), 4.56 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.17 (ddd, *J* = 7.4, 3.4, 1.7 Hz, 1H, H-3), 3.76 (s, 3H, OMe PMB), 3.75 (s, 3H, OMe PMB), 3.62 – 3.52 (m, 3H, H-4, H-6), 2.87 (dd, *J* = 8.1, 3.3 Hz, 1H, 6-OH), 2.09 (ddd, *J* = 17.8, 4.8, 4.8 Hz, 1H, H-7), 2.02 – 1.91 (m, 1H, H-5), 1.85 (dddd, *J* = 18.0, 10.3, 2.8, 2.7 Hz, 1H, H-7); ^{13}C NMR (126 MHz, CDCl$_3$, HSQC): δ 159.3, 159.2, 130.5, 130.5 (C$_{\text{q-arom}}$), 129.8, 129.4 (CH$_{\text{arom}}$), 128.0 (C-1), 126.0 (C-2), 113.9, 113.8 (CH$_{\text{arom}}$), 81.5 (C-4), 80.9 (C-3), 73.8, 70.9 (CH$_2$ PMB), 65.3 (C-6), 55.2, 55.2 (OMe PMB), 40.5 (C-5), 28.0 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{23}H_{28}O_5Na$ 407.1834, found 407.1829.

1,2-Anhydro-3,4-di-*O*-(4-methoxybenzyl)-carba-α-D-glucose (23) and 1,2-Anhydro-3,4-di-*O*-(4-methoxybenzyl)-carba-β-D-mannose (24).



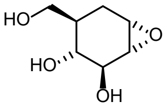


Compound **22** (0.52 g, 1.35 mmol) was dissolved in DCM (13.5 mL, 0.1 M) and *m*-CPBA (0.47 g, 2.7 mmol, 2.0 eq.) was added and stirred overnight at room temperature. Upon full conversion (R_f 0.3 and 0.2 for **23** and **24** respectively (EtOAc:Pentane, 1:1 v:v)), the reaction was quenched with sat. aq. $NaHCO_3$ and sat. aq. NaS_2O_3 followed by extraction with EtOAc. The organic layer was then washed with brine and subsequently dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (40:60 EtOAc:pentane → 70:30 EtOAc:pentane) yielded title compounds **23** (284 mg, 0.71 mmol, 53%) and **24** (142 mg, 0.36 mmol, 26%).

Analytical data for **23**: 1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.38 – 7.15 (m, 4H, CH_{arom}), 6.98 – 6.80 (m, 4H, CH_{arom}), 4.84 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.76 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.65 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.61 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 3.81 (s, 3H, OMe), 3.82 – 3.77 (m, 4H, OMe, H-3), 3.56 (dd, *J* = 11.0, 3.0 Hz, 1H, H-6), 3.45 (dd, *J* = 11.0, 6.2 Hz, 1H, H-6), 3.30 (dd, *J* = 10.7, 8.0 Hz, 1H, H-4), 3.22 (ddd, *J* = 3.5, 1.7, 1.7 Hz, 1H, H-1), 3.13 (dd, *J* = 3.8, 0.7 Hz, 1H, H-2), 2.14 – 2.05 (m, 1H, H-7), 1.77 – 1.57 (m, 2H, H-5, H-7); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 159.6, 159.5, 130.3 ($C_{q\text{-}arom}$), 130.1 (CH_{arom}), 129.9 ($C_{q\text{-}arom}$), 129.4, 114.1 (CH_{arom}), 82.0 (C-4), 80.7 (C-3), 74.0, 72.2 (CH_2 PMB), 65.3 (C-6), 55.4 (OMe), 55.4 (OMe), 54.1 (C-2), 52.9 (C-1), 34.4 (C-5), 27.3 (C-7). HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{23}H_{28}O_6Na$ 423.1784, found 423.1778.

Analytical data for **24**: 1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.40 – 7.21 (m, 4H, CH_{arom}), 6.97 – 6.80 (m, 4H, CH_{arom}), 4.88 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.79 – 4.73 (m, 2H, C*H*H PMB, CH*H* PMB), 4.59 (d, *J* = 10.7 Hz, 1H, CH*H* PMB), 3.84 (dd, *J* = 8.2, 1.8 Hz, 1H, H-3), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.59 (dd, *J* = 10.4, 8.1 Hz, 1H, H-4), 3.49 – 3.43 (m, 2H, H-6), 3.30 (dd, *J* = 4.0, 1.8 Hz, 1H, H-2), 3.25 (dd, *J* = 4.9, 4.0 Hz, 1H, H-1), 2.49 (bs, 1H, 6-OH), 1.97 (ddd, *J* = 14.4, 5.4, 5.4 Hz, 1H, H-7), 1.81 – 1.60 (m, 2H, H-5, H-7); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 159.5, 159.4, 130.4, 130.3 ($C_{q\text{-}arom}$), 130.2, 129.7, 114.1, 114.0 (CH_{arom}), 81.5 (C-3), 79.8 (C-4), 75.0, 72.0 (CH_2 PMB), 64.8 (C-6), 55.4, 55.4 (OMe), 55.3 (C-2), 53.5 (C-1), 41.3 (C-5), 25.8 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{23}H_{28}O_6Na$ 423.1784, found 423.1780.

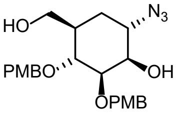
1,2-Anhydro-carba-α-D-glucose (12).



Compound **23** (116 mg, 0.29 mmol) was dissolved in MeOH (14 mL, 0.02 M,) and 5% palladium on carbon (12.3 mg, 60 µmol, 0.2 eq.) was added. The system was flushed with nitrogen and subsequently with hydrogen. The mixture continued to stir for 1 hour at rt whilst kept under a positive hydrogen atmosphere. Upon full conversion was observed (R_f 0.3 (MeOH:DCM, 1:9 v:v)) the mixture was filtered over Celite, and rinsed with MeOH. The filtrate was concentrated under reduced pressure. Flash column chromatography (5:95 MeOH:DCM → 10:90 MeOH:DCM) yielded the title compound **12** (38.6 mg, 0.24 mmol, 83%). Spectral data was in accordance with literature precedence.[27] 1H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 3.68 (dd, *J* = 8.5, 0.8 Hz, 1H, H-3), 3.65 (m, 2H, H-6), 3.43 (ddd, *J* = 4.0, 2.0, 1.9 Hz, 1H, H-1), 3.25 (dd, *J* = 11.4, 8.4 Hz, 1H, H-4), 3.20 (dd, *J* = 3.9, 0.8 Hz, 1H, H-2), 2.24 (dddd, *J* = 15.4, 4.5, 2.2, 0.8 Hz, 1H, H-7), 1.80 (ddd, *J* = 15.4, 12.1, 1.8 Hz, 1H, H-7), 1.51 (ddddd, *J* = 9.6, 9.5, 4.2, 4.1, 4.0 Hz, 1H, H-5); ^{13}C NMR (126 MHz, D_2O, HSQC):

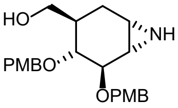
δ 73.0 (C-4), 71.9 (C-3), 61.8 (C-6), 57.0 (C-2), 54.3 (C-1), 34.4 (C-5), 26.5 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_7H_{12}O_4Na$ 183.0633, found 183.0628.

1-Deoxy-1-azido-3,4-di-*O*-(4-methoxybenzyl)-carba-α-D-mannose (25).



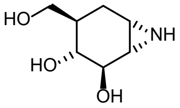
Compound **24** (200 mg, 0.5 mmol) was dissolved in DMF (5.0 mL, 0.1 M) followed by the addition of NaN_3 (488 mg, 7.5 mmol, 15 eq.). The reaction mixture was heated to 130 °C and stirring continued for 16 hours. Upon full conversion was observed (R$_f$ 0.3 (EtOAc:pentane, 3:7 v:v)), the mixture was diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (40:60 → 50:50; EtOAc:pentane) yielded the title compound (133 mg, 0.3 mmol, 60%). 1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.34 – 7.18 (m, 4H, CH$_{\text{arom}}$), 6.97 – 6.74 (m, 4H, CH$_{\text{arom}}$), 4.79 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.65 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.59 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.55 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 3.94 – 3.87 (m, 2H, H-1, H-2), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.72 (dd, *J* = 8.3, 3.0 Hz, 1H, H-3), 3.65 – 3.58 (m, 3H, H-4, H-6), 2.58 (d, *J* = 2.3 Hz, 1H, 2-OH), 2.04 (dd, *J* = 6.9, 4.5 Hz, 1H, 6-OH), 1.96 – 1.88 (m, 1H, H-5), 1.83 (ddd, *J* = 14.4, 11.4, 3.2 Hz, 1H, H-7), 1.67 (dddd, *J* = 14.0, 4.0, 4.0, 1.1 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7, 159.5, 130.4 (C$_{\text{q-arom}}$), 129.9 (CH$_{\text{arom}}$), 129.9 (C$_{\text{q-arom}}$), 129.8, 114.2, 114.1 (CH$_{\text{arom}}$), 81.3 (C-3), 78.3 (C-4), 74.3 (CH_2 PMB), 72.7 (CH_2 PMB), 69.7 (C-2), 64.9 (C-6), 60.0 (C-1), 55.4 (OMe), 39.2 (C-5), 26.5 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{23}H_{29}N_3O_6Na$ 466.1954, found 466.1949.

1,2-Dideoxy-1,2-azabicyclo[4.1.0]-3,4-di-*O*-(4-methoxybenzyl)-carba-α-D-glucose (26).



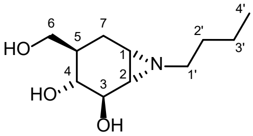
Compound **25** (133 mg, 0.3 mmol) was dissolved in anhydrous acetonitrile (3.0 mL, 0.1 M) followed by the addition of polymer bound triphenyl phosphine (~3 mmol/gram loading, 200 mg, 0.6 mmol, 2.0 eq.) and stirred for 16 hours at 60 °C under protective atmosphere. Upon full conversion was observed (R$_f$ 0.3 (MeOH:DCM, 1:9, v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (3:97 → 5:95; MeOH:DCM) yielded the title compound (51 mg, 0.13 mmol, 43%) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.40 – 7.29 (m, 2H, CH$_{\text{arom}}$), 7.29 – 7.18 (m, 2H, CH$_{\text{arom}}$), 6.94 – 6.82 (m, 4H, CH$_{\text{arom}}$), 4.85 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.74 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.61 (m, , 2H, CH*H* PMB, CH*H* PMB), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.75 (d, *J* = 7.8 Hz, 1H, H-3), 3.52 (dd, *J* = 11.0, 3.2 Hz, 1H, H-6), 3.45 (dd, *J* = 11.0, 6.8 Hz, 1H, H-6), 3.28 (dd, *J* = 10.9, 7.8 Hz, 1H, H-4), 2.64 (s, 1H, 6-OH), 2.33 (d, *J* = 5.7 Hz, 1H, H-1), 2.24 (d, *J* = 5.9 Hz, 1H, H-2), 1.95 (ddd, *J* = 13.7, 4.2, 1.5 Hz, 1H, H-7), 1.69 (dddd, *J* = 14.1, 7.1, 7.1, 3.5 Hz, 1H, H-5), 1.52 (dd, *J* = 13.6, 13.6 Hz, 1H, H-7), 0.59 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 130.5, 130.3 (C$_{\text{q-arom}}$), 130.0, 129.7, 114.0 (CH$_{\text{arom}}$), 83.2 (C-4), 82.4 (C-3), 73.9 (CH_2 PMB), 71.9 (CH_2 PMB), 66.1 (C-6), 55.4 (OMe), 55.4 (OMe), 34.6 (C-5), 33.2 (C-2), 30.4 (C-1), 27.5 (C-7); HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{23}H_{30}NO_5$ 400.2124, found 400.2118.

1,2-Dideoxy-1,2-azabicyclo[4.1.0]-carba-α-D-glucose (13).



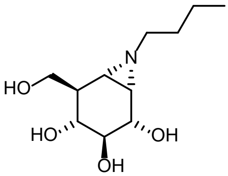
Ammonia (3.0 mL) was condensed at -60 °C followed by the addition of sodium metal (39.0 mg, 1.6 mmol, 20 eq.) and stirring continued for 30 minutes at -60 °C. Compound **26** (32 mg, 80 µmol) was dissolved in THF (1.0 mL) and slowly added to the prepared solution. After stirring for 1 hour at -60 °C, the reaction was quenched by the dropwise addition of water. The mixture was allowed to attain to room temperature followed by direct concentration under reduced pressure. Flash column chromatography (20:80 MeOH:DCM → 30:70 MeOH:DCM) yielded the title compound (11.7 mg, 74 µmol, 92%) as a colorless oil. TLC: R_f 0.3 (MeOH:DCM, 3:7, v:v). ^{1}H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 3.64 – 3.58 (m, 2H, H-6), 3.53 (d, *J* = 8.2 Hz, 1H, H-3), 3.13 (dd, *J* = 11.1, 8.2 Hz, 1H, H-4), 2.36 (bs, 1H, H-1), 2.17 (d, *J* = 6.1 Hz, 1H, H-2), 2.05 (dd, *J* = 14.7, 4.4 Hz, 1H, H-7), 1.65 (dd, *J* = 13.3, 13.3 Hz, 1H, H-7), 1.47 (ddddd, *J* = 11.7, 11.7, 4.8, 4.8, 4.8 Hz, 1H, H-5); ^{13}C NMR (126 MHz, MeOD, HSQC): δ 76.5 (C-4), 75.2 (C-3), 64.4 (C-6), 36.5 (C-2, C-5), 31.4 (C-1), 28.3 (C-7); HRMS (ESI) m/z: [M+H$^+$] calcd for $C_7H_{14}NO_3$ 160.0974, found 160.0969.

***N*-Butyl-1,2-dideoxy-1,2-azabicyclo[4.1.0]-carba-α-D-glucose (17).**



Compound **13** (8.0 mg, 50 µmol) was dissolved in anhydrous DMF (1.0 mL, 0.05 M) followed by the addition of butyl iodide (12 µL, 0.1 mmol, 2.0 eq.) and K_2CO_3 (21 mg, 0.15 mmol, 3.0 eq.). The reaction was stirred overnight at 80 °C under protective atmosphere. Upon full conversion was observed (R_f 0.6 (MeOH:DCM, 3:7, v:v)), the reaction mixture was concentrated and purified by flash column chromatography (4:96 MeOH:DCM → 12:88 MeOH:DCM) yielded the title compound (9.0 mg, 42 µmol, 84%) as a colorless oil. ^{1}H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 3.61 (m, 2H, H-6), 3.54 (d, *J* = 8.2 Hz, 1H, H-3), 3.09 (dd, *J* = 11.0, 8.2 Hz, 1H, H-4), 2.37 – 2.24 (m, 2H, H-1’), 2.08 (ddd, *J* = 14.2, 4.5, 1.3 Hz, 1H, H-7), 1.80 (ddd, *J* = 6.4, 3.5, 1.2 Hz, 1H, H-1), 1.66 – 1.47 (m, 5H, H-2, H-7, H-2’, H-5), 1.45 – 1.34 (m, 2H, H-3’), 0.95 (t, *J* = 7.4 Hz, 3H, H-4’); ^{13}C NMR (126 MHz, MeOD, HSQC): δ 76.3 (C-4), 74.9 (C-3), 64.5 (C-6), 61.4 (C-1’), 45.7 (C-2), 40.9 (C-1), 37.5 (C-5), 32.8 (C-2’), 28.2 (C-7), 21.6 (C-3’), 14.4 (C-4’); HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{11}H_{22}NO_3$ 216.1600, found 216.1594.

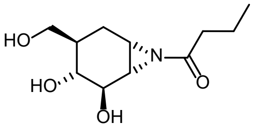
***N*-Butyl-1,7-*epi*-cyclophellitol aziridine (7).**



Compound **3** (8.0 mg, 46 µmol) was dissolved in anhydrous DMF (0.5 mL, 0.1 M) followed by the addition of butyl iodide (16 µL, 137 µmol, 3.0 eq.) and K_2CO_3 (31.5 mg, 228 µmol, 5.0 eq.). The reaction was stirred for 40 hours at 110 °C under protective atmosphere. Upon full conversion was observed (R_f 0.5 (H_2O:MeCN, 4:1, v:v)), the reaction mixture was concentrated and purified by flash column chromatography (10:90 MeOH:DCM → 67:33 MeOH:DCM) followed by reversed phase silica gel purification (95:5 H_2O:MeCN → 1:1 H_2O:MeCN) yielded the title compound (2.5 mg, 11 µmol, 24%) as a colorless solid. ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 3.91 (dd, *J* = 11.2, 3.5 Hz, 1H, H-6), 3.84 (dd, *J* = 8.8, 3.8 Hz, 1H, H-2), 3.73 (dd, *J* = 11.2, 6.6 Hz, 1H, H-6), 3.33 (dd, *J* = 10.2, 8.8 Hz, 1H, H-3), 3.21 (dd, *J* = 10.2, 10.2 Hz, 1H, H-4), 2.31 (dd, *J* = 8.5, 6.7 Hz, 2H, H-1’), 2.07 (dd, *J* = 6.6, 3.9 Hz, 1H, H-1), 1.93 – 1.85 (m, 1H, H-5), 1.83 (dd, *J* = 6.6, 0.9 Hz, 1H, H-7), 1.54 (tq, *J* = 13.1, 8.2

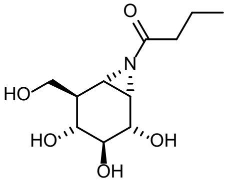
Hz, 2H, H-2’), 1.39 – 1.30 (m, 2H, H-3’), 0.90 (t, *J* = 7.4 Hz, 3H, H-4’); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 74.1 (C-3), 71.5 (C-2), 70.3 (C-4), 61.6 (C-6), 59.8 (C-1’), 44.4 (C-5), 44.3 (C-1), 40.6 (C-7), 30.8 (C-2’), 19.9 (C-3’), 13.3 (C-4’); HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{11}H_{22}NO_4$ 232.15433, found 232.15440.

***N*-Butyryl-1,2-dideoxy-1,2-azabicyclo[4.1.0]-carba-α-D-glucose (18).**



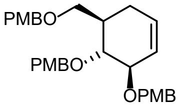
Compound **13** (8.0 mg, 50 µmol) was dissolved in MeOH (1.0 mL, 0.05 M) and cooled on ice. Subsequently, Et_3N (28 µL, 0.2 mmol, 4.0 eq.) and butyryl chloride (11 µL, 0.1 mmol, 2.0 eq.) were added respectively. Stirring continued for 30 minutes while the reaction mixture was kept on 0 °C. Upon full conversion was observed (R_f 0.5 (MeOH:DCM, 2:8, v:v)), the reaction mixture was quenched by adding sat. aq. $NaHCO_3$ (3.0 mL) and then concentrated under reduced pressure to afford the crude product. Flash column chromatography (0:100 MeOH:DCM → 10:90 MeOH:DCM) yielded the title compound (5.7 mg, 25 µmol, 50%) as a colorless oil. ^{1}H NMR (400 MHz, Acetone-d6, HH-COSY, HSQC): δ 4.51 (d, *J* = 4.6 Hz, 1H, 3-OH/6-OH), 4.28 (d, *J* = 3.6 Hz, 1H, 4-OH), 3.71 (d, *J* = 5.4 Hz, 1H, 3-OH/6-OH), 3.62 (m, 3H, H-3, H-6), 3.22 (ddd, *J* = 10.7, 7.9, 2.9 Hz, 1H, H-4), 2.77 (ddd, *J* = 5.9, 2.7, 1.5 Hz, 1H, H-1), 2.60 (d, *J* = 5.8 Hz, 1H, H-2), 2.37 (t, *J* = 7.3 Hz, 2H, 2’), 2.11 (ddd, *J* = 13.8, 3.6, 1.3 Hz, 1H, H-7), 1.71 – 1.49 (m, 4H, H-5, H-7, H-3’), 0.91 (t, *J* = 7.4 Hz, 3H, H-4’); ^{13}C NMR (101 MHz, Acetone-d6, HSQC): δ 185.8 (C-1’), 77.2 (C-4), 74.4 (C-3), 64.8 (C-6), 41.8 (C-2), 38.8 (C-2’), 37.7 (C-1), 36.4 (C-5), 27.9 (C-7), 19.0 (C-3’), 14.0 (C-4’); HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{11}H_{20}NO_4$ 230.1392, found 230.1387.

***N*-Butyryl-1,7-*epi*-cyclophellitol aziridine (8).**



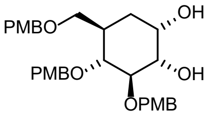
Compound **3** (5.0 mg, 29 µmol) was dissolved in anhydrous MeOH (1.0 mL, 0.03 M) under an inert atmosphere and cooled on ice. Subsequently, Et_3N (59 µL, 0.43 mmol, 15 eq.) and butyryl chloride (8.9 µL, 86 µmol, 3.0 eq.) were added respectively. Stirring continued for 1 hour while the reaction mixture was allowed to attain to room temperature. Upon full conversion was observed (R_f 0.2 (MeOH:DCM, 1:9, v:v)), the reaction mixture was quenched by adding sat. aq. $NaHCO_3$ (3.0 mL) and then concentrated under reduced pressure to afford the crude product. The residue was purified by reversed phase silica gel purification (95:5 H_2O:MeCN → 0:100 H_2O:MeCN) providing aziridine **8** (4.5 mg, 19 µmol, 64%) as colourless solid. ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 3.92 (dd, *J* = 11.3, 3.5 Hz, 1H, H-6), 3.86 (dd, *J* = 8.7, 3.3 Hz, 1H, H-2), 3.75 (dd, *J* = 11.3, 6.4 Hz, 1H, H-6), 3.40 (dd, *J* = 10.2, 8.7 Hz, 1H, H-3), 3.30 (dd, *J* = 10.0, 10.0 Hz, 1H, H-4), 3.10 (dd, *J* = 6.1, 3.3 Hz, 1H, H-1), 2.87 (dd, *J* = 6.1, 0.7 Hz, 1H, H-7), 2.49 (t, *J* = 7.4 Hz, 2H, H-2’), 2.04 (ddd, *J* = 9.8, 6.4, 3.4 Hz, 1H, H-5), 1.61 (sxt, *J* = 7.4 Hz, 2H, H-3’), 0.90 (t, *J* = 7.4 Hz, 3H, H-4’); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 189.8 (C-1’), 73.3 (C-3), 70.4 (C-2), 70.1 (C-4), 61.1 (C-6), 44.3 (C-5), 41.9 (C-1), 38.3 (C-7), 38.0 (C-2’), 18.2 (C-3’), 12.9 (C-4’); HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{11}H_{20}NO_5$ 246.13360, found 246.13349.

3,4,6-Tri-*O*-(4-methoxybenzyl)-carba-D-glucal (27).



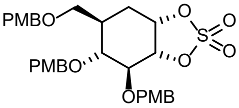
Compound **22** (7.7 g, 20 mmol) was dissolved in DMF (100 mL, 0.2 M) and cooled on ice. Subsequently, PMBCl (4.0 mL, 30 mmol, 1.5 eq.) and NaH (1.6 g, 40 mmol, 2.0 eq.) were added respectively. The mixture was allowed to attain to room temperature and stirred overnight. Upon full conversion was observed (R_f 0.4 (EtOAc:pentane, 3:7, v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (10:90 → 20:80; EtOAc:pentane) yielded the title compound (8.6 g, 17 mmol, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.32 – 7.14 (m, 6H, CH_{arom}), 6.91 – 6.78 (m, 6H, CH_{arom}), 5.79 – 5.69 (m, 1H, H-1), 5.64 (dd, *J* = 10.1, 1.9 Hz, 1H, H-2), 4.79 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.61 (m, 2H, CH_2 PMB), 4.53 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.42 (s, 2H, CH_2 PMB), 4.13 (ddd, *J* = 7.2, 3.6, 1.5 Hz, 1H, H-3), 3.79 (s, 9H, OMe), 3.66 – 3.50 (m, 3H, H-4, H-6), 2.26 – 2.18 (m, 2H, H-7), 2.09 – 1.98 (m, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 159.2, 159.2, 131.3, 131.0, 130.8 ($C_{q\text{-}arom}$), 129.7, 129.5, 129.2, 128.5 (C-1), 126.3 (C-2), 113.9, 113.9, 113.8 (CH_{arom}), 80.9 (C-3), 79.3 (C-4), 74.1, 72.8, 71.2 (CH_2 PMB), 70.3 (C-6), 55.4 (OCH_3), 39.4 (C-5), 29.0 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{31}H_{36}O_6Na$ 527.2410, found 527.2404.

3,4,6-Tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (28).



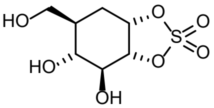
Compound **27** (8.1 g, 16 mmol) was dissolved in a mixture of acetonitrile:EtOAc (1:1, 320 mL, 0.05 M) and cooled on ice. in a second flask, $NaIO_4$ (5.1 gr, 29 mmol, 1.5 eq.) and $RuCl_3$ (232 mg, 1.12 mmol, 0.07 eq.) were dissolved in H_2O (90 mL) and was slowly added to the substrate solution. After 1 hour stirring at 0 °C, TLC confirmed full conversion (R_f 0.1 (EtOAc:pentane, 1:1, v:v)) and the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (50:50 → 70:30; EtOAc:pentane) yielded the title compound (7.8 g, 14.5 mmol, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.33 – 7.11 (m, 6H, CH_{arom}), 6.98 – 6.77 (m, 6H, CH_{arom}), 4.93 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.76 (d, *J* = 10.4 Hz, 1H, C*H*H PMB), 4.59 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.49 (d, *J* = 10.4 Hz, 1H, CH*H* PMB), 4.43 (d, *J* = 11.6 Hz, 1H, C*H*H PMB), 4.38 (d, *J* = 11.6 Hz, 1H, CH*H* PMB), 4.05 (d, *J* = 3.3 Hz, 1H, H-1), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.73 (dd, *J* = 9.1, 4.1 Hz, 1H, H-6), 3.67 (dd, *J* = 9.2, 9.2 Hz, 1H, H-3), 3.50 – 3.42 (m, 2H, H-2, H-4), 3.38 (dd, *J* = 9.1, 2.6 Hz, 1H, H-6), 2.36 (d, *J* = 2.2 Hz, 1H, 2-OH), 2.34 (dd, *J* = 1.7, 1.7 Hz, 1H, 1-OH), 2.14 (dddd, *J* = 16.8, 10.3, 3.2, 3.2 Hz, 1H, H-5), 1.88 (ddd, *J* = 14.7, 3.7, 3.7 Hz, 1H, H-7), 1.64 (ddd, *J* = 12.7, 2.3, 2.3 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 159.3, 159.3, 131.0, 130.9, 130.7 ($C_{q\text{-}arom}$), 129.7, 129.7, 129.4, 114.3, 113.9, 113.9 (CH_{arom}), 83.1 (C-3), 81.0 (C-4), 74.9, 74.6 (CH_2 PMB), 74.4 (C-2), 72.9 (CH_2 PMB), 69.4 (C-6), 68.3 (C-1), 55.4, 55.4 (OMe), 37.5 (C-5), 30.5 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{31}H_{38}O_8Na$ 561.2464, found 561.2459.

1,2-*O*-Sulfate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (29).



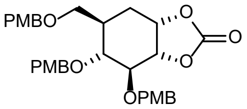
Compound **28** (170 mg, 0.3 mmol) was dissolved in anhydrous DCM (15 mL, 0.02 M) and cooled on ice. Subsequently, Et_3N (166 µL, 1.2 mmol, 4.0 eq.) and $SOCl_2$ (77 µL, 1.05 mmol, 3.5 eq.) were added respectively. The reaction was stirred for 1 hour during which the solution was allowed to attain to room temperature. Upon full conversion was observed (R_f 0.3 (EtOAc:pentane, 3:7, v:v)), the reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. The crude product was dissolved in acetonitrile:H_2O (1:1, 3.0 mL, 0.1 M) and cooled on ice. Subsequently, $RuCl_3$ (6.0 mg, 30 µmol, 0.1 eq.) and $NaIO_4$ (77 mg, 0.36 mmol, 1.2 eq.) were dissolved in H_2O (0.5 mL) and slowly added to the substrate solution. After 15 minutes, the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ solution and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (20:80 → 30:70; EtOAc:pentane) yielded the title compound (83 mg, 0.14 mmol, 46% over two steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.29 – 7.09 (m, 6H, CH_{arom}), 6.89 – 6.80 (m, 6H, CH_{arom}), 5.18 (ddd, *J* = 5.3, 2.9, 2.9 Hz, 1H, H-1), 4.82 – 4.69 (m, 4H, H-2, C*H*H PMB, C*H*H PMB, CH*H* PMB), 4.43 (d, *J* = 10.5 Hz, 1H, CH*H* PMB), 4.40 – 4.33 (m, 2H, C*H*H PMB, CH*H* PMB), 4.10 (dd, *J* = 9.6, 8.1 Hz, 1H, H-3), 3.80 (s, 6H, OMe, OMe), 3.78 (s, 3H, OMe), 3.71 (dd, *J* = 9.2, 3.7 Hz, 1H, H-6), 3.41 (dd, *J* = 9.9, 9.9 Hz, 1H, H-4), 3.37 (dd, *J* = 9.1, 2.4 Hz, 1H, H-6), 2.30 (ddd, *J* = 15.7, 2.9, 2.9 Hz, 1H, H-7), 2.07 – 1.92 (m, 2H, H-5, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.5, 159.4, 130.4, 130.1, 130.0 ($C_{q\text{-}arom}$), 129.9, 129.8, 129.6, 129.5, 114.0, 114.0, 113.9, 113.9 (CH_{arom}), 88.4 (C-2), 82.4 (C-3), 82.0 (C-1), 77.8 (C-4), 75.2, 75.0, 73.0 (CH_2 PMB), 68.2 (C-6), 55.4, 55.4 (OMe), 36.5 (C-5), 27.4 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{31}H_{36}O_{10}SNa$ 623.1927, found 623.1921.

1,2-*O*-Sulfate-carba-α-D-glucose (14).



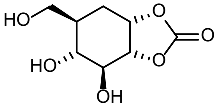
Compound **29** (27.3 mg, 46 µmol) was dissolved in MeOH (5.0 mL, 0.01 M) followed by the addition of $Pd(OH)_2$/C (20% loading, 105 mg, 0.15 mmol, 3.0 eq.). the reaction mixture was kept under 50 atm H_2 atmosphere and stirred for 16 hours. Upon full conversion was observed (R_f 0.2 (MeOH:DCM, 2:8, v:v)), the mixture was filtered over celite and concentrated to yield the crude product. Flash column chromatography (5:95 → 10:90; MeOH:DCM) yielded the title compound (7.5 mg, 31 µmol, 68%) as a colorless oil. ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 5.54 – 5.49 (m, 1H, H-1), 5.02 (dd, *J* = 8.5, 4.8 Hz, 1H, H-2), 4.00 (dd, *J* = 9.9, 8.5 Hz, 1H, H-3), 3.76 (m, 2H, H-6), 3.42 (dd, *J* = 10.1, 10.1 Hz, 1H, H-4), 2.47 (dd, *J* = 12.8, 2.5 Hz, 1H, H-7), 1.95 – 1.83 (m, 2H, H-5, H-7); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 88.9 (C-2), 83.9 (C-1), 74.2 (C-3), 70.3 (C-4), 61.0 (C-6), 37.6 (C-5), 26.3 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_7H_{12}O_7SNa$ 263.0201, found 263.0196.

1,2-*O*-Carbonate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (30).



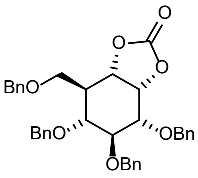
Compound **28** (76.0 mg, 0.14 mmol) was dissolved in DCM (0.7 mL, 0.2 M) and cool on ice. Subsequently, pyridine (50 µL, 0.64 mmol, 4.5 eq.) and triphosgene (27.1 mg, 84 µmol, 0.6 eq.) were added respectively. The reaction was allowed to attain to room temperature and stirred for 1.5 hours. Upon full conversion was observed (R_f 0.8 (EtOAc:pentane, 4:6, v:v)), the mixture was quenched by the addition of sat. aq. $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (30:70 → 40:60; EtOAc:pentane) yielded the title compound (68.1 mg, 0.12 mmol, 86%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.30 – 7.09 (m, 6H, CH_{arom}), 6.91 – 6.81 (m, 6H, CH_{arom}), 4.86 (ddd, *J* = 7.1, 3.5, 3.5 Hz, 1H, H-1), 4.74 – 4.68 (m, 2H, C*H*H PMB, C*H*H PMB), 4.67 – 4.60 (m, 2H, H-2, CH*H* PMB), 4.42 (d, *J* = 10.7 Hz, 1H, CH*H* PMB), 4.40 – 4.32 (m, 2H, C*H*H PMB, CH*H* PMB), 3.80 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.70 (dd, *J* = 8.4, 6.4 Hz, 1H, H-3), 3.62 (dd, *J* = 9.1, 4.1 Hz, 1H, H-6), 3.46 (dd, *J* = 8.7, 8.7 Hz, 1H, H-4), 3.37 (dd, *J* = 9.1, 3.1 Hz, 1H, H-6), 2.21 (ddd, *J* = 15.3, 3.7, 3.7 Hz, 1H, H-7), 1.98 (dddd, *J* = 12.3, 7.4, 3.7, 3.7 Hz, 1H, H-5), 1.89 (ddd, *J* = 15.6, 11.8, 3.9 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 159.4, 154.6 (C=O), 130.5, 130.3, 129.9 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.4, 114.0, 113.9, 113.9 (CH_{arom}), 82.4 (C-3), 81.1 (C-2), 76.8 (C-4), 76.4 (C-1), 74.2, 73.8, 72.9 (CH_2 PMB), 69.4 (C-6), 55.4, 55.4 (OMe), 36.2 (C-5), 27.3 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{32}H_{36}O_9Na$ 587.2257, found 587.2252.

1,2-*O*-Carbonate-carba-α-D-glucose (15).



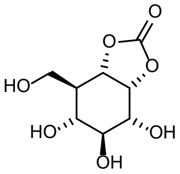
Compound **30** (113 mg, 0.2 mmol) was dissolved in MeOH (5.0 mL, 0.02 M) followed by the addition of Pd/C (5% loading, 43 mg, 20 µmol, 0.1 eq.). the reaction mixture was kept under 1 atm H_2 atmosphere and stirred for 16 hours. Upon full conversion was observed (R_f 0.2 (MeOH:DCM, 2:8, v:v)), the mixture was filtered over celite and concentrated *in vacuo* to yield the title compound (34 mg, 0.17 mmol, 83%) as a colorless oil. ^1H NMR (600 MHz, MeOD, HH-COSY, HSQC): δ 4.87 (ddd, *J* = 6.3, 3.4, 2.4 Hz, 1H, H-1), 4.49 (ddd, *J* = 7.2, 6.5, 0.6 Hz, 1H, H-2), 3.68 (dd, *J* = 10.9, 3.4 Hz, 1H, H-6), 3.61 (dd, *J* = 10.9, 5.4 Hz, 1H, H-6), 3.45 (dd, *J* = 9.5, 7.4 Hz, 1H, H-3), 3.22 (dd, *J* = 9.7, 9.7 Hz, 1H, H-4), 2.24 (dd, *J* = 11.9, 3.1 Hz, 1H, H-7), 1.73 – 1.65 (m, 2H, H-5, H-7); ^{13}C NMR (151 MHz, MeOD, HSQC): δ 157.1 (C=O), 83.5 (C-2), 78.7 (C-1), 77.6 (C-3), 72.2 (C-4), 63.5 (C-6), 39.8 (C-5), 27.9 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_8H_{12}O_6Na$ 227.0532, found 227.0526.

1,7-*Epi*-carbonate-2,3,4,6-tetra-*O*-benzyl-cyclophellitol alkane (32).



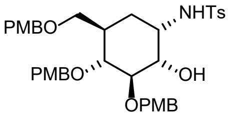
Compound **31** (34 mg, 61 µmol) was dissolved in DCM (1.0 mL, 0.06 M) and cooled on ice. Subsequently, pyridine (22 µL, 0.27 mmol, 4.5 eq.) and triphosgene (11 mg, 40 µmol, 0.6 eq.) were added respectively. The reaction was allowed to attain to room temperature and stirred for 1.5 hours. Upon full conversion was observed (R_f 0.8 (EtOAc:pentane, 3:7, v:v)), the mixture was quenched by the addition of sat. aq. $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted with EtOAc (3x) followed by washing the combined organic layers with H_2O, sat. aq. $NaHCO_3$ and brine respectively. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Flash column chromatography (10:90 → 20:80; EtOAc:pentane) yielded the title compound (32 mg, 55 µmol, 90%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.38 – 7.16 (m, 20H, CH_{arom}), 5.00 (dd, *J* = 9.3, 8.1 Hz, 1H, H-7), 4.75 (dd, *J* = 8.1, 3.5 Hz, 1H, H-1), 4.69 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.63 (d, *J* = 9.8 Hz, 1H, C*H*H Bn), 4.61 (d, *J* = 10.7 Hz, 1H, CH*H* Bn), 4.52 – 4.38 (m, 5H, C*H*H Bn, C*H*H Bn, CH*H* Bn, CH*H* Bn, CH*H* Bn), 3.87 (dd, *J* = 3.3, 3.3 Hz, 1H, H-2), 3.86 – 3.81 (m, 2H, H-3, H-6), 3.62 (dd, *J* = 9.4, 2.3 Hz, 1H, H-6), 3.57 (dd, *J* = 12.3, 5.5 Hz, 1H, H-4), 2.55 (dddd, *J* = 11.8, 9.3, 2.3, 2.3 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 154.8 (C=O), 138.2, 138.0, 137.4, 137.2 ($C_{q\text{-}arom}$), 128.7, 128.6, 128.5, 128.3, 128.3, 128.2, 128.1, 127.9, 127.9, 127.8 (CH_{arom}), 81.8 (C-3), 76.4 (C-4), 75.1 (C-2), 74.6 (C-1), 74.3 (C-7), 73.8, 73.6, 73.4, 72.6 (CH_2 Bn), 65.4 (C-6), 42.2 (C-5); HRMS (ESI) m/z: [$M+Na^+$] calcd for $C_{36}H_{36}O_7Na$ 603.2359, found 603.2353.

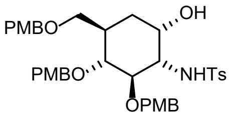
1,7-*Epi*-carbonate-cyclophellitol alkane (9).



Compound **32** (23 mg, 40 µmol) was dissolved in MeOH (1.0 mL, 0.02 M) followed by the addition of $Pd(OH)_2/C$ (20% loading, 6.0 mg, 8.0 µmol, 0.2 eq.). the reaction mixture was kept under 1 atm H_2 atmosphere and stirred for 16 hours. Upon full conversion was observed (R_f 0.5 (MeOH:DCM, 3:7, v:v)), the mixture was filtered over celite and concentrated *in vacuo* to yield the title compound (8.4 mg, 40 µmol, quant.) as a colorless oil. ^1H NMR (400 MHz, D_2O, HH-COSY, HSQC): δ 5.07 (dd, *J* = 6.2, 4.0 Hz, 1H, H-1), 4.94 (dd, *J* = 9.2, 6.2 Hz, 1H, H-7), 3.88 (dd, *J* = 11.8, 3.9 Hz, 1H, H-6), 3.80 (dd, *J* = 9.6, 4.1 Hz, 1H, H-2), 3.75 (dd, *J* = 11.8, 3.0 Hz, 1H, H-6), 3.63 (dd, *J* = 9.4, 9.4 Hz, 1H, H-3), 3.35 (dd, *J* = 11.5, 9.2 Hz, 1H, H-4), 1.94 – 1.82 (m, 1H, H-5); ^{13}C NMR (101 MHz, D_2O, HSQC): δ 156.4 (C=O), 79.6 (C-1), 76.6 (C-7), 73.3 (C-3), 69.1 (C-2), 67.4 (C-4), 57.7 (C-6), 45.4 (C-5); HRMS (ESI) m/z: [$M+H^+$] calcd for $C_8H_{13}O_7$ 221.0661, found 221.0656.

1-Deoxy-1-(*p*-toluenesulfonamido)-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (33) and 2-Deoxy-2-(*p*-toluenesulfonamido)-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (34).



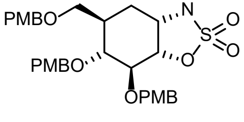


The title compounds were prepared according to a modified literature procedure.[43] Compound **27** (6.9 gr, 13.8 mmol) was dissolved in $CHCl_3:H_2O$ (1:1 v/v; 280 mL, 0.05 M), after which were added chloramine-T trihydrate (7.8 gr, 27.6 mmol, 2.0 eq.), benzyltriethylammonium chloride (188 mg, 0.83 mmol, 6 mol%) and potassium osmate (262 mg, 0.71 mmol, 5 mol%). The biphasic reaction mixture was heated to 60 °C and stirred vigorously overnight. Upon full conversion was observed (R_f 0.6 and 0.4 for **33** and **34** respectively (EtOAc:Pentane, 1:1 v:v)), sat. aq. $Na_2S_2O_3$ was added, and the mixture was heated to 60 °C for 0.5-1 hour to effectively quench the unreacted chloramine-T. The organic layer was separated from the aqueous layer, after which the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed 3x with 1 wt% aq. NaOH, once with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (dry loading on Celite, 30:70 → 50:50; EtOAc:pentane) yielded target compounds **33** (5.1 gr, 7.4 mmol, 54%) as a yellow oil and **34** (2.9 gr, 4.25 mmol, 31%) as an off-white solid, giving an overall yield of 85%.

Analytical data for **33**: ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HH-NOESY, HSQC): δ 7.76 – 7.70 (m, 2H, CH$_{arom}$), 7.29 – 7.12 (m, 8H, CH$_{arom}$), 6.91 – 6.80 (m, 6H, CH$_{arom}$), 4.97 (d, *J* = 3.2 Hz, 1H, 1-NH), 4.76 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.63 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.48 (m, 2H, CH*H* PMB, CH*H* PMB), 4.36 (m, 2H, C*H*H PMB, CH*H* PMB), 3.81 (s, 3H, OMe), 3.80 (s, 6H, OMe, OMe), 3.65 (dd, *J* = 9.2, 4.5 Hz, 1H, H-6), 3.55 (dd, *J* = 7.8, 7.8 Hz, 1H, H-3), 3.50 (dd, *J* = 8.1, 8.1 Hz, 1H, H-4), 3.45 (ddd, *J* = 7.8, 3.9, 3.9 Hz, 1H, H-2), 3.42 (dddd, *J* = 5.0, 3.5, 3.2, 3.2 Hz, 1H, H-1), 3.33 (dd, *J* = 9.2, 3.7 Hz, 1H, H-6), 2.69 (d, *J* = 3.3 Hz, 1H, 2-OH), 2.40 (s, 3H, Me Ts), 2.12 (ddddd, *J* = 10.0, 8.2, 4.2, 4.2, 3.2 Hz, 1H, H-5), 2.07 (ddd, *J* = 14.4, 5.0, 3.9 Hz, 1H, H-7), 1.51 (ddd, *J* = 13.9, 10.2, 3.1 Hz, 1H, H-7); ^{13}C NMR (126 MHz, CDCl$_3$, HSQC): δ 159.5, 159.4, 159.2 , 143.5, 136.7, 130.6, 130.4, 130.4 (C$_{q\text{-}arom}$), 129.8, 129.5, 129.4, 129.3, 127.4, 114.2, 113.9, 113.9 (CH$_{arom}$), 81.7 (C-3), 79.2 (C-4), 74.3, 73.9, 72.8 (CH$_2$ PMB), 71.9 (C-2), 69.3 (C-6), 55.4, 55.4, 55.3 (OMe), 51.8 (C-1), 37.4 (C-5), 27.5 (C-7), 21.6 (Me Ts); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{38}H_{45}NO_9SNa$ 714.2713, found 714.2707.

Analytical data for **34**: ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HH-NOESY, HSQC): δ 7.68 – 7.62 (m, 2H, CH$_{arom}$), 7.27 – 7.15 (m, 4H, CH$_{arom}$), 7.18 – 7.06 (m, 4H, CH$_{arom}$), 6.92 – 6.76 (m, 6H, CH$_{arom}$), 4.76 (d, *J* = 4.2 Hz, 1H, 2-NH), 4.71 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.64 (d, *J* = 10.5 Hz, 1H, C*H*H PMB), 4.51 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.43 – 4.28 (m, 3H, CH*H* PMB, C*H*H PMB, CH*H* PMB), 4.15 – 4.10 (m, 1H, H-1), 3.83 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.67 (dd, *J* = 9.0, 4.2 Hz, 1H, H-6), 3.55 (dd, *J* = 9.7, 8.6 Hz, 1H, H-3), 3.40 (dd, *J* = 10.1, 8.6 Hz, 1H, H-4), 3.34 (dd, *J* = 9.0, 2.9 Hz, 1H, H-6), 2.95 (ddd, *J* = 9.7, 4.4, 2.9 Hz, 1H, H-2), 2.41 (s, 3H, Me Ts), 2.26 (d, *J* = 3.2 Hz, 1H, 1-OH), 2.13 – 2.04 (m, 1H, H-5), 1.81 (ddd, *J* = 14.6, 4.0, 4.0 Hz, 1H, H-7), 1.57 (ddd, *J* = 14.9, 12.2, 2.7 Hz, 1H, H-7); ^{13}C NMR (126 MHz, CDCl$_3$, HSQC): δ 159.6, 159.3, 159.3, 143.7, 136.5, 130.6, 130.5, 130.3 (C$_{q\text{-}arom}$), 129.9, 129.6, 129.6, 129.5, 127.3, 114.3, 113.9, 113.9 (CH$_{arom}$), 81.1 (C-4), 79.7 (C-3), 74.5, 74.5, 72.9 (CH$_2$ PMB), 69.4 (C-6), 66.9 (C-1), 59.7 (C-2), 55.5, 55.4, 55.4 (OMe), 37.2 (C-5), 31.3 (C-7), 21.7 (Me Ts); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{38}H_{45}NO_9SNa$ 714.2713, found 714.2707.

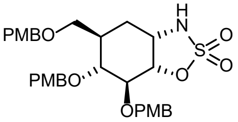
1,2-(*N*-(*p*-tolylsulfonyl),*O*)-sulfamidate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (S4).



Compound **33** (252 mg, 0.36 mmol) was co-evaporated with toluene and dissolved in anhydrous DCM (3.6 mL, 0.1 M). Triethylamine (0.2 mL, 1.4 mmol, 4.0 eq.) was added and the solution was cooled to –78 °C. SO$_2$Cl$_2$ (36 μL, 0.44 mmol, 1.2 eq.) was added dropwise, and the reaction mixture was allowed to slowly warm up to 5 °C over a period of 2-3 hours. Upon full conversion was observed (R$_f$ 0.55 (EtOAc:pentane 4:6 v:v)), the reaction was quenched with sat. aq. NaHCO$_3$. The mixture was then extracted with EtOAc (3x), after which the combined organic layers were washed twice with brine, dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (20:80 → 40:60; EtOAc:pentane) yielded title compound **31** as a yellow oil (275 mg, 0.36 mmol, quant.). ^{1}H NMR (400 MHz, CDCl$_3$, HH-COSY, HSQC): δ 7.85 – 7.79 (m, 2H, CH$_{arom}$), 7.32 – 7.27 (m, 2H, CH$_{arom}$), 7.25 – 7.19 (m, 4H, CH$_{arom}$), 7.15 – 7.10 (m, 2H, CH$_{arom}$), 6.90 – 6.81 (m, 6H, CH$_{arom}$), 4.75 – 4.68 (m, 3H, C*H*H PMB, CH*H* PMB, C*H*H PMB), 4.55 (dd, *J* = 7.5, 6.0

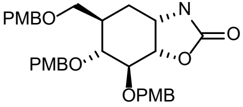
Hz, 1H, H-2), 4.40 (d, *J* = 10.8 Hz, 1H, CH*H* PMB), 4.36 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.27 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.15 – 4.07 (m, 2H, H-1, H-3), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.59 (dd, *J* = 9.2, 3.2 Hz, 1H, H-6), 3.45 (dd, *J* = 9.5, 9.5 Hz, 1H, H-4), 3.32 (dd, *J* = 9.2, 2.6 Hz, 1H, H-6), 2.44 (s, 3H, Me Ts), 2.38 (ddd, *J* = 15.0, 5.1, 5.1 Hz, 1H, H-7), 2.01 – 1.93 (m, 1H, H-5), 1.87 (ddd, *J* = 14.4, 9.3, 3.7 Hz, 1H, H-7); ^{13}C NMR (214 MHz, CDCl$_3$, HSQC): δ 159.5, 159.4, 146.3, 132.7, 130.4, 130.3 (C$_{\text{q-arom}}$), 130.1 (CH$_{\text{arom}}$), 129.9 (C$_{\text{q-arom}}$), 129.8, 129.6, 129.5, 129.0, 114.0, 113.9, 113.9 (CH$_{\text{arom}}$), 84.0 (C-2), 81.0 (C-1), 76.8 (C-4), 74.7, 74.5, 72.9 (CH$_2$ PMB), 69.4 (C-6), 59.0 (C-3), 55.4, 55.4, 55.4 (OMe), 36.7 (C-5), 27.7 (C-7), 21.8 (Me Ts); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{38}H_{43}NO_{11}S_2Na$ 776.2175, found 776.2170.

1,2-(*N*,*O*)-Sulfamidate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (35).



An oven-dried round-bottom flask was equipped with a glass magnetic stirring bar. Naphthalene (4.4 gr, 34.4 mmol, 12 eq.) was added and dissolved in anhydrous THF (57 mL, 0.05 M), after which freshly cut sodium (656 mg, 28.5 mmol, 10 eq.) was added under a N$_2$ atmosphere. The reaction mixture was sonicated for 30 minutes to obtain a dark-green sodium naphthalenide solution which was subsequently cooled to –78 °C. Compound **S4** (1.97 gr, 2.85 mmol) was co-evaporated with toluene 3x and dissolved in anhydrous THF (2 mL) before its dropwise addition to the cooled sodium naphthalenide solution and stirring continued for 30 minutes. Upon full conversion was observed (R$_f$ 0.3 (EtOAc:pentane 1:1 v:v)), the reaction was quenched at –78 °C with sat. aq. NH$_4$Cl until full discoloration of the mixture was observed. The product was allowed to attain to room temperature and extracted with EtOAc (3x), after which the combined organic layers were washed with sat. aq. NaHCO$_3$, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (30:70 → 50:50; EtOAc:pentane) yielded the title compound **35** as a yellow oil (1.3 gr, 2.15 mmol, 75%). ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HSQC): δ 7.31 – 7.11 (m, 6H, CH$_{\text{arom}}$), 6.91 – 6.81 (m, 6H, CH$_{\text{arom}}$), 4.77 (m, 2H, C*H*H PMB, CH*H* PMB), 4.73 – 4.68 (m, 3H, C*H*H PMB, 1-NH, H-2), 4.42 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.39 – 4.33 (m, 2H, C*H*H PMB, CH*H* PMB), 4.24 (dddd, *J* = 6.5, 4.4, 4.4 3.2 Hz, 1H, H-1), 4.06 (dd, *J* = 9.4, 7.8 Hz, 1H, H-3), 3.80 (s, 6H, OMe, OMe), 3.79 (s, 3H, OMe), 3.58 (dd, *J* = 9.1, 4.6 Hz, 1H, H-6), 3.39 (dd, *J* = 9.0, 2.7 Hz, 1H, H-6), 3.36 (dd, *J* = 9.6, 9.6 Hz, 1H, H-4), 2.03 (ddd, *J* = 14.5, 3.3, 3.3 Hz, 1H, H-7), 2.03 – 1.94 (m, 1H, H-5), 1.81 (ddd, *J* = 15.2, 11.5, 4.2 Hz, 1H, H-7); ^{13}C NMR (101 MHz, CDCl$_3$, HSQC): δ 159.5, 159.4, 159.4, 130.4, 130.2 (C$_{\text{q-arom}}$), 129.9, 129.7, 129.5, 114.0, 113.9, 113.9 (CH$_{\text{arom}}$), 88.6 (C-2), 82.0 (C-3), 77.8 (C-4), 75.0, 74.8, 73.0 (CH$_2$ PMB), 69.1 (C-6), 55.4, 55.4 (OMe, OMe, OMe), 36.7 (C-5), 26.9 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{31}H_{37}NO_9SNa$ 622.2087, found 622.2081.

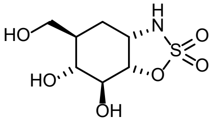
1,2-(*N*,*O*)-Carbamate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (36).



Compound **33** (2.0 g, 2.9 mmol) was co-evaporated with toluene and dissolved in anhydrous DCM (20 mL, 0.15 M) and cooled on ice. Pyridine (1.1 mL, 13 mmol, 4.5 eq.) and triphosgene (0.52 g, 1.7 mmol, 0.6 eq.) were added and after 10 minutes, the ice bath was removed, after which the reaction mixture was stirred at room temperature for 3 h. Upon full conversion was observed, the reaction was quenched with sat. aq. NaHCO$_3$. The mixture was extracted with EtOAc (3x), after which the combined organic layers were washed twice with brine, dried over

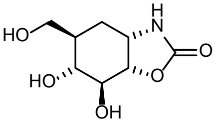
$MgSO_4$, filtered, and concentrated *in vacuo* to obtain the crude *N*-tosyl protected cyclic carbamate. An oven-dried round-bottom flask was equipped with a glass magnetic stirring bar. Naphthalene (4.5 g, 35 mmol, 12 eq.) was added and dissolved in anhydrous THF (60 mL, 0.05 M), after which freshly cut sodium (0.67 g, 29 mmol, 10 eq.) was added under a N_2 atmosphere. The reaction mixture was then sonicated for 10-15 minutes to obtain a dark-green Na/naphthalenide solution. The mixture was cooled to –78 °C and the crude *N*-Ts protected cyclic carbamate intermediate was co-evaporated with toluene (3x) and dissolved in anhydrous THF (3 mL) before its dropwise addition to the cooled Na/naphthalenide solution and stirred for 30 minutes. Upon full conversion was observed (R_f 0.2 (EtOAc:pentane 4:6 v:v)), the reaction was quenched at –78 °C with sat. aq. NH_4Cl until full discoloration of the mixture was observed. The product was allowed to warm up to room temperature and extracted with EtOAc (3x), after which the combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. flash column chromatography (60:40 → 80:20; EtOAc:pentane) provided title compound **36** as a yellow oil (1.2 gr, 2.1 mmol, 71% over 2 steps). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.32 – 7.12 (m, 6H, CH_{arom}), 6.85 (m, 6H, CH_{arom}), 5.57 (bs, 1H, 1-NH), 4.78 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.75 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.67 (d, *J* = 10.8 Hz, 1H, CH*H* PMB), 4.57 (dd, *J* = 7.1, 7.1 Hz, 1H, H-2), 4.41 (d, *J* = 10.7 Hz, 1H, CH*H* PMB), 4.39 – 4.32 (m, 2H, C*H*H PMB, CH*H* PMB), 4.14 (ddd, *J* = 8.0, 3.8, 3.8 Hz, 1H, H-1), 3.81 – 3.73 (m, 10H, OMe, OMe, OMe, H-3), 3.55 (dd, *J* = 9.0, 4.8 Hz, 1H, H-6), 3.40 (dd, *J* = 6.2, 2.7 Hz, 1H, H-6), 3.38 (dd, *J* = 6.7, 6.7 Hz, 1H, H-4), 2.00 (ddddd, *J* = 8.7, 8.7, 4.1, 4.1, 4.1 Hz, 1H, H-5), 1.91 (ddd, *J* = 15.2, 4.0, 4.0 Hz, 1H, H-7), 1.73 (ddd, *J* = 15.4, 11.2, 4.2 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7 (C=O), 159.3, 159.3, 159.3, 130.7, 130.4, 130.4 ($C_{q\text{-}arom}$), 129.7, 129.6, 129.4, 113.9, 113.9, 113.8 (CH_{arom}), 83.6 (C-3), 81.9 (C-2), 77.7 (C-4), 74.3, 74.0, 72.9 (CH_2 PMB), 69.8 (C-6), 55.4, 55.4 (OMe PMB), 52.1 (C-1), 36.5 (C-5), 28.3 (C-7); HRMS (ESI) m/z: [M+Na^+] calcd for $C_{32}H_{37}NO_8Na$ 586.2417, found 586.2411.

1,2-(*N*,*O*)-Sulfamidate-carba-α-D-glucose (15).



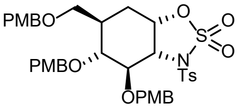
Compound **35** (26.4 mg, 44 µmol) was dissolved in DCM (1.5 mL, 0.03 M) and cooled on ice. Triethylsilane (42 µL, 0.26 mmol, 5.9 eq.) and TFA (34 µL, 0.44 mmol, 10 eq.) were added and the reaction mixture was stirred for 0.5-1 hour. Upon full conversion was observed (R_f 0.2 (MeOH/DCM 1:9 v:v), the reaction mixture was concentrated to dryness. Flash column chromatography (neutralized SiO_2, dry loading on Celite; (0:100 → 10:90; MeOH:DCM) and lyophilization yielded title compound **15** as a colorless transparent film (9.9 mg, 41.4 µmol, 94%). ^1H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 4.55 (dd, *J* = 8.4, 5.7 Hz, 1H, H-2), 4.22 (ddd, *J* = 5.7, 4.5, 2.4 Hz, 1H, H-1), 3.86 (dd, *J* = 9.8, 8.4 Hz, 1H, H-3), 3.73 (dd, *J* = 10.9, 3.8 Hz, 1H, H-6), 3.65 (dd, *J* = 10.9, 5.9 Hz, 1H, H-6), 3.22 (dd, *J* = 10.5, 9.7 Hz, 1H, H-4), 2.08 (ddd, *J* = 15.3, 3.9, 2.4 Hz, 1H, H-7), 1.94 – 1.83 (m, 1H, H-5), 1.70 (ddd, *J* = 15.4, 12.7, 4.5 Hz, 1H, H-7); ^{13}C NMR (126 MHz, MeOD, HSQC): δ 90.0 (C-2), 75.8 (C-3), 73.0 (C-4), 63.4 (C-6), 56.5 (C-1), 39.5 (C-5), 27.5 (C-7); HRMS (ESI) m/z: [M+Na^+] calcd for $C_7H_{13}NO_6SNa$ 262.0361, found 262.0356.

1,2-(*N*,*O*)-Carbamate-carba-α-D-glucose (20).



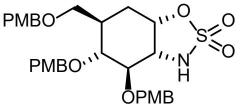
Compound **36** (86.1 mg, 0.15 mmol) was dissolved in DCM (2.0 mL, 0.08 M) and cooled on ice. TES (0.15 mL, 0.94 mmol, 6.0 eq.) and TFA (0.12 mL, 1.6 mmol, 10 eq.) were added and the reaction mixture was stirred for 1 h. Upon full conversion was observed (R_f 0.2 (acetone)), the reaction mixture was concentrated to dryness using a water aspirator. Flash column chromatography (neutralized SiO_2, dry loading on Celite; 10:90 → 90:10; acetone:DCM) yielded the title compound **20** as a white brittle foam (20.3 mg, 100 μmol, 67%). ^{1}H NMR (400 MHz, MeOD, HH-COSY, HSQC): δ 4.36 (dd, *J* = 7.3, 7.3 Hz, 1H, H-2), 4.16 (ddd, *J* = 7.2, 4.3, 2.8 Hz, 1H, H-1), 3.75 (dd, *J* = 10.8, 3.9 Hz, 1H, H-6), 3.63 (dd, *J* = 10.8, 6.1 Hz, 1H, H-6), 3.54 (dd, *J* = 9.6, 7.3 Hz, 1H, H-3), 3.22 (dd, *J* = 9.8, 9.8 Hz, 1H, H-4), 2.03 (ddd, *J* = 15.0, 3.4, 3.4 Hz, 1H, H-7), 1.77 (ddddd, *J* = 12.0, 10.1, 6.1, 4.0, 4.0 Hz, 1H, H-5), 1.58 (ddd, *J* = 15.0, 12.0, 4.4 Hz, 1H, H-7); ^{13}C NMR (101 MHz, MeOD, HSQC); δ 162.3 (C=O), 83.3 (C-2), 77.7 (C-3), 72.7 (C-4), 63.8 (C-6), 53.7 (C-1), 39.8 (C-5), 28.3 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_8H_{13}NO_5Na$ 226.0691, found 226.0686.

1,2-(*O*,*N*-(*p*-tolylsulfonyl))-sulfamidate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (S5).



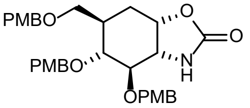
Compound **34** (246 mg, 0.36 mmol) was co-evaporated with toluene and dissolved in anhydrous DCM (3.6 mL, 0.1 M). Triethylamine (0.2 mL, 1.4 mmol, 4.0 eq.) was added, and the solution was cooled to –78 °C. SO_2Cl_2 (35 μL, 0.43 mmol, 1.2 eq.) was added dropwise, and the reaction mixture was allowed to slowly warm up to 5 °C over a period of 2-3 hours. Upon full conversion was observed (R_f 0.5 (EtOAc:pentane 4:6 v:v)), the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was then extracted with EtOAc (3x), after which the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (30:70 → 40:60; EtOAc:pentane) yielded title compound **32** as an off-white foam (270 mg, 0.36 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.98 – 7.91 (m, 2H, CH_{arom}), 7.44 – 7.31 (m, 4H, CH_{arom}), 7.18 – 7.09 (m, 4H, CH_{arom}), 6.91 – 6.80 (m, 6H, CH_{arom}), 4.99 (d, *J* = 9.8 Hz, 1H, C*H*H PMB), 4.81 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.78 (d, *J* = 9.9 Hz, 1H, CH*H* PMB), 4.43 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.36 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H, H-1), 4.33 – 4.29 (m, 2H, C*H*H PMB, CH*H* PMB), 4.14 (dd, *J* = 8.9, 3.9 Hz, 1H, H-2), 4.06 (dd, *J* = 9.1, 9.1 Hz, 1H, H-3), 3.81 – 3.80 (m, 6H, OMe, OMe), 3.78 (s, 3H, OMe), 3.67 (dd, *J* = 9.1, 3.8 Hz, 1H, H-6), 3.43 (dd, *J* = 10.5, 9.4 Hz, 1H, H-4), 3.30 (dd, *J* = 9.1, 2.6 Hz, 1H, H-6), 2.45 (s, 3H, Me Ts), 2.07 (ddd, *J* = 15.7, 3.0, 3.0 Hz, 1H, H-7), 1.99 (ddddd, *J* = 14.0, 10.3, 3.4, 3.4, 3.4 Hz, 1H, H-5), 1.77 (ddd, *J* = 15.8, 12.7, 3.1 Hz, 1H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 159.4, 159.4, 146.1, 134.3, 130.6 ($C_{q\text{-}arom}$), 130.5 (CH_{arom}), 130.2 ($C_{q\text{-}arom}$), 130.1, 129.4, 129.4, 129.1, 113.9, 113.9, 113.9 (CH_{arom}), 82.6 (C-1), 81.9 (C-3), 78.7 (C-4), 76.4, 75.0, 72.9 (CH_2 PMB), 68.2 (C-6), 66.9 (C-2), 55.4, 55.4, 55.4 (OMe), 36.8 (C-5), 27.9 (C-7), 21.9 (Me Ts); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{38}H_{43}NO_{11}S_2Na$ 776.2175, found 776.2170.

1,2-(*O*,*N*)-Sulfamidate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (37).



An oven-dried round-bottom flask was equipped with a glass magnetic stirring bar. Naphthalene (1.5 gr, 11.7 mmol, 12 eq.) was added and dissolved in anhydrous THF (19 mL, 0.05 M), after which freshly cut sodium (221 mg, 9.6 mmol, 10 eq.) was added under a N_2 atmosphere. The reaction mixture was sonicated for 30 minutes to obtain a dark-green sodium naphthalenide solution which was subsequently cooled to –78 °C. Compound **S5** (664 mg, 0.96 mmol) was co-evaporated with toluene (3x) and dissolved in anhydrous THF (2 mL) before its dropwise addition to the cooled sodium naphthalenide solution and stirring continued for 30 minutes. Upon full conversion was observed (R_f 0.3 (EtOAc:pentane 1:1 v:v)), the reaction was quenched at –78 °C with sat. aq. NH_4Cl until full discoloration of the mixture was observed. The product was allowed to attain to room temperature and extracted with EtOAc (3x), after which the combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (30:70 → 50:50; EtOAc:pentane) yielded the title compound **37** as an off-white solid (492 mg, 0.82 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.26 – 7.13 (m, 6H, CH_{arom}), 6.92 – 6.82 (m, 6H, CH_{arom}), 4.94 (ddd, *J* = 3.6, 3.5, 3.5 Hz, 1H, H-1), 4.83 (d, *J* = 4.4 Hz, 1H, 2-NH), 4.80 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.72 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.64 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.48 (d, *J* = 10.7 Hz, 1H, CH*H* PMB), 4.42 – 4.35 (m, 2H, C*H*H PMB, CH*H* PMB), 3.88 (dd, *J* = 8.3, 8.3 Hz, 1H, H-3), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.69 (dd, *J* = 9.2, 4.2 Hz, 1H, H-6), 3.63 (ddd, *J* = 8.7, 4.7, 4.7 Hz, 1H, H-2), 3.47 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4), 3.38 (dd, *J* = 9.1, 3.1 Hz, 1H, H-6), 2.20 (ddd, *J* = 15.6, 3.4, 3.4 Hz, 1H, H-7), 2.07 (ddddd, *J* = 9.5, 9.5 3.7, 3.7, 3.7 Hz, 1H, H-5), 1.95 (ddd, *J* = 15.7, 12.2, 3.6 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7, 159.4, 159.4, 130.3, 130.2, 130.2 ($C_{q\text{-}arom}$), 129.9, 129.6, 129.5, 114.2, 114.0, 113.9 (CH_{arom}), 82.8 (C-1), 80.8 (C-3), 78.5 (C-4), 74.9, 74.4, 72.9 (CH_2 PMB), 68.8 (C-6), 62.0 (C-2), 55.4, 55.4, 55.4 (OMe), 36.8 (C-5), 27.8 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{31}H_{37}NO_9SNa$ 622.2087, found 622.2081.

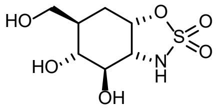
1,2-(*O*,*N*)-Carbamate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucose (38).



Compound **34** (0.75 g, 1.1 mmol) was co-evaporated with toluene and dissolved in anhydrous DCM (10 mL, 0.1 M) and cooled on ice. Pyridine (0.39 mL, 4.8 mmol, 4.5 eq.) and triphosgene (0.19 g, 0.65 mmol, 0.6 eq.) were added and after 10 minutes, the ice bath was removed, after which the reaction mixture was stirred at room temperature for 3 h. Upon full conversion was observed, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc (3x), after which the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the crude *N*-tosyl protected cyclic carbamate. An oven-dried round-bottom flask was equipped with a glass magnetic stirring bar. Naphthalene (1.7 g, 13 mmol, 12 eq.) was added and dissolved in anhydrous THF (22 mL, 0.05 M), after which freshly cut sodium (0.25 g, 11 mmol, 10 eq.) was added under a N_2 atmosphere. The reaction mixture was then sonicated for 10-15 minutes to obtain a dark-green Na/naphthalenide solution. The mixture was cooled to –78 °C and the crude *N*-Ts protected cyclic carbamate intermediate was co-evaporated with toluene (3x) and dissolved in anhydrous THF (3 mL) before its dropwise addition to the cooled Na/naphthalenide solution and stirred for 30 minutes. Upon full conversion was observed (R_f 0.15 (EtOAc:pentane 1:1 v:v)), the reaction was quenched at –78

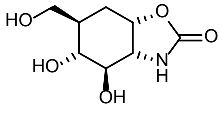
°C with sat. aq. NH_4Cl until full discoloration of the mixture was observed. The product was allowed to warm up to room temperature and extracted with EtOAc (3x), after which the combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. flash column chromatography (40:60 → 70:30; EtOAc:pentane) provided title compound **38** as an off-white solid (488 mg, 0.86 mmol, 79% over 2 steps). ^{1}H NMR (850 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.25 – 7.16 (m, 6H, CH_{arom}), 6.93 – 6.84 (m, 6H, CH_{arom}), 4.86 (d, *J* = 11.5 Hz, 1H, C*H*H PMB), 4.83 (s, 1H, 2-NH), 4.70 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.65 (ddd, *J* = 7.2, 3.5, 3.5 Hz, 1H, H-1), 4.50 (dd, *J* = 11.5, 11.5 Hz, 2H, CH*H* PMB, CH*H* PMB), 4.43 – 4.37 (m, 2H, C*H*H PMB, CH*H* PMB), 3.81 (s, 3H, OMe PMB), 3.80 (s, 3H, OMe PMB), 3.79 (s, 3H, OMe PMB), 3.68 (dd, *J* = 9.1, 4.0 Hz, 1H, H-6), 3.51 – 3.47 (m, 1H, H-2), 3.46 – 3.41 (m, 2H, H-3, H-4), 3.37 (dd, *J* = 9.2, 2.9 Hz, 1H, H-6), 2.14 (ddd, *J* = 15.4, 3.6, 3.6 Hz, 1H, H-7), 1.98 (dddd, *J* = 12.1, 8.6, 4.0, 4.0 Hz, 1H, H-5), 1.91 (ddd, *J* = 15.9, 11.7, 4.4 Hz, 1H, H-7); ^{13}C NMR (214 MHz, $CDCl_3$, HSQC): δ 159.7 (C=O), 159.4, 159.3, 159.2, 130.5, 130.4, 130.3 ($C_{q\text{-}arom}$), 129.7, 129.7, 129.5, 114.4, 114.0, 113.9 (CH_{arom}), 84.6 (C-3), 78.9 (C-4), 76.2 (C-1), 74.6, 74.3, 73.0 (CH_2 PMB), 69.5 (C-6), 58.2 (C-2), 55.5, 55.4, 55.4 (OMe PMB), 37.4 (C-5), 28.3 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{32}H_{37}NO_8Na$ 586.2417, found 586.2411.

1,2-(*O*,*N*)-Sulfamidate-carba-α-D-glucose (16).



Compound **37** (31.7 mg, 53 μmol) was dissolved in DCM (1.3 mL, 0.04 M) and cooled on ice. Triethylsilane (50 μL, 0.32 mmol, 6 eq.) and TFA (41 μL, 0.53 mmol, 10 eq.) were added and the reaction mixture was stirred for 0.5-1 hour. Upon full conversion was observed (R_f 0.4 (MeOH/DCM 2:8 v:v), the reaction mixture was concentrated to dryness. Flash column chromatography (neutralized SiO_2, dry loading on Celite; (0:100 → 10:90; MeOH:DCM) and lyophilization yielded title compound **19** as a colorless transparent film (10.3 mg, 43.1 μmol, 81%). ^{1}H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 4.98 (ddd, *J* = 4.9, 2.8, 2.8 Hz, 1H, H-1), 3.75 (dd, *J* = 9.4, 9.4 Hz, 1H, H-3), 3.73 (dd, *J* = 10.9, 3.6 Hz, 1H, H-6), 3.67 (dd, *J* = 10.9, 5.5 Hz, 1H, H-6), 3.52 (dd, *J* = 9.1, 4.5 Hz, 1H, H-2), 3.25 (dd, *J* = 9.8, 9.8 Hz, 1H, H-4), 2.30 (ddd, *J* = 15.2, 2.7, 2.7 Hz, 1H, H-7), 1.83 – 1.76 (m, 1H, H-5), 1.73 (ddd, *J* = 15.1, 12.9, 3.3 Hz, 1H, H-7); ^{13}C NMR (126 MHz, MeOD, HSQC); δ 85.9 (C-1), 75.9 (C-3), 73.5 (C-4), 64.6 (C-2), 63.2 (C-6), 39.6 (C-5), 29.0 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_7H_{13}NO_6SNa$ 262.0361, found 262.0356.

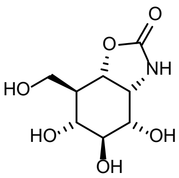
1,2-(*O*,*N*)-Sulfamidate-carba-α-D-glucose (21).



Compound **38** (77 mg, 0.14 mmol) was dissolved in DCM (1.7 mL, 0.08 M) and cooled on ice. TES (0.13 mL, 0.8 mmol, 6.0 eq.) and TFA (0.10 mL, 1.3 mmol, 10 eq.) were added and the reaction mixture was stirred for 1 h. Upon full conversion was observed (R_f 0.3 (acetone)), the reaction mixture was concentrated to dryness using a water aspirator. Flash column chromatography (neutralized SiO_2, dry loading on Celite; 10:90 → 70:30; acetone:DCM) yielded the title compound **21** as a white brittle foam (9.1 mg, 45 μmol, 32%).^{1}H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 4.72 (ddd, *J* = 6.3, 3.7, 2.4 Hz, 1H, H-1), 3.74 (dd, *J* = 10.9, 3.4 Hz, 1H, H-6), 3.66 (dd, *J* = 10.9, 5.4 Hz, 1H, H-6), 3.48 (dd, *J* = 7.9, 6.5 Hz, 1H, H-2), 3.34 (dd, *J* = 9.4, 7.9 Hz, 1H, H-3), 3.21 (dd, *J* = 9.5, 9.5 Hz, 1H, H-4), 2.24 (dd, *J* = 11.6, 2.4 Hz, 1H, H-7), 1.78 – 1.65 (m, 2H, H-5, H-7); ^{13}C NMR (126

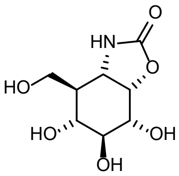
MHz, MeOD,: HSQC) δ 162.4 (C=O), 79.9 (C-3), 78.4 (C-1), 73.0 (C-4), 63.7 (C-6), 60.4 (C-2), 40.3 (C-5), 28.9 (C-7); HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_8H_{13}NO_5Na$ 226.0691, found 226.0686.

1,7-(*S,S*)-(*N,O*)-Carbamate cyclophellitol alkane (10).



Carbamate **40** (23 mg, 50 µmol) was dissolved in anhydrous DCM (0.7 mL, 0.07 M) and cooled on ice. Subsequently TFA (30% v:v, 0.3 mL, 3.9 mmol, 78 eq.) and TES (48 µL, 0.3 mmol, 6.0 eq.) were added and the reaction was stirred on ice for 1 hour and subsequently at room temperature for another 1.5 hours.Upon full conversion was observed (R_f 0.1 (MeOH:DCM, 2:8, v:v)), the reaction was quenched by addition of Et_3N, concentrated at 30 °C. Flash column chromatography (dry loading, 0:100 MeOH:DCM → 17:83 MeOH:DCM) yielded the deprotected carbamate **10** as a colourless oil (8.0 mg, 37 µmol, 74%). ^{1}H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 4.68 (dd, *J* = 9.2, 7.0 Hz, 1H, H-7), 4.20 (dd, *J* = 7.1, 3.2 Hz, 1H, H-1), 3.95 (dd, *J* = 11.1, 2.8 Hz, 1H, H-6), 3.66 (dd, *J* = 11.1, 3.1 Hz, 1H, H-6), 3.58 – 3.48 (m, 2H, H-2, H-3), 3.32 (dd, *J* = 5.7, 2.4 Hz, 1H, H-4), 1.73 (dddd, *J* = 11.9, 9.2, 2.9, 2.9 Hz, 1H, H-5); ^{13}C NMR (126 MHz, MeOD, HSQC): δ 162.1 (C=O), 75.8, 75.6, 71.7 (C-2, C-3, C-7), 69.5 (C-4), 58.9 (C-6), 58.2 (C-1), 48.1 (C-5); HRMS (ESI) m/z: [M + H]$^+$ Calcd. for $C_8H_{13}NO_6$ 220.08156; Found 220.08144.

1,7-(*S,S*)-(*O,N*)-Carbamate cyclophellitol alkane (11).



Carbamate **41** (17 mg, 37 µmol) was dissolved in anhydrous DCM (0.65 mL, 0.07 M) and cooled on ice. Subsequently TFA (30% v:v, 0.3 mL, 3.9 mmol, 105 eq.) and TES-H (50 µL, 0.3 mmol, 8.0 eq.) were added and the reaction was stirred while attaining to room temperature for 1.5 hours. Upon full conversion was observed (R_f 0.1 (MeOH:DCM, 2:8, v:v)), the reaction was concentrated at 30 °C. Flash column chromatography (dry loading, 0:100 MeOH:DCM → 17:83 MeOH:DCM) yielded the deprotected carbamate **11** as a colourless oil (7.0 mg, 32 µmol, 86%). ^{1}H NMR (500 MHz, MeOD, HH-COSY, HSQC): δ 4.69 (dd, *J* = 6.1, 4.1 Hz, 1H, H-1), 3.82 (dd, *J* = 11.0, 4.7 Hz, 1H, H-6), 3.78 – 3.75 (m, 1H, H-7), 3.73 (dd, *J* = 7.7, 3.3 Hz, 1H, H-6), 3.61 (dd, *J* = 9.3, 4.1 Hz, 1H, H-2), 3.53 (dd, *J* = 9.0, 9.0 Hz, 1H, H-3), 3.25 (dd, *J* = 11.3, 8.7 Hz, 1H, H-4), 1.57 (dddd, *J* = 11.3, 9.5, 4.7, 3.5 Hz, 1H, H-5); ^{13}C NMR (126 MHz, MeOD, HSQC): δ 161.6 (C=O), 80.6 (C-1), 75.7 (C-3), 72.1 (C-2), 70.7 (C-4), 60.6 (C-6), 53.6 (C-7), 49.6 (C-5); HRMS (ESI) m/z: [M + H]$^+$ Calcd. for $C_8H_{13}NO_6$ 220.08156; Found 220.08141.

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