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

Ofman, T.P.

Chapter 7

Synthesis of UDP-Glc and UDP-Gal mimetics as putative glycosyl transferase inhibitors – Part II

Introduction

As described in chapter 6, glycosyltransferase (GT) donor substrates exhibit a high degree of rotational freedom.[1] In contrast, crystallographic data of donor substrates in Michaelis complex with corresponding GTs suggest donor substrates to be limited to just four distinct binding conformations when bound within a GT active site.[2–5] These binding orientations range from a linear to a "tucked under" conformation, each stabilized by different interactions within the pocket. Although the donor binding orientation appears crucial for the enzymes' ability to accept donor mimetics,[1,2] inducing conformational bias has been ignored in studies aimed at the design of GT inhibitors.[6–10] It has been postulated that the strategic design of inhibitors with the ability to match the exact binding orientation within the binding pocket could considerably increase enzyme active site binding. Besides an expected increase in the binding affinity, conformationally constrained donor substrate analogues may display GT selectivity as well, especially considering GTs that transfer the same glycosidase but employ different donor substrate binding modes.

Chapter 6 describes the design and synthesis of eight putative glucosyl- and galactosyl transferase inhibitors. These compounds are composed of a bicyclic scaffold with pyrophosphate mimetics related to the ones described by Montero *et al*.[11] and Grimes *et al*.[12], appended to the 1,2-position of the glucose- or galactose configured carbasugar backbone, linked to a uridine 5'monophosphate (UMP) (Figure 1A). In some of these structures the UMP moiety is forced in a tucked-under conformation, mimicking the concaved spatial arrangement observed for the natural substrates of several glucosyl- and galactosyl transferases.[1–5,13–15]

This chapter builds on the design and synthetic methodologies described in chapter 6 (Figure 1B) to expand on the set of putative glucosyltransferase- and galactosyltransferase inhibitors. It was envisioned that fusing the UDP-mimetic structural element at C1 and C7 (cyclophellitol numbering) of the carbasugar would yield a complementary set of putative inhibitors that still exhibit a concaved spatial arrangement.

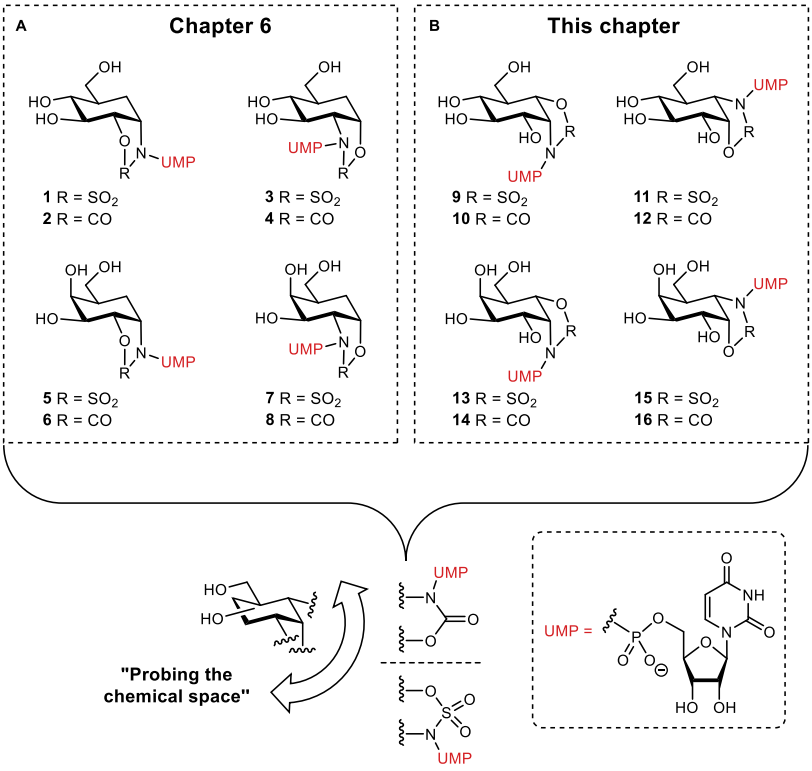


Figure 1. Overview of four glucose- and four galactose configured putative inhibitors (**1** – **8**) proposed and synthesized in chapter 6 for UDP-glucosyl- and UDP galactosyl transferases. (B) four

glucose configured and four galactose configured putative inhibitors (**9** – **16**) proposed in this chapter. In red the uridine 5'-monophosphate (UMP) moiety.

Following the synthetic methodology described in chapter 6, 1,7-cyclic carbamate and -sulfamidate carbasugars **17** – **24** are considered as viable constructs to undergo an Atherton-Todd coupling reaction (Figure 2).[16–22] In turn, the 1,7-cyclic carbamates and sulfamidates are envisioned to be accessible *via* the in chapter 6 described stereoselective Sharpless aminohydroxylation on the corresponding cyclohexene.[23,24] Ideally providing an equimolar regiomeric ratio of the desired α-*cis*-amino alcohols. The glucose- and galactose configured cyclohexenes are easily accessible *via* modified literature procedures.[25,26]

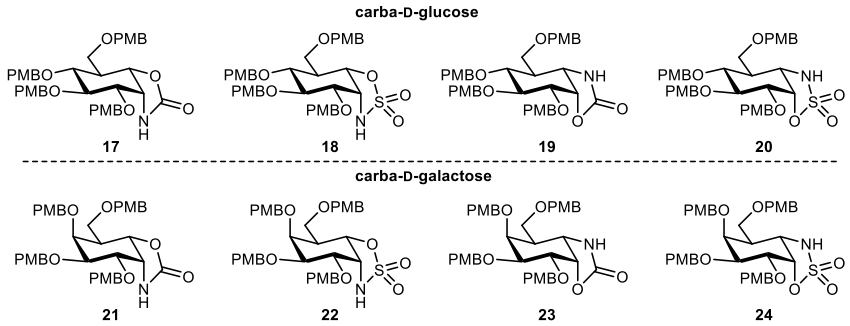


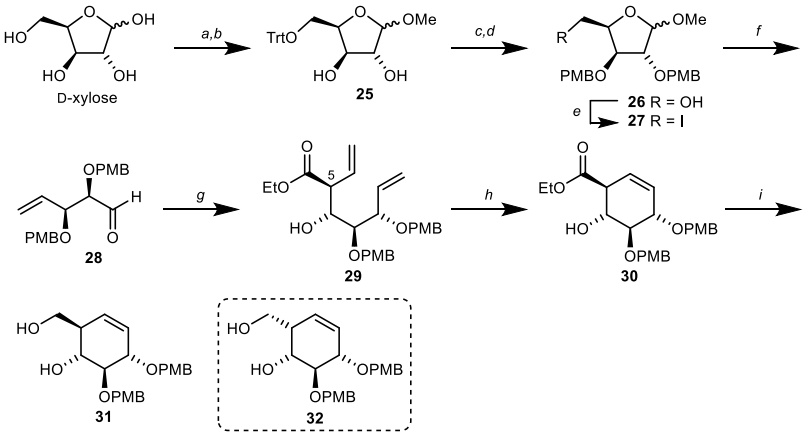
Figure 2. Four carba-glucose- and four carba-galactose configured constructs considered to be suitable amide coupling fragments in an Atherton-Todd type coupling reaction.

Results and discussion

The synthesis of the glucose configured constructs commenced from commercially available D-xylose (Scheme 1). Following modified literature procedures,[25] D-xylose was subjected to kinetic Fischer glycosylation conditions after which the primary hydroxyl of the obtained methyl-xylofuranoside intermediate was protected as a trityl ether to quantitatively yield compound **25**. The secondary hydroxyls in **25** were masked as PMB ethers under standard Williamson etherification conditions (PMBCl, NaH)[27] followed by *p*-TsOH-mediated removal of the trityl group to yield intermediate **26** in 73% yield. Compound **26** was then subjected to an Appel-like reaction to yield iodide **27** in near-quantitative yield (95%).[28] Compound **27** underwent Vasella fragmentation upon treatment with activated zinc and sonication to provide aldehyde **28** in 81% yield. Indium-mediated coupling with ethyl 4-bromocrotonate proceeded with high stereoselectivity and yielded **29** as major compound alongside trace amounts of the C-5 epimer which, at this stage, could not be separated. A ring-closing olefin metathesis, catalyzed by Grubbs-II ruthenium complex, provided glucuronic cyclohexene **30** in high yield (92%). At this stage removal of the C-5 epimeric side product (iduronic

cyclohexene) proved futile. However, after ester reduction using $LiBH_4$, glucose cyclohexene **31** could successfully be separated from idose cyclohexene **32.** In this way cyclohexene **31** was obtained in near quantitative yield together with trace amounts of L-ido congener **32**.

Scheme 1. Synthesis of PMB protected glucose cyclohexene **31** and idose configured cyclohexene **32**.



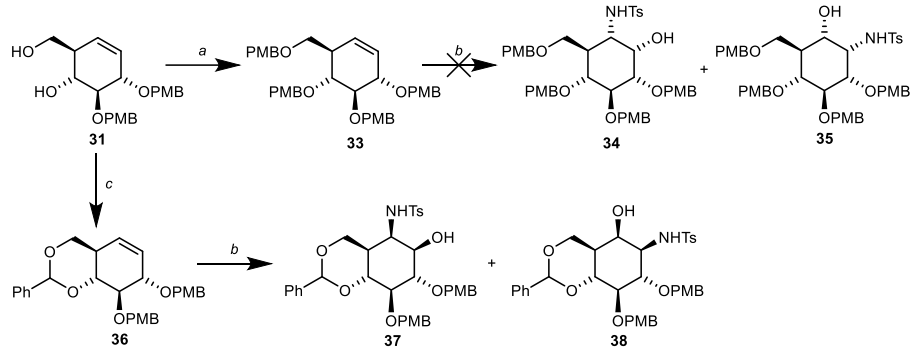
Reagents and conditions: a) AcCl, MeOH, rt, 6.5 h; *b)* TrCl, Et_3N, DMAP, DMF, 30 °C, 16 h (quant.); *c)* PMBCl, NaH, TBAI, DMF, rt, 16 h; *d) p*-TsOH, DCM:MeOH (1:1 v:v), rt, 16 h (73% over two steps); *e)* PPh_3, I_2, imidazole, THF, reflux, 3.5 h (95%); *f)* Zn, sonication, THF:H_2O (9:1 v:v), 40 °C, 12 h (81%); *g)* ethyl 4-bromocrotonate, In, $La(OTf)_3$, H_2O, rt, 5 days (89%); *h)* Grubbs-II, DCM, 38 °C, 2 days (92%); *i)* $LiBH_4$, THF, rt, 5 h, **31** (96%), **32** (2%).

With glucose cyclohexene **31** in hand, initial attempts on investigating the Sharpless aminohydroxylation could be undertaken (Scheme 2). Prior to this, the 4- and 6-hydroxyl were protected as PMB ethers under standard Williamson conditions which yielded fully protected cyclohexene **33** in 92% yield. Based on the results described in chapter 6, cyclohexene **33** was envisioned as a suitable substrate to undergo a Sharpless aminohydroxylation. However, exposure of cyclohexene **33** to aminohydroxylating conditions (chloramine-T hydrate, $K_2[OsO_2(OH)_4]$, 60 °C) did not result in any conversion.

In an alternative attempt, the 4- and 6-OH in cyclohexene **31** were protected as a benzylidene acetal, a known way to conformationally restrict the glucose moiety which could favorably influence the Sharpless aminohydroxylation. This influence can be attributed to the electronic, conformational, and steric effects induced by the rigid protecting group. In addition, benzylidene acetals are commonly removed under aqueous acid conditions, suggesting compatibility with the final deprotection sequences as described in chapter 6.[29–31] Although in low rates, indeed conversion was observed upon treatment of benzylidene protected cyclohexene **36** with the above

aminohydroxylating conditions. The reaction stagnated at roughly 30% conversion based on NMR analysis of the crude material. Purification of the crude resulted in the isolation of two compounds (**37** and **38**) of which NMR analysis allowed for assigning the newly introduced stereocenters to exhibit a *trans* orientation relative to C-2. Effectively, none of the desired *cis* product was observed.

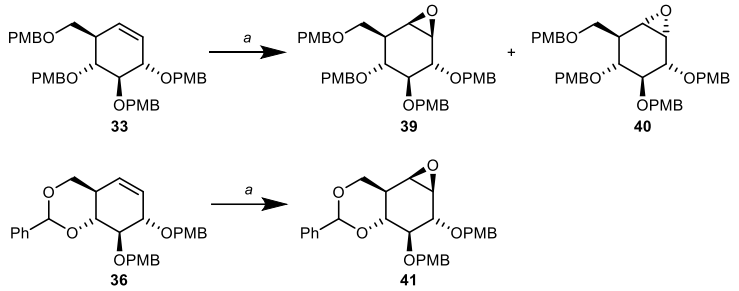
Scheme 2. Sharpless aminohydroxylation studies on glucose cyclohexene **33** and **36**.



Reagents and conditions: a) PMBCl, NaH, TBAI, DMF, rt, 16 h (92%); *b)* CAT·3H_2O, $K_2[OsO_2(OH)_4]$, TEBACl, $CHCl_3$:H_2O (1:1 v:v), 60 °C, 16 h, **37** (8.8%), **38** (5.2%); *c)* $PhCH(OMe)_2$, *p*-TsOH, DMF, rt, 4 h (85%).

In an alternative attempt towards the carbaglucose 1,7-α-*cis*-aminoalcohols, a methodology as described by Kok *et al*. was followed.[32] To this end, the formation of a cyclophellitol epoxide was required (Scheme 3). Treatment of cyclohexene **33** with *m*-CPBA resulted in sluggish product formation, stagnating at around 40% conversion. In addition, the epoxidation appeared not very stereoselective as both epoxides **39** and **40** were obtained as an inseparable mixture in 3:1 ratio. In contrast, treatment of the benzylidene protected cyclohexene **36** did not only increase reaction rate. In addition, the stereoselectivity of the reaction was drastically increased as cyclophellitol epoxide **41** was the only observed product.

Scheme 3. Epoxidation studies of glucose cyclohexenes **33** and **36**.

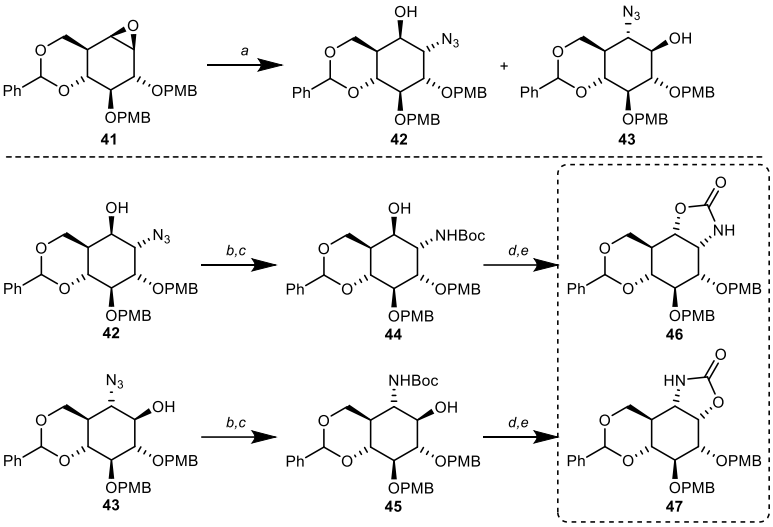


Reagents and conditions: a) m-CPBA, $NaHCO_3$, DCM, 5 °C, 4 days, **39** (32%), **40** (10%), **41** (56%, 70% based on recovered starting material).

The increased stereoselectivity could be attributed to the aforementioned conformational locking of the cyclohexene, effectively favoring the substrate for top-side attack.

Treatment of epoxide **41** with NaN_3 at elevated temperatures and aided by a Lewis acid ($LiClO_4$) resulted in clean conversion to a separable mixture of both regioisomers **42** and **43** in quantitative yield and in a 3:1 ratio respectively (Scheme 4). Both azides were subjected to Staudinger conditions to furnish the corresponding primary amines which were masked with a Boc protecting group to yield secondary carbamates **44** and **45** in a respective 66% and 48% yield over two steps. Mesylation of the secondary hydroxyls in these intermediates proceeded smoothly under standard mesylating conditions (MsCl, Et_3N) and aided by methyl imidazole acting as a nucleophilic catalyst. At elevated temperatures (130 °C), cyclic carbamate formation, induced by attack of the Boc carbonyl substituting the mesylate and subsequently expulsion of butene, was observed. This yielded cyclic carbamates **46** and **47** in 90% and 67% over two steps respectively.

Scheme 4. Synthesis of glucose configured carbamates **46** and **47**.

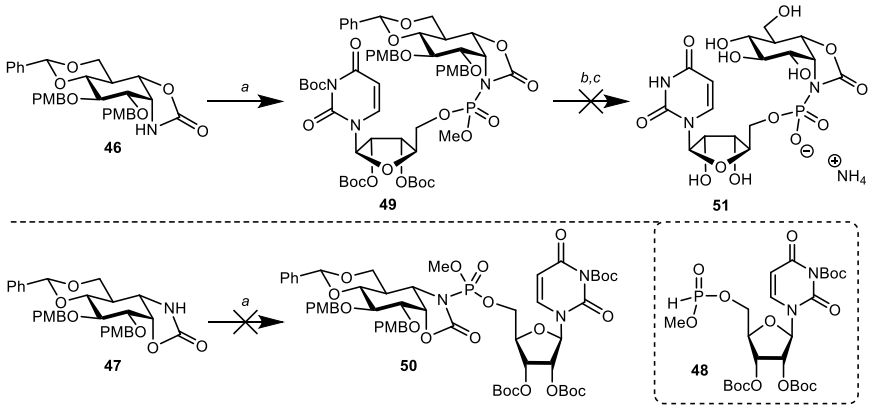


Reagents and conditions: a) NaN_3, $LiClO_4$, DMF, 100 °C, 16 h, **42** (75%), **43** (25%); *b)* TPP, THF/1 M aq. NaOH (1:1 v:v), rt, 16 h; *c)* Boc_2O, Et_3N, DCM, rt, 16 h, **44** (66% over two steps), **45** (48% over two steps); *d)* MsCl, Me-imidazole, Et_3N, DCM, rt, 16 h; *e)* DMF, 130 °C, 16 h, **46** (90% over two steps), **47** (67% over two steps).

Following optimized procedures as described in chapter 6, cyclic carbamates **46** was subjected to an Atherton-Todd phosphorylation using activated H-phosphonate diester **48** (Scheme 5). Sluggish conversion was observed for the carbamate resulting in isolation of phosphoramidate **49** as a mixture of diastereoisomers in only 22% yield. Atherton-Todd phosphorylation of cyclic carbamate **47** did not result in observable amounts of product and consequent recovery of starting material carbamate.

Global deprotection of phosphoramidate **49** proved unsuccesful, and any attempt resulted in degradation of material. Initially, deprotection conditions as optimized in chapter 6 were assessed (TFA, TES *then* pyridine). This resulted in a reductive opening of the benzylidene and the formation of a benzyl ether on either the 4''- and 6''-OH. In order to circumvent this reductive opening of the benzylidene protective group, an additional deprotection step was envisioned based on classical deprotection methods (*p*-TsOH, MeOH). The use of methanol in this deprotection step posed a potential problem as previous treatment of phosphoramidate triesters with methanol showed transesterification and thereby cleavage of the N-P linkage. The transformation to a phosphoramidate diester on the other hand, increases the intrinsic stability. Therefore, compound **49** was first treated with pyridine in order to remove the phosphoramidate methyl ester. However, subsequent treatment with a Brønsted acid (*p*-TsOH) in MeOH/DCM still resulted in degradation of material.

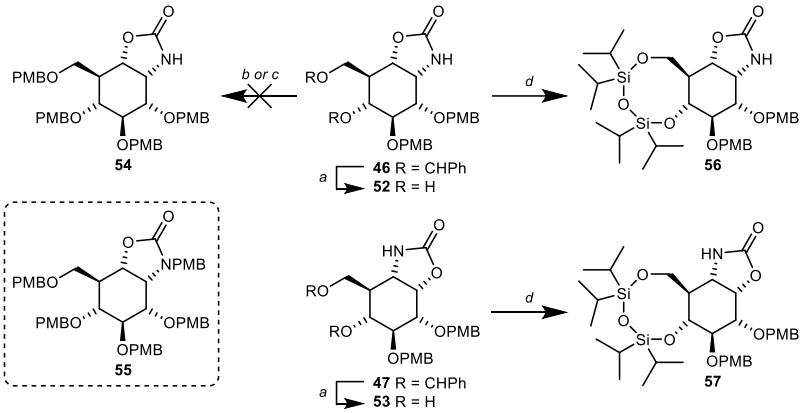
Scheme 5. Attempted Atherton-Todd reaction on cyclic carbamates **46** and **47**.



Reagents and conditions: a) i. **48**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min, *ii.* cyclic carbamate **46** or **47**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; then added activated **48**, rt, 2 h, **49** (22%); *b)* 30% TFA/DCM (v:v), TES, 5 °C, 16 h; *c*) pyridine, 5 °C, 16 h.

In order to circumvent this troublesome global deprotection induced by the presence of the benzylidene protective group, alternative protective group schemes were studied next (Scheme 6). For this purpose, removal of the benzylidene functionality proceeded smoothly upon exposure to a Brønsted acid (*p*-TsOH) in MeOH yielding diols **52** and **53**. Attempts to protect the 4- and 6-OH as PMB ethers, either using standard Williamson etherification conditions or acid catalyzed conditions (PMB-trichloroacetimidate, CSA), proved futile as alkylation of the cyclic carbamate was observed (compound **55**). In order to selectively protect the 4- and 6-OH and prevent alkylation of the cyclic carbamate, the use of the 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) (TIPDS) protecting group was investigated. The TIPDS group has been found to be an useful protecting group of diols and in addition is easily removed in both acidic as fluoride-rich media,[33–36] suggesting its smooth deprotection during the envisioned two-step global deprotection sequence aided by TFA and TES. The 4- and 6-OH could be selectively protected over the cyclic carbamate under standard conditions, and full conversion was achieved within 30 minutes to yield both cyclic carbamates, **56** and **57**, in high yields (88% and 84% respectively).

Scheme 6. Alternative 4- and 6-OH protecting group schemes investigated.

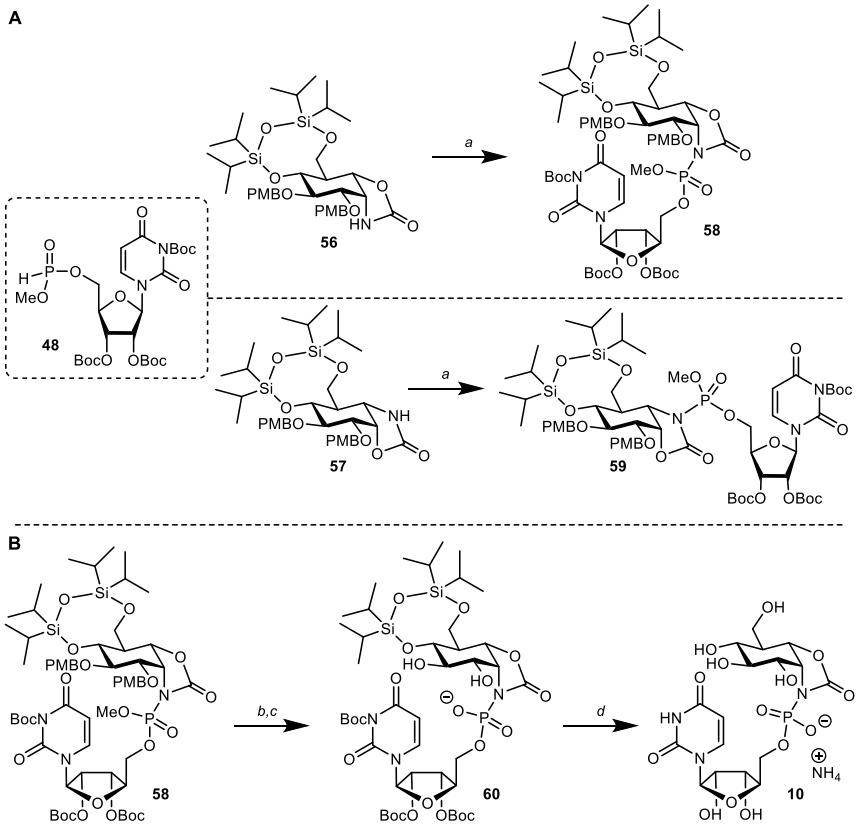


Reagents and conditions: a) p-TsOH, MeOH, 40 °C, 1 h, **52** (90%), **53** (74%); *b)* PMBCl, NaH, DMF, rt, 16 h; *c)* PMB-trichloroacetimidate, CSA, DCM, rt, 16 h; *d)* $TIPDSCl_2$, imidazole, DMF, rt, 30 min, **56** (88%), **57** (84%).

With both TIPDS protected carbamates available, their exposure to Atherton-Todd phosphorylation was examined (Scheme 7A). Relative clean and fast conversion was observed, resulting in the isolation of compounds **58** and **59** as a mixture of phosphorous diastereoisomers in 29% and 14% respectively.

Next, global deprotection of constructs **58** was examined to finalize the construction of target compound **10** (Scheme 7A). To this end, compound **58** was exposed to the in chapter 6 optimized two-step deprotection sequence (TFA/TES *then* pyridine) which allowed for the removal of all PMB and Boc protection groups prior to the removal of phosphorous methyl ester. However, the TIPDS protecting group proved stable under these conditions, as intermediate **60** was observed according to TLC-MS. At this stage, removal of the TIPDS moiety was considered viable because of the increased stability of the phosphoramidate diester by treatment of **60** with a fluoride source. Indeed, clean removal of the TIPDS protection group was observed upon treatment with TBAF, completing the synthesis of *N*-UMP-1'',7''-(*O,N*)-carbamate carba-α-D-glucopyranoside **10**. Due to limited amounts of construct **59**, no attempt to deprotect this construct was undertaken.

Scheme 7. Attempted Atherton-Todd reaction on cyclic carbamates **56** and **57** (A) and consequent global deprotection sequence towards target compound **10** (B).

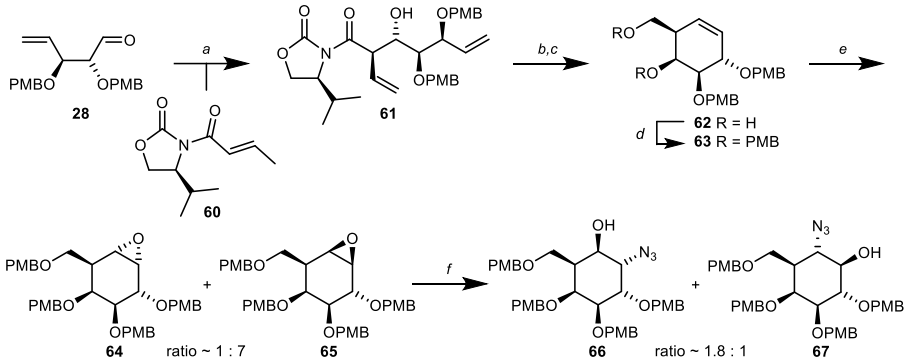


Reagents and conditions: a) i. **48**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min, *ii.* cyclic carbamate **56** or **57**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; then added activated **48**, rt, 2 h, **58** (29%), **59** (14%, 34% brsm); *b)* TFA (30% v:v), TES, DCM, rt, 16 h; *c*) pyridine, 35 °C, 24 h; *d*) TBAF, THF, rt, 16 h (18% over three steps).

Upon successfully completing the synthesis towards *N*-UMP-1'',7''-(*O,N*)-carbamate carba-α-D-glucopyranoside **10**, attention was shifted to construction of the carba-galactoside targets **13** – **16**. The synthesis of the galactose configured constructs advanced from previously described intermediate **28** following modified procedures as described by Artola *et al*. (Scheme 8).[37] Aldehyde **28** readily underwent an asymmetric aldol condensation when treated with chiral Evans aldol **60** (prepared in four steps from commercially available Boc-L-valine, see Appendix Scheme S1)[38,39] and freshly prepared Bu_2BOTf (prepared in two steps from $BF_3{\cdot}OEt_2$, see Appendix Scheme S2)[40] to yield compound **61** in a stereoselective manner and near-quantitative yield (97%). Reductive cleavage of the auxiliary aided by $LiBH_4$ proceeded smoothly, giving rise to the primary hydroxyl. Treatment of the crude mixture to a Grubbs-II catalyzed ring-closing

metathesis provided galactose configured cyclohexene **62** in 66% yield over two steps. Protection of the 4- and 6-OH as a PMB ether proceeded sluggishly under standard Williamson etherification conditions and required elevated temperature in order to achieve full conversion to give compound **63**. Epoxidation of compound **63**, by treatment with *m*-CPBA, provided a separable mixture of epoxides **64** and **65** in modest stereoselectivity and yield in favor of the desired epoxide **65**.

Scheme 8. Construction of azide adducts **66** and **67** from pentenal **28**.

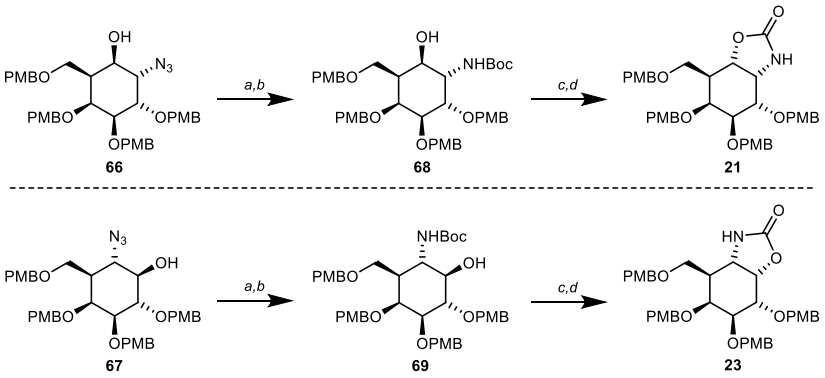


Reagents and conditions: a) **60**, Bu_2BOTf, Et_3N, 3Å molecular sieves, DCM, -78 °C → -30 °C, 16 h (98%); *b)* $LiBH_4$, THF:H_2O (9:1 v:v), 0 °C → rt, 1 h; *c)* Grubbs-II, DCM, 40 °C, 16 h (66% over two steps); *d)* PMBCl, NaH, TBAI, DMF, 45 °C, 16 h (73%); *e) m*-CPBA, $NaHCO_3$, DCM, 5 °C, 3 days, **64** (7%), **65** (43%); *f)* NaN_3, DMF, 140 °C, 16 h, **66** (45%), **67** (34%).

Treatment of compound **65** with NaN_3 at elevated temperatures neatly provided near-equimolar amounts of azide adducts **66** and **67** in 79% overall yield.

Each of the azides **66** and **67** were treated with Staudinger conditions (Scheme 9) to furnish the corresponding primary amines which were readily transformed into the *N*-Boc protected species to yield secondary carbamates **68** and **69** in near quantitative yields (96% and 95% over two steps respectively).

Scheme 9. Synthesis of galactose configured carbamates **21** and **23**.

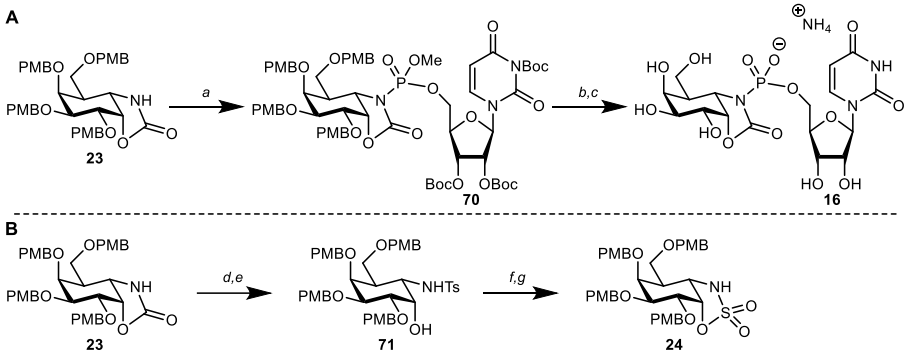


Reagents and conditions: a) TPP, THF : 1 M aq. NaOH (1:1 v:v), rt, 16 h; *b)* Boc_2O, Et_3N, DCM, rt, 16 h, **68** (96% over two steps), **69** (95% over two steps); *c)* MsCl, Me-imidazole, Et_3N, DCM, rt, 16 h; *d)* DMF, 130 °C, 16 h, **21** (59% over two steps), **23** (65% over two steps).

Mesylation of the secondary hydroxyl proceeded smoothly after which the crude mesylate was treated at elevated temperatures (130 °C) in order to induce cyclic carbamate formation. This provided cyclic carbamates **21** and **23** in 59% and 65% over two steps respectively, envisioned as suitable coupling partners in the upcoming Atherton-Todd reaction.

To this end, an Atherton-Todd phosphorylation of compound **23** (activation of H-phosphonate diester **48** with $BrCCl_3$ prior to addition to deprotected carbamate **23**) proceeded smoothly and showed almost full conversion towards the product after 2 hours at room temperature (Scheme 10A). Subsequent global deprotection using the two-step deprotection sequence, followed by Dowex NH_4^+ ion exchange and lyophilization afforded the *N*-UMP-1'',7''-(*O,N*)-carbamate carba-α-D-galactopyranoside target **16** as a NH_4^+ salt in good yield (63% over two steps).

Scheme 8. Atherton-Todd coupling of carbamate **23** and consequent deprotection towards target compound **16** (A) and preparation of cyclic sulfamidate **24** (B).

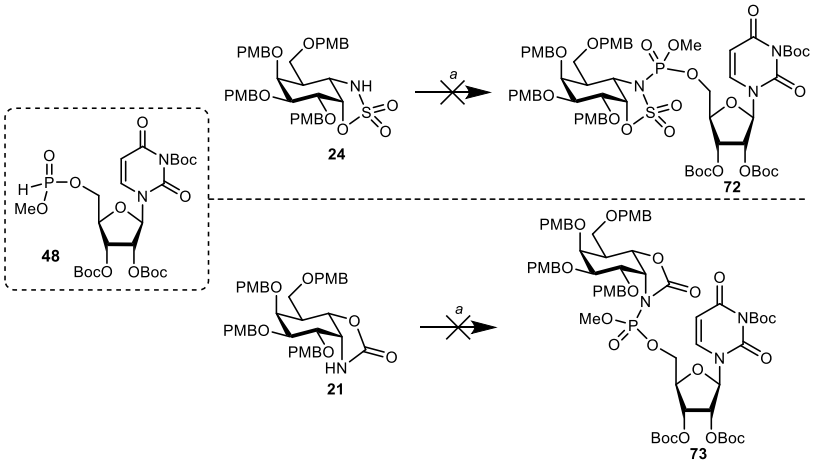


Reagents and conditions: a) i. **48**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min, *ii.* cyclic carbamate **23**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; then added activated **48**, rt, 2 h (23%, 55% brsm); *b)* TFA (30% v:v), TES, DCM, rt, 24 h; *c*) pyridine, 35 °C, 24 h (63%); *d)* NaOH, EtOH:H_2O (4:1 v:v), 70 °C, 2 h; *e)* TsCl, Et_3N, THF, 0 °C, 1 h (70% over two steps); *f)* SO_2Cl_2, Et_3N, DCM, -78 °C → 0 °C, 2 h; g) Na, naphthalene, THF, -78 °C, 1 h (74% over two steps).

After successfully obtaining *N*-UMP-1'',7''-(*O,N*)-carbamate carba-α-D-galactopyranoside **16**, attention was then turned to create 1,7-(*O,N*)-sulfamidate **24**. Starting from cyclic carbamate **23**, alkaline induced hydrolysis of the cyclic carbamate at elevated temperatures neatly provided the primary amine which was readily protected as a tosylate (compound **71**, Scheme 10B). Following procedures as described in chapter 6, tosylate **71** was treated with SO_2Cl_2 at low temperature to provide the cyclic sulfamidate. Removal of the tosyl protecting group was effected by treatment of the intermediate with a sodium naphthalenide solution at low temperature, yielding cyclic sulfamidate **24** in 74% over two steps.

Subjecting of either cyclic carbamate **21** or sulfamidate **24** to an Atherton-Todd phosphorylation with H-phosphonate diester **48** did not result in product formation, but to full recovery of the starting materials (Scheme 11).

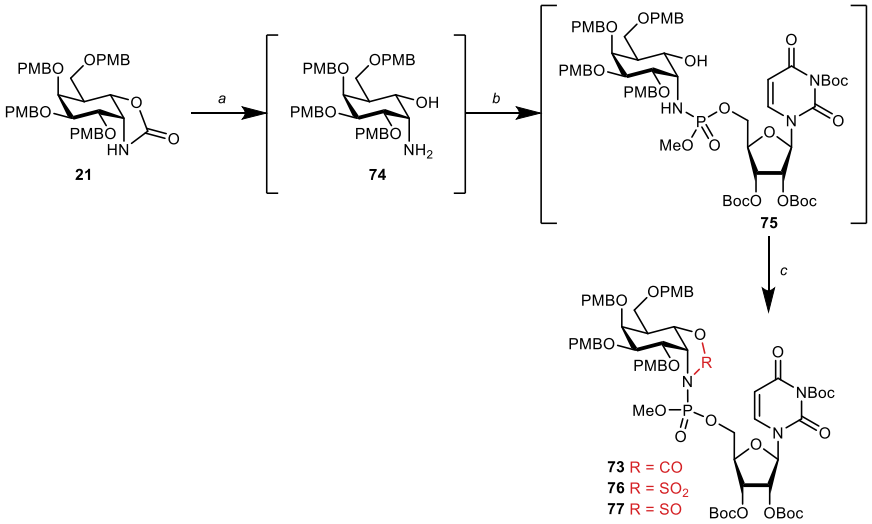
Scheme 9. Atherton-Todd reaction on cyclic sulfamidate **24** and cyclic carbamate **21**.



Reagents and conditions: a) i. **48**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min, *ii.* cyclic sulfamidate **24** or carbamate **21**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; then added activated **48**, rt, 2 h.

With the inability to couple sulfamidate **24** or carbamate **21** to H-phosphonate diester **48** under Atherton-Todd conditions, an alternative synthesis route towards these constructs was sought for. Literature has shown primary amine phosphorylation to be selective over that of secondary hydroxyls and therefore an approach was taken to first install the phosphate on the primary amine and subsequently forge the cyclic carbamate or sulfamidate.[41–44] Indeed, reaction of crude amino-alcohol **74**, prepared by treatment of **21** with sodium hydroxide in ethanol/water (4:1) (Scheme 12), with H-phosphonate diester **48** under Atherton-Todd conditions led to clean and rapid conversion to phorsporamidate **75** as observed by ^{31}P NMR (signal at 20 ppm) and ^{1}H NMR. Upon prolonged reaction time (one day), migration of the UMP-moiety to the 7''-OH was observed as indicated by ^{31}P (signal at 14 ppm) and ^{1}H NMR.[43] Because of this observation, intermediate **75** was used without work-up and purification in the next step. Thus, crude **75** was subjected to a variety of different conditions to explore 1,7-(*N*,*O*)-bicycle formation (Table 1). Subjection of crude **75** to CDI, triphosgene or phosgene (Entries 1 – 3) all resulted in degradation of the starting material. The same holds true for treatment of crude **75** with SO_2Cl_2 (Entry 4): again, complete degradation was observed. In an attempt to minimize the degradation of the starting material *via* the aforementioned UMP migration, a two-step one-pot procedure was explored (Entries 5 and 6). Also in these instances degradation of the starting material was observed. Switching from SO_2Cl_2 to thionyl chloride ($SOCl_2$, Entry 7) in contrast allowed for the isolation of cyclic sulfamidite **77** in 37% yield over three steps.

Scheme 10. Alternative synthetic route towards *N-P* coupled carba-galactosides.



Reagents and conditions: a) NaOH, EtOH:H_2O (4:1 v:v), 70 °C, 2 h; *b)* **48**, $BrCCl_3$, DiPEA, DCM, 0 °C, 15 min; *c)* see Table 1.

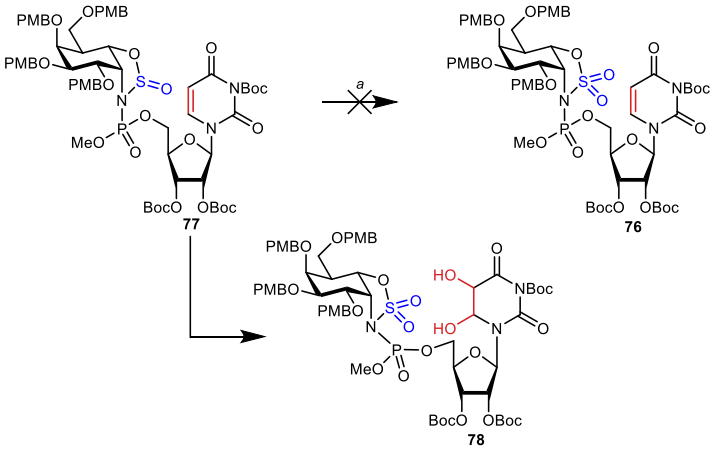
Table 1. Late stage 1,7-(*N*,*O*)-bicycle formation.

Entry	Conditions	R-group	Observations
1.	CDI, Et_3N, DCM, 0 °C, 2 h	R = CO (**73**)	Degradation of starting material
2.	Triphosgene, Et_3N, DCM, 0 °C, 2 h	R = CO (**73**)	Degradation of starting material
3.	$COCl_2$, DMAP, DBU, DCM, -78 °C → 0 °C, 2 h	R = CO (**73**)	Degradation of starting material
4.	SO_2Cl_2, Et_3N, DCM, 0 °C, 2 h	R = SO_2 (**76**)	Degradation of starting material
5.	$COCl_2$, one-pot with Atherton-Todd, -78 °C → 0 °C, 2 h	R = CO (**73**)	Degradation of starting material
6.	SO_2Cl_2, one-pot with Atherton-Todd, -40 °C → 0 °C, 16 h	R = SO_2 (**76**)	Degradation of starting material
7.	$SOCl_2$, one-pot with Atherton-Todd, -40 °C → 0 °C, 16 h	R = SO (**77**)	Clean conversion to **77** (37% over three steps)

Oxidation of the cyclic sulfamidite in **77** to the corresponding sulfamidate would yield target compound **76**. To this end, cyclic sulfamidite **77** was treated with standard S(IV) oxidation conditions ($RuCl_3$, $NaIO_4$).[45–48] Within 20 minutes, full conversion of the

starting material was observed. Unfortunately, NMR spectroscopy and MS revealed that overoxidation had occurred. Besides oxidation of the S(IV) centre, oxidation of the uracil moiety to the diol was observed (compound **78**, Scheme 13). Based on literature precedent, dihydroxylation of uracil is common occurrence when subjected to these harsh oxidation conditions ($RuCl_3$, $NaIO_4$).[49]

Scheme 11. Attempted oxidation of cyclic sulfamidite **77** towards cyclic sulfamidate **76**.



Reagents and conditions: a) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 0 °C, 20 min, **78** (50%).

In order to prevent overoxidation of the uracil moiety, a milder S(IV) oxidation method was sought for (Table 2). Both *m*-CPBA and $KMnO_4$ have been used to accomplish the transformation of sulfamidites to sulfamidates,[47,48,50–52] and are known to be compatible with uracil bearing constructs. Sulfamidite oxidation by *m*-CPBA (Entry 1) proved unsuccessful as no conversion was observed. The use of $KMnO_4$ proved unsuccessful as well, this time resulting in slow degradation of the starting material without any indication of product formation (Entry 2). A last attempt was prompted by literature precedent stating that superior $KMnO_4$ oxidations were achieved when catalytic amounts (20%) of MnO_2 were added (Entry 3).[53] However, these conditions also resulted in complete degradation of the starting material.

Table 2. Attempted oxidation of cyclic sulfamidite **77** towards cyclic sulfamidate **76**.

Entry	Conditions	Observations
1.	*m*-CPBA, DCM, 0 °C → rt, 16 h	No conversion
2.	$KMnO_4$, DCM, 0 °C → rt, 16 h	Degradation of starting material
3.	$KMnO_4$, MnO_2, DCM, 0 °C → rt, 16 h	Degradation of starting material

Conclusions

In conclusion, this chapter describes the synthetic endeavors towards UMP linked glucose and galactose configured constructs, envisioned as putative inhibitors of UDP-Glc and UDP-Gal processing glycosyl transferases. Expanding on the 1,2-carbamate and -sulfamidate inhibitors described in chapter 6, this chapter is focused on the synthesis of constructs bearing cyclic carbamates and sulfamidates over the 1,7-position. By means of rigidification as induced by the annelated ring system, the set of compounds **9** – **16** are thought to resemble the concaved orientation often observed in crystallographic data of the donor substrate in Michaelis complexes with various GTs.

Initial attempts towards glucose configured cyclic carbamates and sulfamidates **9** – **12** focused on the synthetic methodology as described in chapter 6. Here, the key Sharpless aminohydroxylation of protected cyclophellitol cyclohexenes **31** and **36** resulted in sluggish transformations and with limited stereoselectivity and regioselectivity. Alternative methodologies provided access to the cyclic carbamates **46** and **47** as divergent building blocks in the construction of all four target structures **9** – **12**. The use of a TIPDS protecting group proved crucial during both the Atherton-Todd reaction and the global deprotection sequence and allowed for the isolation of the first target structure *N*-UMP-1'',7''-(*N,O*)-carbamate carba-α-D-glucopyranoside **10**. Following identical deprotection methodology, future deprotection of construct **59** should be feasible.

Following identical chemical transformations, both galactopyranose-configured cyclic carbamates **21** and **23** were efficiently synthesized. The Atherton-Todd coupling between H-phosphonate diester **48** and cyclic carbamate **23** followed by the global deprotection sequence provided target compound *N*-UMP-1'',7''-(*O,N*)-carbamate carba-α-D-galactopyranoside **16**. All attempted Atherton-Todd coupling reactions with either the sulfamidate analogue **24** or the carbamate 1,7-regioisomer **21** however resulted in full recovery of starting material. In a final attempt to obtain compounds **13** – **15**, carbamate **21** was hydrolyzed prior to exposure to Atherton-Todd conditions. This resulted in clean and fast conversion to phosphoramidate **75**. This intermediate was foreseen to be a divergent building block and could provide the cyclic carbamate and sulfamidate constructs upon exposure to carbamylating- or sulfamylating agents. Unfortunately, degradation of the starting material was observed, proving this synthesis route to be unfeasible.

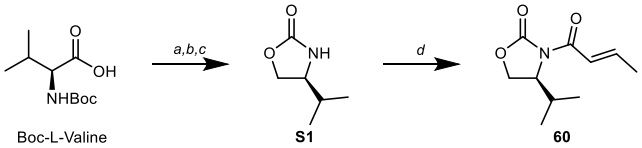
In sum, the here described synthetic methodologies and the identified synthetic pitfalls could in turn pave the way for construction of the remaining cyclic carbamate and cyclic sulfamidate constructs. The assessment of the synthesized compounds as GT inhibitors requires the establishment of suitable enzyme inhibition assays, which hopefully will be available in the near future.

Acknowledgements

Anne-mei Klein and Duncan de Graaf are kindly acknowledged for their synthesis work in the context of their MSc internships. Acknowledgments are due to Roy Steneker for our collaborative efforts in the preparation of dibutyl boron triflate, as well as for our insightful discussions. Pascal Balić is acknowledged for our insightful discussions in relation to the phosphorus chemistries.

Appendix

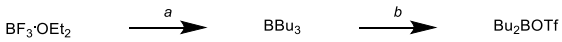
Scheme S1. Preparation of Evans auxiliary **60** from commercially available Boc-L-valine.



Boc-L-Valine **S1** **60**

Reagents and conditions: a) ethyl chloroformate, Et_3N, THF, 0 °C, 1 h; *b)* $NaBH_4$, H_2O, rt, 30 min; *c)* $SOCl_2$, THF, rt, 16 h (35% over three steps); *d) n*-BuLi, crotonyl chloride, THF, -78 °C → rt, 3 h (68%).

Scheme S2. Preparation of Bu_2BOTf from boron trifluoride etherate.



Reagents and conditions: a) n-BuLi, Et_2O, reflux, 2 h (66%); *b)* TfOH, 50 °C, 1 h (95%).

Synthetic procedures.

General procedure A: *N*-phosphorylation of per-*O*-(4-methoxybenzyl) cyclic carbamates and sulfamidates using protected methyl H-phosphonate diester

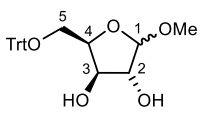
Per-*O*-(4-methoxybenzyl) cyclic carbamate or sulfamidate was co-evaporated with anhydrous $CHCl_3$ and added to an oven-dried round-bottom flask. The flask was connected to a Schlenk line and subjected to three vacuum-N_2 backfill cycles before dissolving in anhydrous THF (0.2-0.3 M). The solution was cooled on ice, after which 15-crown-5 ether (5.0 eq.) and NaH (60 wt% dispersion in mineral oil; 1.5 eq.) were added. After 5 minutes, the reaction mixture was removed from the ice bath and stirred at room temperature for 30 minutes. In parallel, another oven-dried round-bottom flask was charged with methyl H-phosphonate **48** (2.0 eq.) and also put under a N_2 atmosphere using a Schlenk line prior to dissolving in anhydrous DCM (0.3-0.4 M). The solution was cooled on ice, after which anhydrous DiPEA (6.0 eq.) and bromotrichloromethane ($BrCCl_3$; 4.0 eq.) were added. The reaction mixture was stirred on ice for 15-30 minutes, after which full conversion to the bromophosphate was confirmed by both TLC and ^{31}P NMR analysis (δ = –4.9, –5.1 ppm; 121 MHz, acetone-d_6 probe). The flask containing deprotonated cyclic carbamate or sulfamidate was cooled back on ice, after which the cooled bromophosphate solution was transferred using a N_2-flushed syringe. The resulting reaction mixture was stirred on ice for 1.5-2 h. After full conversion was observed by TLC, the reaction was quenched on ice with sat. aq. $NaHCO_3$. The crude product was extracted with EtOAc (3x), after which the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography of the crude material (SiO_2, EtOAc in pentane) followed by Sephadex™ LH-20 size exclusion chromatography yielded the protected *N*-acyl- or *N*-sulfonylphosphoramidate as a mixture of P(V) diastereomers.

Note: The P(V) diastereomers were partially separable using silica and size-exclusion column chromatography, making it possible to obtain clean NMR spectra of the individual diastereomers for easier structure elucidation. Aside from this, the phosphoramidate products were collected and subsequently deprotected as a mixture.

General procedure B: One-pot global deprotection and demethylation of protected *N*-acyl- or *N*-sulfonylphosphoramidate

Protected *N*-acyl- or *N*-sulfonylphosphoramidate compound (as a mixture of P(V) diastereomers) was dissolved in anhydrous DCM (0.05 M) and cooled on ice. TES (10 eq.) and TFA (30% v:v) were added and the reaction mixture was stirred on ice for 3-16 h. After full conversion was observed by TLC-MS analysis (MeOH:DCM, 2:8 v:v), pyridine (20 eq. with respect to TFA) was added while stirring on ice. The resulting reaction mixture was stirred overnight at 25 °C to 35 °C, during which the demethylation of the methyl phosphoramidates took place. After full conversion was observed by ^{31}P NMR analysis (acetone-d_6 probe), the mixture was concentrated to dryness under reduced pressure. Purification of the crude product by flash column chromatography (neutralized SiO_2, dry loading on Celite; distilled DCM then H_2O in MeCN) followed by Dowex 50WX4 NH_4^+ ion or Na^+ ion exchange (stored on 0.10 M NH_4OAc or 0.10 M NaOAc) and subsequent lyophilization yielded the 1,7-UMP cyclic carbamates or sulfamidate target compounds as their NH_4^+ or Na^+ salts.

Methyl 6-*O*-trityl-α/β-D-xylofuranoside (25).

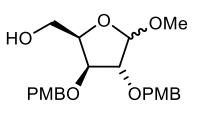


D-xylose (45 g, 300 mmol) was dissolved in MeOH (600 mL, 0.5 M) and cooled on ice. Acetyl chloride (10.7 mL, 150 mmol, 0.5 eq.) was added and the reaction mixture was stirred for 6.5 hours at room temperature to full conversion (R_f 0.5 (H_2O:MeCN, 1:9 v:v)). The reaction mixture was quenched with Et_3N to pH 8.0 and concentrated under reduced pressure. The crude, brown oil was co-evaporated with DMF (3x 120 mL) under N_2 atmosphere, dissolved in DMF (600 mL, 0.5 M) and flushed with N_2. Trityl chloride (100 g, 360 mmol, 1.2 eq.), Et_3N (66.7 mL, 480 mmol, 1.6 eq.) and DMAP (1.83 g, 15 mmol, 0.05 eq.) were added, and the reaction was stirred overnight at 30 °C. Upon full conversion (R_f 0.5 (EtOAc:pentane, 6:4, v:v)) the reaction was quenched with MeOH and concentrated *in vacuo*. The residue was dissolved in Et_2O and washed with H_2O, and the aqueous phase was extracted with Et_2O (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (40:60 EtOAc:pentane → 60:40 EtOAc:pentane) yielded **25** as a yellow oil and as anomeric mixture (132 g, 300 mmol, α:β ratio; 1.3:1, quant. over two steps). Spectroscopic data is in full agreement with literature data.[54]

Analytical data for the α-anomer: ^{1}H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.54 – 7.41 (m, 5H, CH_{arom}), 7.34 – 7.17 (m, 10H, CH_{arom}), 5.05 (d, *J* = 3.9 Hz, 1H, H-1), 4.33 – 4.12 (m, 3H, H-2, H-3, H-4), 3.53 – 3.24 (m, 4H, H-5, 1-OMe), 3.04 – 2.94 (m, 1H, 2-OH/3-OH), 2.86 (d, *J* = 6.3 Hz, 1H, 2-OH/3-OH); ^{13}C NMR (75 MHz, $CDCl_3$, HSQC): δ 143.4, 128.7, 128.5, 128.1, 127.9, 127.3, 127.0 ($C_{q\text{-}arom}$, CH_{arom}), 101.9 (C-1), 87.4 (C_q Trt), 79.8, 78.5, 77.7, 77.1 (C-2$_\beta$, C-2, C-3, C-4), 62.7 (C-5), 55.9 (1-OMe).

Analytical data for the β-anomer: ^{1}H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.54 – 7.41 (m, 5H, CH_{arom}), 7.34 – 7.17 (m, 10H, CH_{arom}), 4.86 (s, 1H, H-1), 4.49 (ddd, *J* = 6.5, 4.4, 4.4 Hz, 1H, H-4), 4.33 – 4.12 (m, 1H, H-2), 3.98 (ddd, *J* = 10.2, 4.5, 1.4 Hz, 1H, H-3), 3.53 – 3.24 (m, 4H, H-5, 1-OMe), 3.04 – 2.94 (m, 1H, 2-OH/3-OH), 2.77 (d, *J* = 4.3 Hz, 1H, 2-OH/3-OH); ^{13}C NMR (75 MHz, $CDCl_3$, HSQC): δ 143.4, 128.7, 128.5, 128.1, 127.9, 127.3, 127.0 ($C_{q\text{-}arom}$, CH_{arom}), 108.7 (C-1), 82.0 (C-4), 86.9 (C_q Trt), 79.8, 78.5, 77.7, 77.1 (C-2, C-2$_\alpha$, C-3$_\alpha$, C-4$_\alpha$), 76.8 (C-3), 63.6 (C-5), 55.3 (1-OMe); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{25}H_{26}NaO_5$ 429.1673; Found 429.1671.

Methyl 2,3-di-*O*-(4-methoxybenzyl)-α/β-D-xylofuranoside (26).



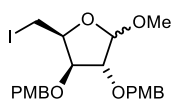
The furanose **25** (136 g, 334 mmol) was co-evaporated with toluene and dissolved in anhydrous DMF (557 mL, 0.6 M). Subsequently PMBCl (269 mL, 2.0 mol, 6.0 eq.) and TBAI (6.2 g, 17 mmol, 0.05 eq.) were added, and the reaction mixture was stirred and cooled to 0 °C. Then NaH (80 g (60% wt.), 2.0 mol, 6 eq.) was added portionwise, after which the reaction was allowed to warm to room temperature and stirred overnight. Upon full conversion (R_f 0.75 (EtOAc:pentane, 1:1 v:v)) the reaction was quenched with MeOH and concentrated under reduced pressure. The crude intermediate was dissolved in EtOAc and washed with H_2O. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*, providing a yellow oil. The crude intermediate was dissolved in a 1:1 mixture of DCM and MeOH (1.3 L, 0.25 M) and the pH was reduced to 2.0 as consequence of the addition of *p*-TsOH. The reaction was stirred overnight at room temperature. Upon full conversion

(R_f 0.25 (EtOAc:pentane, 7:3 v:v)) the reaction was quenched with Et_3N to pH 6.0 and concentrated under reduced pressure. The crude product was dissolved in EtOAc and washed with sat. aq. $NaHCO_3$ and extracted with EtOAc (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (33:67 EtOAc:pentane → 50:50 EtOAc:pentane) yielded **26** as an anomeric mixture (98.51 g, 244 mmol, α:β ratio; 1.44:1, 73% over two steps). ^{1}H NMR- and ^{13}C NMR-data correspond to literature data.[54]

Analytical data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.35 – 7.17 (m, 3H, CH_{arom}), 6.94 – 6.83 (m, 5H, CH_{arom}), 4.87 (d, *J* = 1.9 Hz, 1H, H-1), 4.62 – 4.37 (m, 4H, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.27 (ddd, *J* = 6.9, 4.8, 4.8 Hz, 1H, H-4), 4.15 (dd, *J* = 6.9, 3.9 Hz, 1H, H-3), 4.06 (dd, *J* = 3.5, 1.8 Hz, 1H, H-2), 3.81 s, 6H, OMe), 3.78 – 3.66 (m, 1H, H-5) 3.40 (s, 3H, 1-OMe), 2.52 (dd, *J* = 6.6, 6.6 Hz, 1H, 5-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.6 ($C_{q\text{-}arom}$), 130.0 (CH_{arom}), 129.8, 129.7 ($C_{q\text{-}arom}$), 129.7, 129.6, 129.6, 114.0, 114.0, 114.0 (CH_{arom}), 108.1 (C-1), 87.0 (C-2), 82.7 (C-3), 80.6 (C-4), 72.5, 72.4, 72.2, 72.0 (CH_2 $PMB_{\alpha/\beta}$), 62.4 (C-5), 55.8 (1-OMe), 55.4 (OMe).

Analytical data for the β- anomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.35 – 7.17 (m, 3H, CH_{arom}), 6.94 – 6.83 (m, 5H, CH_{arom}), 4.77 (d, *J* = 4.2 Hz, 1H, H-1), 4.62 – 4.37 (m, 4H, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.39 (d, *J* = 14.2 Hz, 1H, H-3), 4.21 – 4.16 (m, 1H, H-4), 4.01 (dd, *J* = 6.5, 4.2 Hz, 1H, H-2), 3.80 (s, 6H, OMe), 3.78 – 3.66 (m, 1H, H-5), 3.37 (s, 3H, 1-OMe), 2.41 (dd, *J* = 8.8, 5.0 Hz, 1H, 5-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.6 ($C_{q\text{-}arom}$), 130.0 (CH_{arom}), 129.8, 129.7 ($C_{q\text{-}arom}$), 129.7, 129.6, 129.6, 114.0, 114.0, 114.0 (CH_{arom}), 100.3 (C-1), 84.3 (C-2), 82.0 (C-3), 76.3 (C-4), 72.5, 72.4, 72.2, 72.0 (CH_2 $PMB_{\alpha/\beta}$), 62.4 (C-5), 55.4 (OMe), 55.2 (1-OMe); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{22}H_{28}NaO_7$ 427.1727; Found 427.1726.

Methyl 2,3-di-*O*-(4-methoxybenzyl)-5-deoxy-5-iodo-α/β-D-xylofuranoside (27).

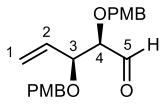


Alcohol **26** (98.6 g, 244 mmol) was co-evaporated with toluene (3x) and dissolved in anhydrous THF (750 mL, 0.3 M). Triphenylphosphine (95.9 g, 366 mmol, 1.5 eq.) and imidazole (33.2 g, 488 mmol, 2.0 eq.) were added, and the reaction was brought to reflux. I_2 (92.8 g, 366 mmol, 1.5 eq.) was dissolved in anhydrous THF (250 mL) and added dropwise to the reaction mixture, and the reaction was refluxed for another 3.5 hours. Upon full conversion was observed (R_f 0.4 (EtOAc:pentane, 2:8 v:v)), the reaction was allowed to attain to room temperature and concentrated *in vacuo*. The crude was dissolved in EtOAc and washed with sat. aq. $Na_2S_2O_3$, H_2O, and brine. The aqueous layers were extracted with EtOAc (2x), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (5:95 EtOAc:pentane → 20:80 EtOAc:pentane) yielded iodide **27** as an anomeric mixture (120 g, 233 mmol, α:β ratio; 1.44:1, 95%).

Analytical data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.16 (m, 4H, CH_{arom}), 6.95 – 6.81 (m, 4H, CH_{arom}), 4.91 (s, 1H, H-1), 4.66 – 4.31 (m, 5H, H-4, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.05 – 3.94 (m, 2H, H-2, H-3), 3.80 (s, 6H, OMe), 3.42 (s, 3H, 1-OMe), 3.39 – 3.29 (m, 2H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.6, 159.4 ($C_{q\text{-}arom}$), 129.9, 129.8 (CH_{arom}), 129.7, 129.7 ($C_{q\text{-}arom}$), 129.6, 129.6, 114.0, 114.0, 113.9 (CH_{arom}), 108.5 (C-1), 86.5 (C-2), 82.1, 81.7, 81.5 (C-3, C-4, C-3_β), 72.4 (CH_2 PMB), 56.2 (1-OMe), 55.4 (OMe), 4.8 (C-5).

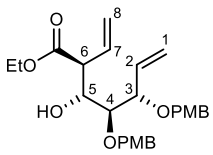
Analytical data for the β- anomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.16 (m, 4H, CH_{arom}), 6.95 – 6.81 (m, 4H, CH_{arom}), 4.82 (d, *J* = 4.3 Hz, 1H, H-1), 4.66 – 4.31 (m, 5H, H-4, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.18 – 4.12 (m, 1H, H-3), 4.05 – 3.94 (m, 1H, H-2), 3.80 (s, 6H, OMe), 3.40 (s, 3H, 1-OMe), 3.39 – 3.29 (m, 1H, H-5), 3.18 (dd, *J* = 10.3, 7.4 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.6, 159.5 ($C_{q\text{-}arom}$), 129.9, 129.8 (CH_{arom}), 129.7, 129.7 ($C_{q\text{-}arom}$), 129.7, 129.6, 114.0, 114.0, 113.9 (CH_{arom}), 101.0 (C-1), 83.6 (C-2), 82.1, 81.7, 81.5 (C-3, C-3$_\alpha$, C-4$_\alpha$), 77.7 (C-4), 71.9 (CH_2 PMB), 55.6 (1-OMe), 55.4 (OMe), 3.3 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{22}H_{27}INaO_6$ 537.0745; Found 537.0747.

(2*R*,3*S*)-2,3-Di-*O*-(4-methoxybenzyl)-pent-4-enal (28).



27 (96.3 g, 187 mmol) was dissolved in THF/H_2O (9:1, 936 mL, 0.2 M) and purged with argon gas. Meanwhile, zinc dust was stirred in 3.0 M HCl (aq.) for 10 minutes. The acidic solution was removed by filtration and the activated zinc was consecutively washed with H_2O (3x), acetone (3x) and Et_2O (3x). The zinc was subsequently dried *in vacuo*. The activated zinc (3.4 mol, 218 g, 18 eq.) was added to the THF/H_2O solution of **27**, and the reaction mixture was purged with argon. The reaction was sonicated for 12 hours while maintaining a temperature of 40 °C. Upon full conversion was observed (R_f 0.6 (EtOAc:pentane, 3:7, v:v)), the suspension was filtered over a celite plug and rinsed with Et_2O (6x). The filtrate was concentrated under reduced pressure at 30 °C to remove THF. The crude mixture was dissolved in Et_2O and washed with H_2O (2x). The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 30 °C. Flash column chromatography (10:90 EtOAc:pentane → 30:70 EtOAc:pentane) yielded **28** as a yellowish oil (54.2 g, 152 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 9.61 (d, *J* = 1.6 Hz, 1H, H-5), 7.25 – 6.85 (m, 8H, CH_{arom}), 5.91 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1H, H-2), 5.33 (m, 2H, H-1), 4.65 (d, *J* = 11.8 Hz, 1H, C*H*H PMB), 4.61 – 4.51 (m, 2H, C*H*H PMB, CH*H* PMB), 4.27 (d, *J* = 11.7 Hz, 1H, CH*H* PMB), 4.12 (dddd, *J* = 7.6, 4.0, 1.0, 1.0 Hz, 1H, H-3), 3.80 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.77 (dd, *J* = 4.0, 1.6 Hz, 1H, H-4); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 203.0 (C-5), 159.7, 159.4 ($C_{q\text{-}arom}$), 134.1 (C-2), 130.0, 129.7 (CH_{arom}), 129.7, 129.2 ($C_{q\text{-}arom}$), 119.8 (C-1), 114.8, 113.4 (CH_{arom}), 85.0 (C-4), 79.7 (C-3), 73.3, 70.4 (CH_2 PMB), 55.4, 55.4 (OMe); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{21}H_{24}NaO_5$ 379.1516; Found 379.1513.

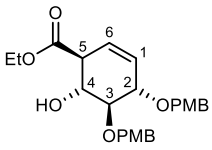
Ethyl (2*S*,3*R*,4*S*,5*S*)-3-hydroxy-4,5-bis((4-methoxybenzyl)oxy)-2-vinylhept-6-enoate (29).



28 (20 g, 56.1 mmol) was suspended in H_2O (280 mL, 0.2 M), and stirred vigorously. Consecutively, ethyl-4-bromocrotonate (42.9 mL, 252 mmol, 4.5 eq.), $La(OTf)_3$ (66.1 g, 112 mmol, 2 eq.) and indium powder (8.3 g, 73 mmol, 1.3 eq) were added. The reaction was stirred vigorously. At day 2 and 3 more indium powder was added (3.2 g, 28 mmol, 0.5 eq, each day). The reaction was stirred 5 days in total at room temperature to full conversion (R_f 0.55 (EtOAc:pentane, 3:7, v:v)). The suspension was filtered over a celite plug, and the residue was rinsed with Et_2O (6x). The filtrate was washed with sat. aq. $NaHCO_3$, and the aqueous phase was extracted with Et_2O (3x). The combined organic phases were washed once again with sat. aq. $NaHCO_3$, and the aqueous phase was extracted with Et_2O. All organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 5:95 EtOAc:pentane → 30:70 EtOAc:pentane) yielded glucose configured **29** as a colorless

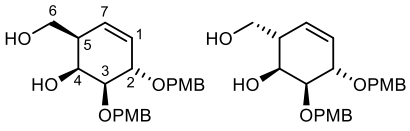
oil contaminated with an unidentifiable amount of L-idose configured diene (23 g, 50 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.43 – 7.07 (m, 4H, CH_{arom}), 6.99 – 6.65 (m, 4H, CH_{arom}), 5.80 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H, H-2), 5.69 (ddd, *J* = 17.2, 10.2, 9.3 Hz, 1H, H-7), 5.42 – 5.34 (m, 2H, H-1), 5.15 (ddd, *J* = 10.2, 1.3, 0.4 Hz, 1H, H-8), 5.06 (ddd, *J* = 17.2, 1.4, 0.8 Hz, 1H, H-8), 4.89 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.55 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.50 (d, *J* = 10.8 Hz, 1H, CH*H* PMB), 4.33 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.12 (m, 3H, H-3, CH_2 Et), 3.95 (ddd, *J* = 9.9, 9.2, 1.2 Hz, 1H, H-5), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.50 (dd, *J* = 7.5, 1.2 Hz, 1H, H-4), 3.25 (dd, *J* = 9.2, 9.2 Hz, 1H, H-6), 2.66 (d, *J* = 9.8 Hz, 1H, 5-OH), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 172.6 (C=O), 159.4, 159.3 ($C_{q\text{-}arom}$), 135.2 (C-2), 133.1 (C-7), 130.7, 130.6 ($C_{q\text{-}arom}$), 129.8, 129.5 (CH_{arom}), 119.9, 119.8 (C-1, C-8), 113.9 (CH_{arom}), 82.7 (C-3), 79.0 (C-4), 74.2 (CH_2 PMB), 72.2 (C-5), 70.6 (CH_2 PMB), 60.9 (CH_2 Et), 55.4, 55.4, 55.3 (C-6, OMe), 14.2 (CH_3 Et); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{27}H_{34}NaO_7$ 493.2197; Found 493.2194.

Ethyl (1*S*,4*S*,5*S*,6*R*)-6-hydroxy-4,5-bis((4-methoxybenzyl)oxy)cyclohex-2-ene-1-carboxylate (30).



Diene **29** (23 g, 50 mmol) was dissolved in anhydrous DCM (415 mL, 0.12 M) and purged in argon gas. Second generation Grubbs catalyst (1.7 g, 0.04 eq.) was added in the dark and the flask was purged again in argon gas. The reaction was stirred two days at 38 °C in the dark. Upon full conversion (R_f 0.3 (EtOAc:pentane, 3:7, v:v)) the reaction was concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 30:70 EtOAc:pentane) yielded **30** as a brown oil contaminated with an unidentifiable amount of L-idose configured cyclohexene (20.2 g, 46 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.29 – 7.22 (m, 4H, CH_{arom}), 6.90 – 6.84 (m, 4H, CH_{arom}), 5.76 (ddd, *J* = 10.2, 2.9, 2.2 Hz, 1H, H-6), 5.64 (ddd, *J* = 10.2, 2.2, 2.2 Hz, 1H, H-1), 4.87 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.70 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.62 – 4.58 (m, 2H, CH*H* PMB, CH*H* PMB), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2 Et), 4.14 (dddd, *J* = 7.5, 3.3, 2.1, 2.1 Hz, 1H, H-2), 4.09 (ddd, *J* = 9.8, 8.9, 2.4 Hz, 1H, H-4), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.60 (dd, *J* = 9.8, 7.5 Hz, 1H, H-3), 3.23 (dddd, *J* = 8.8, 3.1, 3.1, 2.5 Hz, 1H, H-5), 2.98 (d, *J* = 2.5 Hz, 1H, 4-OH), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 172.0 ($C_{q\text{-}arom}$), 171.9 (C=O), 159.4, 130.6, 130.2 ($C_{q\text{-}arom}$), 129.6, 129.6 (CH_{arom}), 128.5 (C-6), 124.0 (C-1), 114.0, 113.9 (CH_{arom}), 82.2 (C-3), 79.0 (C-2), 74.5, 71.7 (CH_2 PMB), 70.4 (C-4), 61.3 (CH_2 Et), 55.3 (OMe), 50.2 (C-5), 14.3 (CH_3 Et); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{25}H_{30}NaO_7$ 465.1884; Found 465.1886.

2,3-Di-*O*-(4-methoxybenzyl)-cyclophellitol alkene (31) and 2,3-Di-*O*-(4-methoxybenzyl)-5-*epi*-cyclophellitol alkene (32).



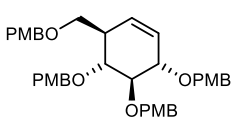
Cyclohexene **30** (20.2 g, 46 mmol) was co-evaporated once with toluene, dissolved in anhydrous THF (457 mL, 0.1 M), purged with N_2 gas and cooled to 0 °C. While stirring, $LiBH_4$ (4 M in THF, 28.6 mL, 2.5 eq.) was slowly added. The reaction was allowed to warm to room temperature and stirred for 5 hours. Upon full conversion was observed (R_f 0.2 and 0.3 for the D-glucose and L-idose configured diol respectively (EtOAc:pentane, 7:3, v:v)) the reaction was quenched with sat.

aq. NH_4Cl. The layers were separated and the green aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 50:50 EtOAc:pentane) yielded the D-glucose and L-idose configured diol **31** and **32** as a colourless solid and brown oil respectively (17.6 g, 43.8 mmol, 96% for the glucose configuration and 0.37 g, 0.91 mmol, 2% for the idose configuration).

Analytical data for the glucose configured diol **31**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.32 –6.84 (m, 8H, CH_{arom}), 5.75 (ddd, *J* = 10.2, 2.9, 2.1 Hz, 1H, H-7), 5.49 (ddd, *J* = 10.3, 2.0, 2.0 Hz, 1H, H-1), 4.94 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.70 – 4.61 (m, 2H, C*H*H PMB, CH*H* PMB), 4.58 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.16 (ddd, *J* = 7.1, 3.6, 1.7 Hz, 1H, H-2), 3.81 (s, 6H, OMe), 3.79 – 3.55 (m, 4H, H-3, H-4, H-6), 2.89 (d, *J* = 1.3 Hz, 1H, 4-OH), 2.53 – 2.46 (m, 1H, H-5), 2.43 (dd, *J* = 8.2, 2.9 Hz, 1H, 6-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 130.6, 130.3 ($C_{q\text{-}arom}$), 129.8, 129.7 (CH_{arom}), 127.7 (C-7), 127.3 (C-1), 114.1, 114.1 (CH_{arom}), 83.0 (C-3), 80.0 (C-2), 74.6 (CH_2 PMB), 73.0 (C-4), 71.3 (CH_2 PMB), 65.7 (C-6), 55.4 (OMe), 45.3 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{23}H_{28}NaO_6$ 423.1778; Found 423.1778.

Analytical data for the idose configured diol **32** : ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.33 – 7.18 (m, 3H, CH_{arom}), 6.95 – 6.84 (m, 5H, CH_{arom}), 5.78 (ddd, *J* = 10.2, 2.7, 1.8 Hz, 1H, H-1), 5.63 (ddd, *J* = 10.2, 4.1, 1.6 Hz, 1H, H-7), 4.86 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.69 – 4.47 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.08 – 4.00 (m, 2H, H-2, H-4), 3.81 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.80 – 3.76 (m, 2H, H-3, H-6), 3.67 (ddd, *J* = 11.7, 8.8, 3.2 Hz, 1H, H-6), 3.16 (d, *J* = 3.4 Hz, 1H, 4-OH), 3.13 (dd, *J* = 8.8, 3.6 Hz, 1H, 6-OH), 2.89 – 2.73 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 130.4, 130.0 ($C_{q\text{-}arom}$), 129.7, 129.7 (CH_{arom}), 127.6 (C-7), 127.1 (C-1), 114.2 114.1 (CH_{arom}), 78.2, 78.2 (C-2, C-3), 73.9 (CH_2 PMB), 71.3 (C-4), 71.3 (CH_2 PMB), 64.1 (C-6), 55.5, 55.4 (OMe), 41.9 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{23}H_{28}NaO_6$ 423.1778; Found 423.1775.

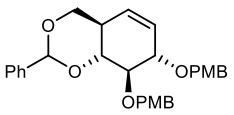
2,3,4,6-Per-*O*-(4-methoxybenzyl)-cyclophellitol alkene (33).



Cyclohexene diol **31** (3.2 g, 5.0 mmol) was co-evaporated with toluene (1x), dissolved in anhydrous DMF (20 mL, 0.25 M) and cooled on ice. Subsequently, PMBCl (1.1 mL, 20 mmol, 4.0 eq.), TBAI (0.02 g, 0.05 mmol, 0.01 eq.) and NaH (60% wt., 0.8 g, 20 mmol, 4.0 eq.) were added. The reaction was purged in N_2 and stirred overnight at room temperature. Upon full conversion (R_f 0.5 (EtOAc:pentane, 3:7 v:v)), the reaction was quenched with MeOH and concentrated under reduced pressure. The crude was dissolved in EtOAc, and washed with H_2O. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 20:80 EtOAc:pentane) yielded cyclohexene **33** as a yellow oil (2.9 g, 4.6 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.32 – 7.16 (m, 6H, CH_{arom}), 7.14 – 7.06 (m, 2H, CH_{arom}), 6.89 – 6.78 (m, 8H, CH_{arom}), 5.70 – 5.60 (m, 2H, H-1, H-7), 4.86 – 4.78 (m, 3H, C*H*H PMB, C*H*H PMB, C*H*H PMB), 4.63 – 4.59 (m, 2H, C*H*H PMB, CH*H* PMB), 4.41 (d, *J* = 11.9 Hz, 1H, CH*H* PMB), 4.36 – 4.30 (m, 2H, CH*H* PMB, CH*H* PMB), 4.20 (dddd, *J* = 7.5, 3.7, 1.8, 1.8 Hz, 1H, H-2), 3.80 (s, 6H, OMe), 3.79 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.73 (d, *J* = 7.9 Hz, 1H, H-3), 3.59 (dd, *J* = 9.8, 9.8 Hz, 1H, H-4), 3.47 (d, *J* = 4.1 Hz, 2H, H-6), 2.48 (dddd, *J* = 5.1, 5.1, 2.9, 2.9 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.3, 159.3, 159.2, 131.3, 131.0, 130.8, 130.4 ($C_{q\text{-}arom}$), 129.8,

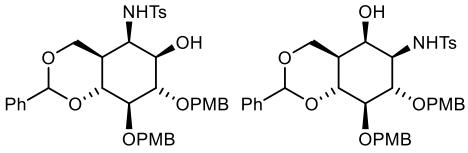
129.7, 129.6, 129.6 (CH_{arom}), 129.3, 127.1 (C-1, C-7), 113.9, 113.9, 113.9 (CH_{arom}), 85.3 (C-3), 80.8 (C-2), 78.3 (C-4), 75.1, 75.0, 72.8, 71.9 (CH_2 PMB), 68.9 (C-6), 55.4, 55.4 (OMe), 44.5 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{44}NaO_8$ 663.2928; Found 663.2924.

2,3-Di-*O*-((4-methoxybenzyl)-4,6-*O*-benzylidene-cyclophellitol alkene (36).



Diol **31** (3.6 g, 9.0 mmol) was dissolved in anhydrous DMF (18 mL, 0.5 M) after which benzaldehyde dimethyl acetal (2.7 mL, 18 mmol, 2.0 eq.) and *p*-TsOH (17 mg, 90 µmol, 0.01 eq.) were added. The mixture was rotated under reduced pressure (<20 mbar) at 25 °C for 4 hours. Upon full conversion (R_f 0.6 (EtOAc:pentane, 3:7, v:v)) the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 25:75 EtOAc:pentane) yielded **36** as a colorless oil (3.7 g, 7.7 mmol, 85%). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.59 – 7.45 (m, 2H, CH_{arom}), 7.43 – 7.13 (m, 3H, CH_{arom}), 6.94 – 6.70 (m, 8H, CH_{arom}), 7.59 – 7.45 (m, 1H, H-7), 5.62 (s, 1H, CHPh), 5.40 – 5.34 (m, 1H, H-1), 4.94 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.73 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.66 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.59 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.28 (dd, *J* = 10.8, 4.6 Hz, 1H, H-6), 4.24 (dddd, *J* = 5.4, 2.8, 2.8, 2.8 Hz, 1H, H-2), 3.96 (dd, *J* = 10.4, 6.9 Hz, 1H, H-3), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.77 (d, *J* = 9.6 Hz, 1H, H-4), 3.64 (dd, *J* = 11.2, 11.2 Hz, 1H, H-6), 2.68 (dddd, *J* = 13.9, 8.3, 4.2, 4.2 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 138.4, 131.1, 130.7 ($C_{q\text{-}arom}$), 129.9, 129.6 (CH_{arom}), 129.3 (C-7), 128.9, 128.3, 126.1 (CH_{arom}), 125.1 (C-1), 113.9, 113.9 (CH_{arom}), 101.7 (CHPh), 82.3 (C-4), 81.8 (C-3), 80.5 (C-2), 74.5, 72.1 (CH_2 PMB), 70.2 (C-6), 55.4 (OMe), 38.7 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{32}NaO_6$ 511.2091; Found 511.2090.

2,3,-Di-*O*-(4-methoxybenzyl)-4,6-di-*O*-benzylidene-7-(*R*)-(*p*-toluenesulfonamido)-1-(*R*)-ol cyclophellitol alkane (37) and 1-(*R*)-(*p*-toluenesulfonamido)-2,3-di-*O*-(4-methoxybenzyl)-4,6-di-*O*-benzylidene-7-(*R*)-ol cyclophellitol alkane (38).

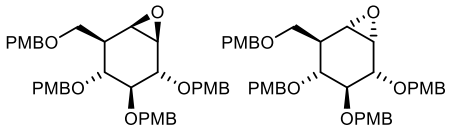


Cyclohexene **36** (0.12 g, 0.25 mmol) was dissolved in $CHCl_3$ (2.5 mL, 0.1 M) and flushed in N_2. Subsequently, chloramine-T hydrate (0.1 g, 0.5 mmol, 2.0 eq.) was added and the reaction was stirred vigorously. After 5 min, benzyltriethylammonium chloride (TEBACl, 0.003 g, 0.015 mmol, 0.06 eq.) was added and stirred vigorously. After 5 min, H_2O (2.5 mL) was added and stirred vigorously for 10 min. Finally, potassium osmate ($K_2[OsO_2(OH)_4]$) (0.005 g, 0.013 mmol, 0.05 eq.) was added and the reaction was stirred vigorously overnight at 60 °C. Upon partial conversion (R_f 0.8 and 0.6 for **37** and **38** respectively (EtOAc:pentane 1:1 v:v)), the reaction was cooled to room temperature, quenched with sat. aq. $Na_2S_2O_3$ and stirred for 30 min at 60 °C. The mixture was extracted with Et_2O (3x), and the organic layers were washed with 1% wt. NaOH (3x) and brine. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 20:80 EtOAc:pentane → 40:60 EtOAc:pentane) yielded the starting material (44 mg, 0.09 mmol) and regioisomers as colorless oils (15 mg, 22 µmol, 8.8% for **37** and 9 mg, 13 µmol, 5.2% for **38**, and 28 mg, 0.041 mmol, 16.5% mix fractions, 66% brsm). Analytical

data for **37**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.78 – 7.31 (m, 8H, CH_{arom}), 7.31 – 7.10 (m, 5H, CH_{arom}), 6.95 – 6.72 (m, 4H, CH_{arom}), 5.54 (s, 1H, CHPh), 4.90 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.87 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.71 (d, *J* = 5.9 Hz, 1H, 7-NHTs), 4.68 (d, *J* = 10.8 Hz, 1H, CH*H* PMB), 4.56 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.16 – 4.03 (m, 2H, H-6), 3.97 (dd, *J* = 11.0, 9.1 Hz, 1H, H-4), 3.81 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.59 (dd, *J* = 9.1, 9.1 Hz, 1H, H-3), 3.57 – 3.52 (m, 2H, H-1, H-7), 3.34 (dd, *J* = 9.2, 9.2 Hz, 1H, H-2), 2.41 (s, 3H, $PhCH_3$), 2.18 (d, *J* = 1.9 Hz, 1H, 1-OH), 1.83 (dddd, *J* = 10.8, 10.8, 4.8, 2.5 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HH-COSY, HSQC): δ 159.6, 159.4, 143.9, 138.1, 136.4, 130.7, 130.4 ($C_{q\text{-}arom}$), 129.9, 129.8, 129.6, 128.9, 128.3, 127.9, 126.0, 114.1, 113.9 (CH_{arom}), 100.8 (CHPh), 82.7 (C-3), 80.8 (C-2), 79.2 (C-4), 75.4, 75.1 (CH_2 PMB), 71.6 (C-1), 68.9 (C-6), 55.4 (OMe), 52.8 (C-7), 37.8 (C-5), 21.8 ($PhCH_3$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{37}H_{41}NNaO_9S$ 698.2394; Found 698.2396.

Analytical data for **38**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.69 – 6.71 (m, 17H, CH_{arom}), 5.56 (s, 1H, CHPh), 4.89 (d, *J* = 10.4 Hz, 1H, C*H*H PMB), 4.78 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.63 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.59 (d, *J* = 3.1 Hz, 1H, 1-NHTs), 4.49 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.22 – 4.07 (m, 4H, H-4, H-6, H-7), 3.84 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.65 – 3.55 (m, 2H, H-2, H-3), 2.89 (ddd, *J* = 10.2, 3.0, 3.0 Hz, 1H, H-1), 2.55 (d, *J* = 3.0 Hz, 1H, 7-OH), 2.42 (s, 3H, $PhCH_3$), 1.77 (ddd, *J* = 10.8, 10.8, 6.9 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.75, 159.35, 144.07, 138.33, 135.72, 130.77, 130.04 ($C_{q\text{-}arom}$), 129.95, 129.91, 129.62, 128.87, 127.37, 126.12, 114.37, 113.83 (CH_{arom}), 100.81 (CHPh), 84.00 (C-2/C-3), 78.63 (C-4), 77.24 (C-2/C-3), 75.11, 74.95 (CH_2PMB), 68.31 (C-6), 67.23 (C-7), 59.94 (C-1), 55.44 (OMe), 39.13 (C-5), 21.73 ($PhCH_3$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{37}H_{41}NNaO_9S$ 698.2394; Found 698.2393.

2,3,4,6-Tetra-*O*-(4-methoxybenzyl) cyclophellitol (39) and 1,7-*Epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl) cyclophellitol (40).

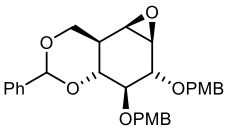


Per-PMB protected cyclohexene **33** (6.66 g, 10.4 mmol) was dissolved in anhydrous DCM (104 mL, 0.1 M) and cooled on ice. Subsequently, *m*-CPBA (3.9 g, 22.9 mmol, 2.2 eq.) was added and the reaction was purged with argon gas. The reaction was stirred overnight at room temperature. Upon partial conversion (R_f 0.32 and 0.26 for the β- and α-epoxide respectively (acetone:pentane, 2:8 v:v)) the reaction was quenched with sat. aq. $Na_2S_2O_4$. The aqueous layer was extracted with Et_2O (3x). The organic layers were combined and washed with sat. aq. $NaHCO_3$. The bicarb layer was extracted once with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (dry loading, 3:97 acetone:pentane → 15:85 acetone:pentane) yielded the epoxides as colourless oils (0.66 g, 1.0 mmol, 9.7% for α-epoxide **40** and 2.2 g, 3.4 mmol, 32% for β-epoxide **39**). Analytical data for α-epoxide **40**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.03 (m, 8H, CH_{arom}), 6.94 – 6.77 (m, 8H, CH_{arom}), 4.80 – 4.70 (m, 5H, C*H*H PMB, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.38 (d, *J* = 11.8 Hz, 1H, C*H*H PMB), 4.31 – 4.16 (m, 2H, CH*H* PMB, CH*H* PMB), 3.83 (dd, *J* = 8.5, 1.8 Hz, 1H, H-2), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.66 (dd, *J* = 10.2, 8.5 Hz, 1H, H-3), 3.55 – 3.47 (m, 2H, H-6), 3.41 (dd, *J* = 10.0, 10.0 Hz, 1H, H-4), 3.27 (dd, *J* = 4.0, 1.8 Hz, 1H, H-1), 3.13 (d, *J* = 4.0 Hz, 1H, H-7), 2.16 (ddd, *J* = 10.0, 3.4, 3.4 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.3, 159.2, 159.2, 131.1, 130.8, 130.7, 130.1 ($C_{q\text{-}arom}$), 129.6, 129.6,

129.5, 113.8, 113.8, 113.8 (CH_{arom}), 82.2 (C-3), 79.6 (C-2), 77.4 (C-4), 75.4, 74.9, 72.8, 72.5 (CH_2 PMB), 67.9 (C-6), 55.3, 55.3, 55.2, 54.8 (C-1, C-7, OMe), 42.9 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{44}NaO_9$ 679.2878; Found 679.2874.

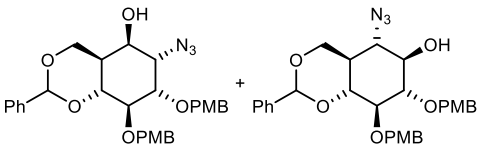
Analytical data for β-epoxide **39**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.17 (m, 5H, CH_{arom}), 7.16 – 7.04 (m, 2H, CH_{arom}), 6.95 – 6.71 (m, 9H, CH_{arom}), 4.87 – 4.55 (m, 5H, C*H*H PMB, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.45 (m, 2H, C*H*H PMB, CH*H* PMB), 4.30 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 3.82 (d, *J* = 0.9 Hz, 1H, H-2), 3.80 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.80 (s, 6H, OMe), 3.69 (dd, *J* = 8.8, 3.5 Hz, 1H, H-6), 3.56 – 3.39 (m, 3H, H-3, H-6, H-7), 3.19 (dd, *J* = 10.0, 10.0 Hz, 1H, H-4), 3.15 (d, *J* = 3.7 Hz, 1H, H-1), 2.23 (dddd, *J* = 10.2, 8.8, 3.5, 1.6 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.4, 159.3, 159.3, 131.1, 130.6, 130.5, 130.0 ($C_{q\text{-}arom}$), 129.8, 129.8, 129.6, 129.4, 114.1, 113.9, 113.9, 113.9 (CH_{arom}), 84.9 (C-3), 79.8 (C-2), 75.2, 75.1 (CH_2 PMB), 75.0 (C-4), 73.0, 73.0 (CH_2 PMB), 68.4 (C-6), 55.8 (C-7), 55.4, 55.4, 55.4 (OMe), 54.1 (C-1), 42.7 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{44}NaO_9$ 679.2878; Found 679.2876.

2,3-Di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene cyclophellitol (41).



Cyclohexene **36** (0.70 g, 1.3 mmol) was dissolved in anhydrous DCM (23 mL, 0.06 M). Subsequently, $NaHCO_3$ (1.1 g, 13 mmol, 10 eq.) and *m*-CPBA (0.6 g, 3.3 mmol, 2.5 eq.) were added. The reaction was stirred under N_2 atmosphere at 5 °C for 6 days. Upon partial conversion was observed (R_f 0.4 (EtOAc:pentane, 3:7, v:v)), the reaction was quenched with sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were subsequently washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 10:90 EtOAc:pentane → 30:70 EtOAc:pentane) yielded **41** as a single diastereoisomer (0.37 g, 0.74 mmol, 56%) and starting material (98 mg, 0.18 mmol, 14%) 70% brsm ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.56 – 7.16 (m, 9H, CH_{arom}), 6.96 – 6.77 (m, 4H, CH_{arom}), 5.58 (s, 1H, CHPh), 4.84 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.70 – 4.68 (m, 2H, C*H*H PMB, CH*H* PMB), 4.65 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.35 (dd, *J* = 11.0, 4.3 Hz, 1H, H-6), 4.00 (dd, *J* = 11.1, 11.1 Hz, 1H, H-6), 3.92 (d, *J* = 7.1 Hz, 1H, H-2), 3.83 (d, *J* = 10.0 Hz, 1H, H-4), 3.81 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.66 (dd, *J* = 10.4, 7.0 Hz, 1H, H-3), 3.15 (d, *J* = 3.8 Hz, 1H, H-1), 3.07 (d, *J* = 3.7 Hz, 1H, H-7), 2.36 (dddd, *J* = 11.2, 9.9, 4.2, 1.1 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.3, 138.2, 130.9, 129.9 ($C_{q\text{-}arom}$), 129.9, 129.8, 128.9, 128.3, 126.1, 114.1, 113.8 (CH_{arom}), 101.4 (CHPh), 81.4 (C-3), 78.9 (C-2), 77.0 (C-4), 74.6, 73.3 (CH_2 PMB), 68.7 (C-6), 55.4, 55.4 (OMe), 53.2 (C-7), 53.0 (C-1) , 37.9 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{32}NaO_7$ 527.2040; Found 527.2041.

1-(*S*)-Azido-2,3-di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene-7-(*R*)-ol cyclophellitol alkane (42) and 2,3-Di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene-7-(*S*)-azido-1-(*R*)-ol cyclophellitol alkane (43).



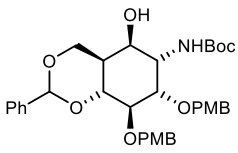
Epoxide **41** (6.1 g, 12 mmol) was dissolved in anhydrous DMF (121 mL, 0.1 M). Subsequently NaN_3 (16 g, 242 mmol, 20 eq.) and $LiClO_4$ (2.6 g, 24 mmol, 2.0 eq.) were added. The reaction was stirred under argon

atmosphere at 100 °C overnight. Upon full conversion was observed (R_f 0.5 and 0.7 for **42** and **43** respectively (EtOAc:pentane, 3.5:6.5, v:v)) the reaction was allowed to cool to room temperature and diluted with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine. The organic layers were subsequently dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 40:60 EtOAc:pentane) yielded the 1,7-(*N*,*O*) and –(*O*,*N*) regioisomers as a yellowish oil and solid respectively (5.0 g, 9.1 mmol, 75% for the 1,7-(*N*,*O*) isomer **42** and 1.7 g, 3.1 mmol, 25% for the 1,7-(*O*,*N*) isomer **43**).

Analytical data for the 1,7-(*N*,*O*) regioisomer **42**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.56 – 7.44 (m, 2H, CH_{arom}), 7.42 – 7.27 (m, 7H, CH_{arom}), 6.91 – 6.80 (m, 4H, CH_{arom}), 5.54 (s, 1H, CHPh), 4.85 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.80 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.73 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.65 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.14 (dd, *J* = 10.8, 4.4 Hz, 1H, H-6), 4.09 – 3.82 (m, 5H, H-1, H-2, H-3, H-4, H-6), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 – 3.71 (m, 1H, H-7), 2.13 (dddd, *J* = 11.0, 11.0, 4.4, 2.2 Hz, 1H, H-5), 1.57 (d, *J* = 4.4 Hz, 1H, 7-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 138.2, 131.2, 130.5 ($C_{q\text{-}arom}$), 129.9, 129.7, 128.9, 128.3, 126.1, 114.0, 113.8 (CH_{arom}), 101.0 (CHPh), 80.7 (C-2), 78.9, 78.7 (C-3, C-4), 75.5, 73.7 (CH_2 PMB), 68.8 (C-1), 68.1 (C-6), 64.8 (C-7), 55.4 (OMe), 36.9 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{33}N_3NaO_7$ 570.2211; Found 570.2209.

Analytical data for the 1,7-(*O*,*N*) regioisomer **43**: ^{1}H NMR (500 MHz, $CDCl_3$ HH-COSY, HSQC): δ 7.53 – 7.20 (m, 8H, CH_{arom}), 6.92 – 6.81 (m, 5H, CH_{arom}), 5.54 (s, 1H, CHPh), 4.94 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.90 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.71 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.61 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.44 (dd, *J* = 11.1, 4.4 Hz, 1H, H-6), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.72 – 3.64 (m, 3H, H-3, H-4, H-6), 3.62 (ddd, *J* = 9.4, 9.4, 2.2 Hz, 1H, H-1), 3.37 (ddd, *J* = 9.1, 6.6, 2.5 Hz, 1H, H-2), 3.09 (dd, *J* = 11.8, 9.5 Hz, 1H, H-7), 2.54 (d, *J* = 2.3 Hz, 1H, 1-OH), 1.77 (dddd, *J* = 10.8, 10.7, 10.7, 4.3 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 137.9, 130.6 ($C_{q\text{-}arom}$), 130.1, 129.9, 129.1, 128.4, 126.1, 114.3, 114.0 (CH_{arom}), 101.5 (CHPh), 82.4 (C-2), 82.1 , 81.0 (C-3, C-4), 76.5 (C-1), 75.5, 75.3 (CH_2 PMB), 69.5 (C-6), 61.1 (C-7), 55.4, 55.4 (OMe), 38.3 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{33}N_3NaO_7$ 570.2211; Found 570.2206.

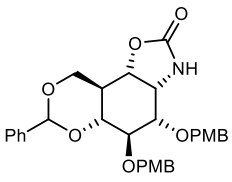
1-(*S*)-(*N*-(Tert-butoxycarbonyl)-2,3-di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene-7-(*R*)-ol cyclophellitol alkane (44).



Azide **42** (0.27 g, 0.5 mmol) was dissolved in a 1:1 solution of THF and aq. 1.0 M NaOH (5.0 mL, 0.1 M). Subsequently triphenylphosphine (0.5 g, 2.0 mmol, 4.0 eq.) was added and the reaction was stirred vigorously overnight at room temperature. Upon full conversion of the starting material was observed, the reaction was diluted with sat. aq. $NaHCO_3$ and EtOAc. The aqueous phase was separated and subsequently extracted with EtOAc (3x), the organic layers were then washed with brine. The brine layer was extracted once with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude amine was dissolved in anhydrous DCM (2.5 mL, 0.2 M) and cooled on ice. While stirring, Boc_2O (0.13 g, 0.6 mmol, 1.2 eq.) and Et_3N (0.35 mL, 2.5 mmol, 5.0 eq.) were added. The flask was flushed in N_2 and the reaction was stirred at room temperature for 22 hours until full conversion was observed (R_f 0.4 (EtOAc:pentane, 4:6, v:v)). The reaction was quenched with

sat. aq. NH_4Cl and the aqueous layer separated. Subsequently, the aqueous layer was extracted with EtOAc (3x), and the combined organic layers were washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 10:90 EtOAc:pentane → 50:50 EtOAc:pentane) yielded **44** as a white, brittle foam (0.2 g, 0.33 mmol, 66% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.53 – 7.48 (m, 2H, CH_{arom}), 7.41 – 7.32 (m, 3H, CH_{arom}), 7.27 (m, 4H, CH_{arom}), 6.84 (m, 4H, CH_{arom}), 5.58 (s, 1H, CHPh), 4.90 (d, *J* = 3.9 Hz, 1H, 1-NHBoc), 4.82 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.71 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.56 (m, 2H, CH*H* PMB, CH*H* PMB), 4.22 – 4.12 (m, 3H, H-3, H-6, H-7), 4.09 (dd, *J* = 11.0, 11.0 Hz, 1H, H-6), 4.02 – 3.96 (m, 2H, H-1, H-4), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.62 (dd, *J* = 8.7, 8.7 Hz, 1H, H-5), 2.13 (dd, *J* = 11.5, 11.5 Hz, 1H, H-2), 2.05 (s, 1H, 7-OH), 1.45 (s, 9H, $C(CH_3)_3$ Boc); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7, 159.4 ($C_{q\text{-}arom}$), 138.5 (C=O Boc), 131.2, 130.2 ($C_{q\text{-}arom}$), 129.7, 129.7, 128.8, 128.3, 126.1, 114.0, 113.8 (CH_{arom}), 100.9 (CHPh), 80.6 (C-5), 80.3 (*C*$(CH_3)_3$) 78.6 (C-3, C-7), 76.7 (C-4), 75.1, 72.1 (CH_2 PMB), 68.5 (C-6), 55.4 (OMe), 54.8 (C-1), 36.8 (C-2), 28.1 (C(*C*$H_3)_3$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{35}H_{43}NNaO_9$ 644.2830; Found 644.2831.

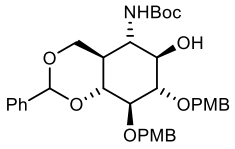
1,7-(*S*,*S*)-(*N*,*O*)-Carbamate-2,3-di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene cyclophellitol alkane (46).



The Boc-protected amino alcohol **44** (6.0 g, 9.7 mmol) was co-evaporated with toluene, dissolved in anhydrous $CHCl_3$ (97 mL, 0.1 M) and cooled on ice. Subsequently Me-imidazole (7.8 mL, 97 mmol, 10 eq.), MsCl (3.8 mL, 49 mmol, 5.0 eq.) and Et_3N (6.8 mL, 49 mmol, 5.0 eq.) were added. The reaction was flushed with N_2 and stirred overnight at room temperature. Upon full conversion (R_f 0.6 (EtOAc:pentane, 4:6, v:v)) the reaction was diluted with EtOAc and washed with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous DMF (487 mL, 0.02 M), flushed with argon gas and stirred at 120 °C overnight. Upon full conversion (R_f 0.7 (EtOAc:pentane, 9:1, v:v)) the reaction was cooled to room temperature and concentrated to a fifth of its original volume. The residue was diluted with EtOAc and washed with H_2O and consequently brine. The aqueous layers were back-extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 50:50 EtOAc:pentane → 90:10 EtOAc:pentane) yielded the carbamate **46** as a yellowish, brittle foam (3.3 g, 6.0 mmol, 68% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.51 – 7.47 (m, 2H, CH_{arom}), 7.39 (m, 3H, CH_{arom}), 7.24 – 7.17 (m, 4H, CH_{arom}), 6.91 – 6.80 (m, 4H, CH_{arom}), 5.51 (s, 1H, CHPh), 5.28 (s, 1H, 1-NH), 4.70 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.67 (d, *J* = 11.7 Hz, 1H, C*H*H PMB), 4.60 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.54 (dd, *J* = 11.1, 4.9 Hz, 1H, H-6), 4.43 (d, *J* = 11.8 Hz, 1H, CH*H* PMB), 4.22 (dd, *J* = 9.4, 7.6 Hz, 1H, H-7), 3.95 (dd, *J* = 7.7, 4.1 Hz, 1H, H-1), 3.86 (dd, *J* = 7.3, 5.1 Hz, 1H, H-3), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.70 (d, *J* = 11.0 Hz, 1H, H-6), 3.61 (dd, *J* = 11.9, 7.3 Hz, 1H, H-4), 3.54 (dd, *J* = 4.6, 4.6 Hz, 1H, H-2), 2.61 (dddd, *J* = 15.7, 10.9, 4.8, 4.8 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7 ($C_{q\text{-}arom}$), 159.5 (C=O), 158.9, 137.8, 129.9 ($C_{q\text{-}arom}$), 129.8, 129.8 (CH_{arom}), 129.4 ($C_{q\text{-}arom}$), 129.1, 128.4, 126.2, 114.2, 114.0 (CH_{arom}), 101.2 (CHPh), 78.7, 78.5 (C-3, C-4), 76.3

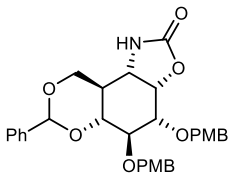
(C-5), 74.6 (C-7), 73.6, 72.9 (CH_2 PMB), 70.1 (C-6), 55.4 (OMe), 53.6 (C-1), 37.3 (C-2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{33}NNaO_8$ 570.2098; Found 570.2098.

2,3-Di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene-7-(*S*)-(*N*-(*tert*-butoxycarbonyl)-1-(*R*)-ol cyclophellitol alkane (45).



Azide **43** (1.53 g, 2.8 mmol) was dissolved in a 1:1 solution of THF and aq. 1.0 M NaOH (28 mL, 0.1 M). Subsequently, triphenylphosphine (2.9 g, 11.2 mmol, 4.0 eq.) was added and the reaction was stirred vigorously overnight at room temperature. Upon full conversion of the starting material the reaction was washed with sat. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc (3x) and the organic layers were then washed with brine. The brine layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude amine was dissolved in anhydrous DCM (14 mL, 0.2 M) and cooled on ice. While stirring, Boc_2O (0.73 g, 3.4 mmol, 1.2 eq.) and Et_3N (1.9 mL, 14 mmol, 5.0 eq.) were added. The flask was flushed with N_2 and the reaction was stirred at room temperature for 19 hours until full conversion was observed (R_f 0.4 (EtOAc:pentane, 4:6, v:v)). The reaction was quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with EtOAc (3x), and the combined organic layers were washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 10:90 EtOAc:pentane → 40:60 EtOAc:pentane) yielded **45** as a colourless solid (0.83 g, 1.34 mmol, 48% over two steps). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.53 – 7.46 (m, 2H, CH_{arom}), 7.41 – 7.32 (m, 3H, CH_{arom}), 7.31 – 7.14 (m, 4H, CH_{arom}), 7.04 – 6.72 (m, 4H, CH_{arom}), 5.54 (s, 1H, CHPh), 4.97 – 4.87 (m, 2H, C*H*H PMB, C*H*H PMB), 4.71 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.66 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.45 (d, *J* = 8.1 Hz, 1H, 7-NHBoc), 4.27 (dd, *J* = 11.4, 4.4 Hz, 1H, H-6), 3.84 – 3.79 (m, 1H, H-6), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.72 (dd, *J* = 9.3, 9.3 Hz, 1H, H-4), 3.68 – 3.63 (m, 1H, H-3), 3.52 – 3.14 (m, 3H, H-1, H-2, H-7), 2.56 (s, 1H, 1-OH), 1.78 (dddd, *J* = 10.8, 10.8, 10.8, 4.7 Hz, 1H, H-5), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6 (C=O Boc), 159.4, 156.4, 138.1, 130.7, 130.6 ($C_{q\text{-}arom}$), 130.0, 129.9, 129.0, 128.4, 126.1, 114.2, 113.9 (CH_{arom}), 101.2 (CHPh), 83.1 (C-2), 82.4 (C-3), 81.5 (C-4), 80.3 ($C(CH_3)_3$) 75.5, 75.3 (CH_2 PMB), 75.1 (C-1), 68.4 (C-6), 55.4 (OMe), 51.5 (C-7), 40.0 (C-5), 28.4 ($C(CH_3)_3$ Boc); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{35}H_{43}NNaO_9$ 644.2830; Found 644.2829.

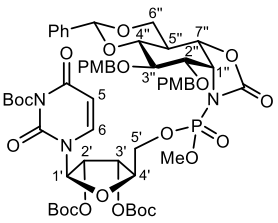
1,7-(*S*,*S*)-(*O*,*N*)-Carbamate-2,3-di-*O*-(4-methoxybenzyl)-4,6-*O*-benzylidene cyclophellitol alkane (47).



The boc-protected amino alcohol **45** (0.9 g, 1.46 mmol) was co-evaporated with toluene, dissolved in anhydrous $CHCl_3$ (14.6 mL, 0.1 M) and cooled to 0 °C. Subsequently Me-imidazole (1.1 mL, 14.6 mmol, 10 eq.), MsCl (0.56 mL, 7.3 mmol, 5.0 eq.) and Et_3N (1.0 mL, 7.3 mmol, 5.0 eq.) were added. The reaction was flushed in N_2 and stirred overnight at room temperature. Upon full conversion (R_f 0.6 (EtOAc:pentane, 4:6, v:v)) the reaction was diluted with EtOAc and washed with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous DMF

(73 mL, 0.02 M), flushed in argon gas and stirred at 130 °C overnight. Upon full conversion (R_f 0.7 (EtOAc:pentane, 9:1, v:v)) the reaction was cooled to room temperature, diluted with EtOAc and washed with H_2O and brine. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 50:50 EtOAc:pentane → 90:10 EtOAc:pentane) yielded the carbamate **47** as a yellowish, brittle foam (0.54 g, 1.0 mmol, 67% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.53 – 7.14 (m, 9H, CH_{arom}), 6.89 – 6.77 (m, 4H, CH_{arom}), 6.67 (s, 1H, 7-NH), 5.48 (s, 1H, CHPh), 4.73 (dd, *J* = 8.7, 3.0 Hz, 1H, H-1), 4.64 – 4.44 (m, 4H, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.49 – 4.36 (m, 1H, H-6), 3.84 – 3.81 (m, 2H, H-2, H-4), 3.79 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.66 – 3.42 (m, 4H, C-3, C-6, C-7), 2.57 (dddd, *J* = 10.8, 10.8, 10.8, 4.8 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7, 159.5 ($C_{q\text{-}arom}$), 159.5 (C=O), 137.9, 130.0 ($C_{q\text{-}arom}$), 129.8, 129.6, 129.0, 128.3, 126.2, 113.9 (CH_{arom}), 101.1 (CHPh), 79.6 (C-3), 79.0 (C-4), 76.4 (C-2), 75.1 (C-1), 73.2, 72.6 (CH_2 PMB), 70.5 (C-6), 55.4 (OMe), 51.5 (C-7), 37.2 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{33}NNaO_8$ 570.2098; Found 570.2110.

1'',7''-(*N,O*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridinyl))-carbamate-2'',3''-di-*O*-(4-methoxybenzyl)-4'',6''-di-*O*-benzylidene cyclophellitol alkane (49).

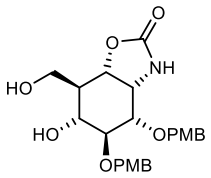


Compound **49** was prepared according to general procedure A using carbamate **46** (0.16 g, 0.3 mmol), 15-crown-5 (0.3 mL, 1.5 mmol, 5.0 eq.), anhydrous THF (1.5 mL, 0.2 M), NaH (60% wt., 0.02 g, 0.45 mmol, 1.5 eq.); and H-phosphonate **48** (0.47 g, 0.75 mmol, 2.5 eq.), anhydrous DCM (2.5 mL, 0.3 M), anhydrous DiPEA (0.4 mL, 0.75 mmol, 7.5 eq.) and $BrCCl_3$ (0.15 mL, 1.5 mmol, 5.0 eq.). Flash column chromatography (30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and size exclusion yielded a P(V) diastereomeric mixture (ratio 1:1.3) of **49** as a colourless film (77 mg, 66 µmol, 22%, R_f 0.3 and 0.4 (EtOAc:pentane, 1:1 v:v)). Data for the first diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.71 (d, *J* = 8.3 Hz, 1H, H-6), 7.52 – 7.11 (m, 9H, CH_{arom}), 6.90 – 6.78 (m, 4H, CH_{arom}), 6.10 (d, *J* = 6.0 Hz, 1H, H-1'), 5.79 (d, *J* = 8.2 Hz, 1H, H-5), 5.52 (s, 1H, CHPh), 5.21 (dd, *J* = 5.2, 5.2 Hz, 1H, H-3'), 5.15 (ddd, *J* = 5.6, 5.4, 5.4 Hz, 1H, H-2'), 4.64 – 4.37 (m, 6H, H-1'', H-7'', C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.31 (dd, *J* = 6.6, 2.4 Hz, 2H, H-5'), 4.19 (dddd, *J* = 5.2, 5.2, 2.5, 2.5 Hz, 1H, H-4'), 4.15 (d, *J* = 2.0 Hz, 1H, H-3''), 3.90 (s, 3H, P(O)OMe), 3.90 (d, *J* = 9.4 Hz, 1H, H-2''), 3.80 (s, 6H, OMe), 3.79 – 3.64 (m, 3H, H-4'', H-6''), 2.93 – 2.77 (m, 1H, H-5''), 1.60 (s, 9H, $C(CH_3)_3$), 1.48 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.5, 159.4 ($C_{q\text{-}arom}$), 155.3 (d, J = 8.8 Hz, C=O cyclic carbamate), 152.2 (C=O carbamate), 152.1 (C=O uracil), 148.7, 148.6 (C=O carbonate), 139.4 (C-6), 137.7, 137.6 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.5, 129.5, 129.3 ($C_{q\text{-}arom}$), 129.2, 129.1, 128.6, 128.5, 128.3, 126.1, 126.1, 114.0, 113.9, 113.9 (CH_{arom}), 103.4 (C-5), 101.2 (CHPh), 86.9 ($C(CH_3)_3$), 86.2 (C-1'), 83.8, 83.7 ($C(CH_3)_3$), 80.0 (C-4'), 78.8 (C-4''), 77.5 (C-3''), 76.5 (C-2''), 74.8, 74.7 (C-1'', C-2'), 72.1, 71.9 (CH_2PMB), 71.8 (C-3'), 70.6 (C-6''), 67.00 (d, *J* = 6.1 Hz, C-5'), 56.65 (d, *J* = 5.0 Hz, C-7''), 55.4 (OMe), 55.1 (P(O)OMe), 35.0 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ -2.39.

Data for the second diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.59 (d, *J* = 8.2 Hz, 1H, H-6), 7.52 – 7.11 (m, 9H, CH_{arom}), 6.90 – 6.78 (m, 4H, CH_{arom}), 6.14 (d, *J* = 5.9 Hz, 1H, H-1'),

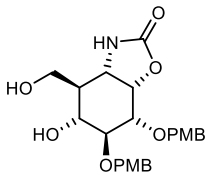
5.85 (d, *J* = 8.2 Hz, 2H, H-5), 5.52 (s, 1H, CHPh), 5.28 (dd, *J* = 5.3, 5.3 Hz, 1H, H-3'), 5.15 (ddd, *J* = 5.6, 5.4, 5.4 Hz, 1H, H-2'), 4.64 – 4.37 (m, 7H, H-1'', H-5', H-7'', C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.35 (dd, *J* = 4.7, 2.5 Hz, 1H, H-4'), 4.11 (d, *J* = 4.4 Hz, 1H, H-3''), 3.90 (d, *J* = 9.4 Hz, 1H, H-2''), 3.87 (s, 3H, P(O)OMe), 3.76 (s, 6H, OMe), 3.79 – 3.64 (m, 3H, H-4'', H-6''), 2.93 – 2.77 (m, 1H, H-5''), 1.49 (s, 9H, $C(CH_3)_3$), 1.46 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 160.2 (C=O uracil), 159.5, 159.3 ($C_{q\text{-}arom}$), 155.1 (d, J = 8.9 Hz, C=O cyclic carbamate), 152.0 (C=O carbamate), 151.9 (C=O uracil), 147.6, 147.6 (C=O carbonate), 139.4 (C-6), 137.7, 137.6 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.5, 129.5, 129.3 ($C_{q\text{-}arom}$), 129.2, 129.1, 128.6, 128.5, 128.3, 126.1, 126.1, 114.0, 113.9, 113.9 (CH_{arom}), 103.1 (C-5), 101.1 (CHPh), 87.1, ($C(CH_3)_3$), 86.7 (C-1'), 83.8, 83.6 ($C(CH_3)_3$), 79.9 (C-4'), 78.8 (C-4''), 77.3 (C-3''), 76.4 (C-2''), 74.7 74.6 (C-1'', C-2'), 71.8, (C-3'), 71.8, 71.7 (CH_2PMB), 70.5 (C-6''), 66.40 (d, *J* = 5.3 Hz, C-5'), 56.55 (d, *J* = 5.2 Hz, C-7''), 55.3 (OMe), 55.0 (P(O)OMe), 34.9 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ -1.85; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{56}H_{70}N_3NaO_{22}P$ 1190.4081; Found 1190.4086.

1,7-(*S,S*)-(*N,O*)-Carbamate-2,3-di-*O*-(4-methoxybenzyl) cyclophellitol alkane (52).



Carbamate **46** (0.55 g, 1.0 mmol) was dissolved in MeOH (40 mL, 0.025 M) and *p*-TsOH (0.1 g, 0.5 mmol, 0.5 eq.) was added. The reaction was stirred at 40 °C for 1 hour until full conversion was observed (R_f 0.3 (EtOAc:pentane, 9:1, v:v)). The reaction was quenched with Et_3N to neutral pH and concentrated under reduced pressure. Flash column chromatography (dry loading, 70:30 EtOAc:pentane → 100:0 EtOAc:pentane) yielded **52** as a white, brittle foam (0.41 g, 0.9 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.43 – 7.14 (m, 4H, CH_{arom}), 6.96 – 6.76 (m, 4H, CH_{arom}), 5.63 (s, 1H, 1-NH), 4.81 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.65 (d, *J* = 11.5 Hz, 1H, C*H*H PMB), 4.62 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.52 (d, *J* = 11.5 Hz, 1H, CH*H* PMB), 4.46 (dd, *J* = 9.4, 7.0 Hz, 1H, H-7), 4.04 (dd, *J* = 7.1, 4.4 Hz, 1H, H-1), 4.00 – 3.91 (m, 1H, H-6), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.69 (dd, *J* = 10.9, 3.9 Hz, 1H, H-6), 3.61 (dd, *J* = 8.3, 8.3 Hz, 1H, H-3), 3.49 (dd, *J* = 8.0, 4.5 Hz, 1H, H-2), 3.41 (dd, *J* = 11.5, 8.7 Hz, 1H, H-4), 3.21 (d, *J* = 2.7 Hz, 1H, 4-OH), 2.80 (s, 1H, 6-OH), 1.97 (ddd, *J* = 16.1, 8.3, 4.1 Hz, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 159.7 (C=O), 159.6, 159.1, 130.3 ($C_{q\text{-}arom}$), 129.8, 129.7 (CH_{arom}), 129.6 ($C_{q\text{-}arom}$), 114.2, 114.1 (CH_{arom}), 81.5 (C-3), 77.6 (C-2), 74.7 (CH_2 PMB), 74.0 (C-7), 73.0 (CH_2 PMB), 68.8 (C-4), 59.8 (C-6), 55.4 (OMe), 54.7 (C-1), 45.6 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{24}H_{29}NNaO_8$ 482.1785; Found 482.1783.

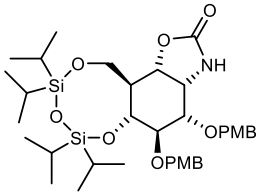
1,7-(*S,S*)-(*O,N*)-Carbamate-2,3-di-*O*-(4-methoxybenzyl) cyclophellitol alkane (53).



Carbamate **47** (27 mg, 50 µmol) was dissolved in MeOH (2.0 mL, 0.025 M) and *p*-TSOH (5.0 mg, 25 µmol, 0.5 eq.) was added. The reaction was rotated at 40 °C for 1 hour to full conversion (R_f 0.1 (EtOAc:pentane, 9:1, v:v)). The reaction was quenched with Et_3N till neutral pH was reached and concentrated under reduced pressure. Flash column chromatography (dry loading, 70:30 EtOAc:pentane → 100:0 EtOAc:pentane) yielded **53** as a white, brittle foam (17 mg, 37 µmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.34 – 7.15 (m, 4H, CH_{arom}), 6.98 – 6.81 (m, 4H, CH_{arom}), 6.40 (s, 1H, 7-NH), 4.73 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.70 – 4.66 (m, 2H, H-1, C*H*H PMB), 4.58 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.52 (d, *J* = 11.1 Hz,

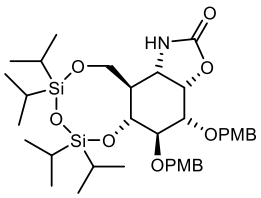
1H, CH*H* PMB), 3.86 (dd, *J* = 11.0, 4.5 Hz, 1H, H-6), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.69 – 3.55 (m, 4H, H-2, H-3, H-6, H-7), 3.27 (dd, *J* = 11.3, 7.4 Hz, 1H, H-4), 3.03 – 2.93 (m, 2H, 4-OH, 6-OH), 2.02 – 1.90 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6 (C=O), 159.4, 130.2 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.7 ($C_{q\text{-}arom}$), 114.1, 114.1 (CH_{arom}), 81.4 (C-3), 76.0 (C-1, C-2), 74.0, 72.6 (CH_2 PMB), 70.2 (C-4), 62.7 (C-6), 55.4 (OMe), 53.4 (C-7), 46.6 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{24}H_{29}NNaO_8$ 482.1785; Found 482.1785.

1,7-(*S*,*S*)-(*N*,*O*)-Carbamate-2,3-di-*O*-(4-methoxybenzyl)-4,6-di-*O*-diisopropyldisiloxane cyclophellitol alkane (56).



Diol **52** (0.29 g, 0.64 mmol) was dissolved in anhydrous DMF (3.2 mL, 0.2 M). $TIPDSiCl_2$ (0.31 mL, 0.96 mmol, 1.5 eq.) and imidazole (0.17 g, 2.6 mmol, 4 eq.) were added after which the flask was purged with N_2. The reaction was stirred at room temperature for 30 min, upon which full conversion was observed (R_f0.2 (EtOAc:pentane, 3:7 v:v)). The mixture was dissolved in sat. aq. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 20:80 EtOAc:pentane → 50:50 EtOAc:pentane) yielded carbamate **56** as a white foam (0.39 g, 0.56 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 4H, CH_{arom}), 6.91 – 6.79 (m, 4H, CH_{arom}), 5.78 (s, 1H, CHPh), 4.77 (dd, *J* = 9.7, 7.5 Hz, 1H, H-7), 4.64 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.60 (d, *J* = 11.5 Hz, 1H, C*H*H PMB), 4.50 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.46 (d, *J* = 11.6 Hz, 1H, CH*H* PMB), 4.04 (d, *J* = 11.2 Hz, 1H, H-6), 3.99 – 3.92 (m, 1H, H-1), 3.87 (d, *J* = 11.2 Hz, 1H, H-6), 3.80 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.69 – 3.56 (m, 2H, H-3, H-4), 3.50 (d, *J* = 4.4 Hz, 1H, H-2), 2.08 (ddd, *J* = 9.5, 9.4, 1.8 Hz, 1H, H-5), 1.13 – 0.95 (m, 28H, C*H*(CH_3)$_2$, CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 159.6 ($C_{q\text{-}arom}$), 159.4 (C=O), 159.2, 130.5, 129.8 ($C_{q\text{-}arom}$), 129.6, 129.2, 114.1, 113.8 (CH_{arom}), 83.1 (C-3), 77.1 (C-2), 73.9 (CH_2PMB), 73.6 (C-7), 72.9 (CH_2PMB), 68.7 (C-4), 57.1 (C-6), 55.4 (OMe), 53.8 (C-1), 45.8 (C-5), 17.6, 17.6, 17.5, 17.5, 17.4 (CH(*C*H$_3$)$_2$), 13.5, 13.4, 13.0, 12.9 (*C*H(CH$_3$)$_2$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{36}H_{55}NNaO_9Si_2$ 724.3308; Found 724.3301.

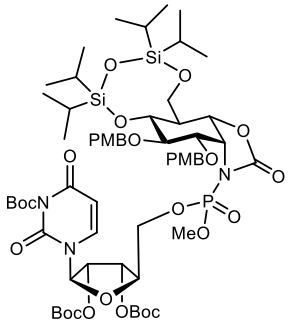
1,7-(*S*,*S*)-(*O*,*N*)-Carbamate-2,3-di-*O*-(4-methoxybenzyl)-4,6-di-*O*-diisopropyldisiloxane cyclophellitol alkane (57).



Diol **53** (0.27 g, 0.59 mmol) was dissolved in anhydrous DMF (2.95 mL, 0.2 M). $TIPSDSiCl_2$ (0.28 mL, 0.89 mmol, 1.5 eq.) and imidazole (0.16 g, 2.4 mmol, 4.0 eq.) were added after which the flask was purged with N_2. The reaction was stirred at room temperature for 30 min, upon which full conversion was observed (R_f 0.6 (EtOAc:pentane, 4:6 v:v)). The mixture was dissolved in sat. aq. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 15:85 EtOAc:pentane → 40:60 EtOAc:pentane) yielded carbamate **57** (0.57 g, 0.82 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.50 – 7.08 (m, 4H, CH_{arom}), 6.95 – 6.73 (m, 4H, CH_{arom}), 6.01 (s, 1H, 7-NH), 4.70 (dd, *J* = 8.7, 3.7 Hz, 1H, H-1),

4.65 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.55 – 4.48 (m, 2H, C*H*H PMB, CH*H* PMB), 4.35 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.14 (ddd, *J* = 9.8, 8.6, 1.1 Hz, 1H, H-7), 4.08 (dd, *J* = 11.9, 2.1 Hz, 1H, H-6), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 – 3.74 (m, 1H, H-2), 3.66 – 3.56 (m, 3H, H-3, H-4, H-6), 2.10 (dddd, *J* = 11.9, 9.9, 2.1, 2.1 Hz, 1H, H-5), 1.14 – 0.81 (m, 28H, C*H*(CH_3)$_2$, CH(C*H*$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 159.5, 159.3, 130.3, 130.0 ($C_{q\text{-}arom}$), 129.8, 129.3, 113.9, 113.8 (CH_{arom}), 84.1 (C-3), 76.4 (C-2), 75.2 (C-1), 73.2, 72.9 (CH_2PMB), 69.8 (C-4), 57.7 (C-6), 55.4, 55.4 (OMe), 49.8 (C-7), 45.4 (C-5), 17.6, 17.5, 17.5, 17.5, 17.4, 17.4 (CH(*C*H$_3$)$_2$), 13.5, 13.4, 12.9, 12.8 (*C*H(CH_3)$_2$); HRMS (ESI) m/z: $[M + H]^+$ Calcd. for $C_{36}H_{55}NO_9Si_2$ 702.3488; Found 702.3486.

1'',7''-(*S,S*)-(*N,O*-(3-*N*-(T*ert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxy carbonyl)uridinyl))-carbamate-2'',3''-di-*O*-(4-methoxybenzyl)-4'',6''-di-*O*- diisopropyldisiloxane cyclophellitol alkane (58).

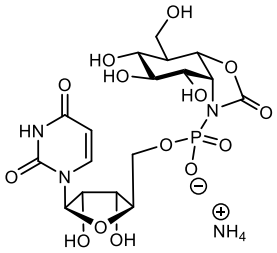


Compound **58** was prepared according to general procedure A using carbamate **56** (0.21 g, 0.3 mmol), 15-crown-5 (0.3 mL, 1.5 mmol, 5.0 eq.), anhydrous THF (1.5 mL, 0.2 M), NaH (60% wt., 0.02 g, 0.45 mmol, 1.5 eq.); and H-phosphonate **48** (0.56 g, 0.9 mmol, 3.0 eq.), anhydrous DCM (3 mL, 0.3 M), anhydrous DiPEA (0.47 mL, 2.7 mmol, 9.0 eq.) and $BrCCl_3$ (0.18 mL, 1.8 mmol, 6.0 eq.). Flash column chromatography (dry loading, 20:80 EtOAc:pentane → 40:60 EtOAc:pentane) and size exclusion yielded the P(V) diastereoisomeric mixture (ratio 1:1.39) of **58** as a colourless oil (113 mg, 86 µmol, 29%, R_f 0.3 and 0.4 (EtOAc:pentane, 4:6 v:v)). Data for the first P(V) diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 1H, H-6), 7.35 – 7.10 (m, 4H, CH_{arom}), 6.97 – 6.75 (m, 4H, CH_{arom}), 6.15 (d, *J* = 5.4 Hz, 1H, H-1'), 5.82 (d, *J* = 8.2 Hz, 1H, H-5), 5.32 (dd, *J* = 5.2, 5.2 Hz, 1H, H-3'), 5.17 (ddd, *J* = 9.0, 5.5, 5.5 Hz, 1H, H-2'), 4.96 (dd, *J* = 9.0, 9.0 Hz, 1H, H-7''), 4.63 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.53 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.52 – 4.38 (m, 4H, H-5', CH*H* PMB, CH*H* PMB), 4.36 – 4.31 (m, 2H, H-1'', H-4'), 4.10 (d, *J* = 3.3 Hz, 1H, H-2''), 4.03 (ddd, *J* = 11.3, 9.1, 2.1 Hz, 1H, H-6''), 3.88 (s, 3H, P(O)OMe), 3.87 – 3.82 (m, 1H, H-6''), 3.76 (s, 6H, OMe), 3.78 – 3.66 (m, 2H, H-3'', H-4''), 2.42 (ddd, *J* = 11.5, 9.6, 1.9 Hz, 1H, H-5''), 1.59 (s, 9H, C(CH_3)$_3$), 1.55 – 1.38 (m, 18H, C(CH_3)$_3$), 1.15 – 0.91 (m, 28H, CH(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.5, 159.4 ($C_{q\text{-}arom}$), 155.3 (d, *J* = 8.5 Hz, C=O cyclic carbamate), 152.0 (C=O carbamate), 151.9 (C=O uracil), 148.7, 147.6 (C=O carbonate), 139.5 (C-6), 129.8 (CH_{arom}), 129.6, 129.5 ($C_{q\text{-}arom}$), 128.5, 128.4, 114.0, 114.0, 113.9 (CH_{arom}), 103.1 (C-5), 86.9 (*C*(CH_3)$_3$), 86.7 (C-1'), 83.7, 83.7 (*C*(CH_3)$_3$), 82.2 (C-3''), 80.0 (d, *J* = 8.5 Hz, C-4'), 76.7 (C-2''), 74.8 (C-2'), 73.6 (d, *J* = 8.7 Hz, C-7''), 72.1, 72.1, 72.0 (CH_2PMB), 71.8 (CH_2PMB), 71.6 (C-3'), 69.3 (C-4''), 66.1 (d, *J* = 5.5 Hz, C-5'), 57.0 (C-6''), 56.4 (d, *J* = 4.9 Hz, C-1''), 55.4 (OMe), 55.0 (P(O)OMe), 43.4 (C-5''), 27.7, 27.5 (C(*C*H$_3$)$_3$), 17.5, 17.5, 17.4, 17.4 (CH(*C*H$_3$)$_2$), 13.4, 12.8, 12.8, 12.7 (*C*H(CH_3)$_2$); ^{31}P NMR (202 MHz, $CDCl_3$) δ -1.92.

Data for the second P(V) diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 1H, H-6), 7.35 – 7.10 (m, 4H, CH_{arom}), 6.97 – 6.75 (m, 4H, CH_{arom}), 6.11 (d, *J* = 5.9 Hz, 1H, H-1'), 5.77 (d, *J* = 8.2 Hz, 1H, H-5), 5.22 (dd, *J* = 5.5, 4.1 Hz, 1H, H-3'), 5.17 (ddd, *J* = 9.0, 5.5, 5.5 Hz, 1H, H-2'), 4.99 (dd, *J* = 9.0, 9.0 Hz, 1H, H-7''), 4.64 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.55 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.52 – 4.38 (m, 2H, CH*H* PMB, CH*H* PMB), 4.36 – 4.31 (m, 2H, H-5'), 4.29 (dd, *J* = 8.8, 3.0 Hz,

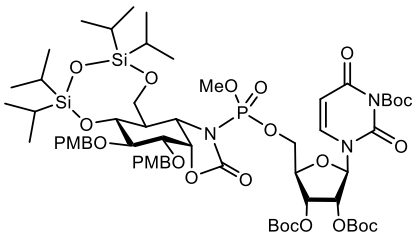
1H, H-1''), 4.19 (dddd, *J* = 5.1, 2.5 Hz, 1H, H-4'), 4.14 (d, *J* = 3.2 Hz, 1H, H-2''), 4.03 (ddd, *J* = 11.3, 9.1, 2.1 Hz, 1H, H-6''), 3.90 (s, 3H, P(O)OMe), 3.87 – 3.82 (m, 1H, H-6''), 3.80 (s, 6H, OMe), 3.78 – 3.66 (m, 2H, H-3'', H-4''), 2.42 (ddd, *J* = 11.5, 9.6, 1.9 Hz, 1H, H-5''), 1.59 (s, 9H, $C(CH_3)_3$), 1.55 – 1.38 (m, 18H, $C(CH_3)_3$), 1.15 – 0.91 (m, 28H, $CH(CH_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.5, 159.4 ($C_{q\text{-}arom}$), 155.6 (d, *J* = 8.9 Hz, C=O cyclic carbamate), 152.2 (C=O carbamate), 151.9 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.5 (C-6), 129.7 (CH_{arom}), 129.6, 129.5 ($C_{q\text{-}arom}$), 128.5, 128.4, 114.0, 114.0, 113.9 (CH_{arom}), 103.1 (C-5), 86.8 ($C(CH_3)_3$), 86.0 (C-1'), 83.7, 83.6 ($C(CH_3)_3$), 82.4 (C-3''), 80.0 (d, *J* = 7.3 Hz, C-4'), 76.7 (C-2''), 74.6 (C-2'), 73.6 (d, *J* = 8.7 Hz, C-7''), 72.1, 72.1, 72.0 (CH_2PMB), 71.9 (C-3'), 71.8 (CH_2PMB), 69.3 (C-4''), 67.0 (d, *J* = 6.3 Hz, C-5'), 57.0 (C-6''), 56.5 (d, *J* = 4.5 Hz, C-1''), 55.4 (OMe), 54.9 (P(O)OMe), 43.4 (C-5''), 27.7, 27.5 ($C(CH_3)_3$), 17.5, 17.5, 17.4, 17.4 ($CH(CH_3)_2$), 13.4, 12.8, 12.8, 12.7 ($CH(CH_3)_2$); ^{31}P NMR (202 MHz, $CDCl_3$) δ -2.13; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{61}H_{92}N_3NaO_{23}PSi_2$ 1344.5900; Found 1344.5295.

1'',7''(*S,S*)-(*N,O*-(5'-*O*-Phosphoryluridinyl))-carbamate cyclophellitol alkane (10).



1,7-UMP carbamate **58** (28 mg, 21 µmol) was dissolved in DCM (0.28 mL, 0.08 M), cooled to 0 °C and purged with N_2. Subsequently, TFA (30% v:v, 0.13 mL, 1.65 mmol, 79 eq.) and TES (10 µL, 63 µmol, 3 eq.) were added. The reaction was stirred overnight at room temperature. Upon full conversion (R_f 0.2 (MeOH:DCM, 1:9 v:v)) the reaction was quenched with pyridine and heated to 35 °C. The reaction was stirred for 27 hours until ^{31}P NMR showed full conversion of the starting material. The reaction was concentrated under reduced pressure and purified by flash column chromatography (dry loading, neutralized silica, 0:100 H_2O:acetonitrile → 15:85 H_2O:acetonitrile) yielded the TIPDS-protected intermediate as an insoluble amphiphile **60** (6 mg, 8 µmol). Intermediate **60** was redissolved in anhydrous THF (1.0 mL, 0.008 M) and TBAF (1.0 M in THF, 16 µL, 16 µmol, 2.0 eq.) was added. The reaction was stirred overnight at room temperature. Upon full conversion (R_f 0.4 (H_2O:ACN, 2:8 v:v)), the reaction was concentrated under reduced pressure. Flash column chromatography (dry loading, neutralized silica, 0:100 H_2O:acetonitrile → 15:85 H_2O:acetonitrile) and subsequent gel filtration (NH_4HCO_3 in H_2O, ACN) yielded the title compound **10** as colourless oil (2 mg, 3.8 µmol, 18%). ^{1}H NMR (850 MHz, D_2O, HH-COSY, HSQC): δ 7.94 (d, *J* = 8.1 Hz, 1H, H-6), 5.97 (d, *J* = 5.0 Hz, 1H, H-1'), 5.94 (d, *J* = 8.0 Hz, 1H, H-5), 4.81 (ddd, *J* = 8.8, 4.5, 4.5 Hz, 1H, H-4''), 4.38 (dd, *J* = 5.1, 5.1 Hz, 1H, H-2'), 4.32 (dd, *J* = 5.0, 5.0 Hz, 1H, H-3'), 4.29 (dd, *J* = 4.7, 2.4 Hz, 1H, H-5'), 4.28 – 4.27 (m, 1H, H-4'), 4.23 (ddd, *J* = 8.3, 3.2, 1.1 Hz, 1H, H-3''), 4.21 – 4.18 (m, 1H, H-5'), 4.08 (dd, *J* = 2.3, 2.3 Hz, 1H, H-2''), 3.88 – 3.81 (m, 3H, H-1'', H-6''), 3.46 (dd, *J* = 12.4, 6.4 Hz, 1H, H-7''), 2.37 (ddd, *J* = 12.0, 8.7, 4.3 Hz, 1H, H-5''); ^{13}C NMR (214 MHz, D_2O, HSQC): δ 167.1 (C=O uracil), 159.8 (C=O carbamate), 152.7 (C=O uracil), 142.8 (C-6), 103.4 (C-5), 89.7 (C-1'), 83.9 (d, *J* = 8.8 Hz, C-4'), 78.6 (C-1''), 76.3 (C-4''), 74.6 (C-2'), 73.2 (C-2''), 70.9 (C-7''), 70.6 (C-3'), 65.9 (d, *J* = 5.4 Hz, C-5'), 60.0 (C-6''), 58.1 (C-3''), 43.2 (C-5''); ^{31}P NMR (202 MHz, D_2O) δ -6.57; HRMS (ESI) m/z: $[M + H + NH_4]^+$ Calcd. for $C_{17}H_{23}N_3NaO_{14}P$ 543.1334; Found 543.1335.

1'',7''-(*S,S*)-(*O,N*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxy carbonyl)uridinyl))-carbamate-2'',3''-di-*O*-(4-methoxybenzyl)-4'',6''-di-*O*-diisopropyl disiloxane cyclophellitol alkane (59).

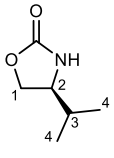


Compound **59** was prepared according to general procedure A using carbamate **57** (0.21 g, 0.3 mmol), 15-crown-5 (0.3 mL, 1.5 mmol, 5.0 eq.), anhydrous THF (1.5 mL, 0.2 M), NaH (60% wt., 0.02 g, 0.45 mmol, 1.5 eq.); and H-phosphonate **48** (0.56 g, 0.9 mmol, 3.0 eq.), anhydrous DCM (3 mL, 0.3 M), anhydrous DiPEA (0.47 mL, 2.7 mmol, 9.0 eq.) and $BrCCl_3$ (0.18 mL, 1.8 mmol, 6.0 eq.). Flash column chromatography (dry loading, 20:80 EtOAc:pentane → 40:60 EtOAc:pentane) and size exclusion yielded the starting material (41 mg, 58 µmol, 20%) and a P(V) diastereoisomeric mixture (ratio 1:1.74) of **59** as a colourless oil (57 mg, 43 µmol, 14%, R_f 0.3 and 0.4 (EtOAc:pentane, 4:6 v:v), 34% brsm). Data for the first P(V) diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.71 (d, *J* = 8.2 Hz, 1H, H-6), 7.35 – 7.09 (m, 4H, CH_{arom}), 6.97 – 6.78 (m, 4H, CH_{arom}), 6.12 (d, *J* = 3.9 Hz, 1H, H-1'), 5.86 (d, *J* = 8.2 Hz, 1H, H-5), 5.24 (dd, *J* = 10.2, 5.0 Hz, 1H, H-3'), 5.17 (dd, *J* = 5.6, 5.6 Hz, 1H, H-2'), 4.77 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.70 (m, 3H, H-1'', C*H*H PMB, CH*H* PMB), 4.65 – 4.57 (m, 1H, CH*H* PMB), 4.39 – 4.29 (m, 4H, H-4', H-5', H-7''), 4.18 – 4.01 (m, 2H, H-6''), 3.85 (s, 3H, P(O)OMe), 3.80 (s, 6H, OMe), 3.74 – 3.60 (m, 2H, H-3'', H-4''), 3.56 (ddd, *J* = 8.4, 7.9, 3.8 Hz, 1H, H-2''), 1.90 (dd, *J* = 10.5, 10.5 Hz, 1H, H-5''), 1.60 (s, 9H, $C(CH_3)_3$), 1.48 (s, 18H, $C(CH_3)_3$), 1.09 – 0.93 (m, 28H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.6, 159.1 ($C_{q\text{-}arom}$), 155.1 (d, *J* = 4.0 Hz, C=O cyclic carbamate), 152.0 (C=O carbamate), 148.7, 147.7 (C=O carbonate), 139.5 (C-6), 130.7 ($C_{q\text{-}arom}$), 129.9 (CH_{arom}), 129.7 ($C_{q\text{-}arom}$), 129.2, 114.0, 113.7 (CH_{arom}), 103.2 (C-5), 87.0 ($C(CH_3)_3$), 86.8 (C-1'), 83.7, 83.6 ($C(CH_3)_3$), 81.6 (C-3''), 79.9 (d, *J* = 7.1 Hz, C-4'), 77.5 (d, *J* = 7.1 Hz, C-1''), 77.4 (C-2''), 74.7 (C-2'), 74.5, 73.0 (CH_2PMB), 71.7 (C-3'), 68.8 (C-4''), 66.8 (d, *J* = 6.0 Hz, C-5'), 57.0 (C-6''), 55.8 (d, *J* = 3.8 Hz, C-7''), 55.4, 55.4 (OMe), 54.8 (P(O)OMe), 47.6 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$), 17.7, 17.6, 17.5, 17.4 ($CH(CH_3)_2$), 13.5, 13.5, 13.4, 13.1, 13.1, 13.0, 12.9 ($CH(CH_3)_2$); ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.83.

Data for the second P(V) diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.62 (d, *J* = 8.2 Hz, 1H, H-6), 7.35 – 7.09 (m, 4H, CH_{arom}), 6.97 – 6.78 (m, 4H, CH_{arom}), 6.11 (d, *J* = 3.8 Hz, 1H, H-1'), 5.81 (d, *J* = 8.2 Hz, 1H, H-5), 5.24 (dd, *J* = 10.2, 5.0 Hz, 1H, H-3'), 5.17 (dd, *J* = 5.6, 5.6 Hz, 1H, H-2'), 4.77 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.70 (m, 3H, H-1'', C*H*H PMB, CH*H* PMB), 4.65 – 4.57 (m, 1H, CH*H* PMB), 4.52 – 4.39 (m, 2H, H-5'), 4.39 – 4.29 (m, 1H, H-7''), 4.29 (dd, *J* = 3.5, 3.5 Hz, 1H, H-4'), 4.18 – 4.01 (m, 2H, H-6''), 3.83 (s, 3H, P(O)OMe), 3.80 (s, 6H, OMe), 3.74 – 3.60 (m, 2H, H-3'', H-4''), 3.56 (ddd, *J* = 8.4, 7.9, 3.8 Hz, 1H, H-2''), 1.83 (dd, *J* = 10.2 Hz, 1H, H-5''), 1.60 (s, 9H, $C(CH_3)_3$), 1.47 (s, 18H, $C(CH_3)_3$), 1.09 – 0.93 (m, 28H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.2 (C=O uracil), 159.5, 159.1 ($C_{q\text{-}arom}$), 155.0 (d, *J* = 4.6 Hz, C=O cyclic carbamate), 152.1 (C=O carbamate), 148.6, 147.6 (C=O carbonate), 139.4 (C-6), 130.8 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.5 ($C_{q\text{-}arom}$), 129.2, 113.9, 113.6 (CH_{arom}), 103.1 (C-5), 87.0 ($C(CH_3)_3$), 86.7 (C-1'), 83.8, 83.7 ($C(CH_3)_3$), 81.6 (C-3''), 80.0 (d, *J* = 8.2 Hz, C-4'), 77.9 (d, *J* = 7.2 Hz, C-1''), 77.4 (C-2''), 75.0 (CH_2PMB), 74.5 (C-2'), 72.9 (CH_2PMB), 71.9 (C-3'), 68.8 (C-4''), 67.2 (d, *J* = 5.2 Hz, C-5'), 56.9 (C-6''), 56.0 (d, *J* = 3.4 Hz, C-7''), 55.4, 55.3 (OMe), 54.8 (P(O)OMe), 47.6 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$), 17.7, 17.6, 17.5, 17.4

(*C*H(CH$_3$)$_2$), 13.5, 13.5, 13.4, 13.1, 13.1, 13.0, 12.9 (CH(*C*H$_3$)$_2$); ^{31}P NMR (202 MHz, CDCl$_3$) δ -0.26; HRMS (ESI) m/z: [M + Na]$^+$ Calcd. for $C_{61}H_{92}N_3NaO_{23}PSi_2$ 1344.5900; Found 1344.5289.

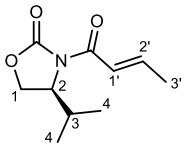
(*S*)-4-Isopropyloxazolidin-2-one (S1).



Boc-L-valine (43 g, 0.20 mol) was dissolved in THF (0.50 L, 0.40 M). Et$_3$N (31 mL, 0.22 mol, 1.1 eq.) and ethyl chloroformate (25 mL, 0.26 mol, 1.3 eq.) were added on ice. The reaction mixture was stirred for 1 h at 0°C. Upon precipitate formation, the reaction mixture was cooled and filtered off, while rinsing with THF. The filtrate was carefully added to a solution of NaBH$_4$ (13 g, 0.34 mol, 1.7 eq.) in H$_2$O (0.13 L, 1.5 M). The reaction mixture was stirred for 1 h at room temperature, before adding additional NaBH$_4$ (4.0 g, 0.1 mol, 0.50 eq.) portion-wise. The reaction mixture was stirred for 30 min. at room temperature, before quenching with 1.0 M aq. HCl until pH 2 was reached. The mixture was diluted with sat. aq. NaHCO$_3$, the organic layer was separated, the aqueous layer was extracted thrice with EtOAc and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*.

The crude intermediate was dissolved in THF (0.75 L, 0.27 M). SOCl$_2$ (36 mL, 050 mol, 2.5 eq.) was added on ice. The reaction mixture was stirred overnight at room temperature. Upon full conversion on TLC (R$_f$ 0.6 (1:1, EtOAc:pentane v:v)), the reaction mixture was concentrated *in vacuo* and co-evaporated with toluene. Flash column chromatography (30:70 EtOAc:pentane → 70:30 EtOAc:pentane) yielded the title compound **S1** (9.2 g, 71 mmol, 35% over three steps). Analytical data in full agreement with literature data.[38] 1H NMR (500 MHz, CDCl3, HH-COSY, HSQC): δ 5.73 (bs, 1H, NH), 4.45 (dd, J = 8.6, 8.6 Hz, 1H, H-1), 4.11 (dd, J = 8.7, 6.3 Hz, 1H, H-1), 3.61 (dddd, J = 8.4, 7.2, 6.3, 1.1 Hz, 1H, H-2), 1.74 (dq, *J* = 13.5, 6.8 Hz, 1H, H-3), 0.96 (d, *J* = 6.7 Hz, 3H, H-4), 0.91 (d, *J* = 6.7 Hz, 3H, H-4); ^{13}C NMR (126 MHz, CDCl$_3$, HSQC): δ 68.7 (C-1), 58.4 (C-2), 32.8 (C-3), 18.2, 17.8 (C-4); HRMS (ESI) m/z: [M+H]$^+$ Calcd. for $C_6H_{12}NO_2$ 130.0863; Found 130.0862.

(*S*,*E*)-3-(But-2-enoyl)-4-isopropyloxazolidin-2-one (60).



Compound **S1** (9.2 g, 71 mmol) was dissolved in anhydrous THF (0.35 mL, 0.20 M). *n*-BuLi (2.5 M solution in THF; 31 mL, 78 mmol, 1.1 eq.) was added at -78°C. The reaction mixture was stirred for 15 min. at -78°C, before adding crotonyl chloride (10 mL, 92 mmol, 1.3 eq.) at -78°C. The reaction mixture was stirred for 30 min. at -78°C and 3 h at room temperature. Upon full conversion on TLC (R$_f$ 0.6 (EtOAc:pentane, 2:8 v:v)), the reaction was quenched with sat. aq. NH$_4$Cl. The mixture was diluted with sat. aq. NaHCO$_3$, the organic layer was separated, the aqueous layer was extracted thrice with EtOAc and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Flash column chromatography (5:95 Et$_2$O:pentane → 40:60 Et$_2$O:pentane) yielded the title compound **60** (9.4 g, 48 mmol, 68%). Analytical data in full agreement with literature data.[39] ^{1}H NMR (400 MHz, CDCl$_3$, HH-COSY, HSQC): δ 7.28 (dd, *J* = 15.2, 1.6 Hz, 1H, H-1'), 7.13 (dq, *J* = 15.2, 6.7 Hz, 1H, H-2'), 4.50 (ddd, *J* = 8.3, 3.5, 3.5 Hz, 1H, H-2), 4.32 (dd, *J* = 8.7, 8.7 Hz, 1H, H-1), 4.23 (dd, *J* = 9.1, 3.1 Hz, 1H, H-1), 2.39 (pd, *J* = 7.0, 3.9 Hz, 1H, H-3), 1.96 (dd, *J* = 6.8, 1.6 Hz, 3H, H-3'), 0.93 (d, *J* = 7.1 Hz, 3H, H-4), 0.88 (d, *J* = 7.0 Hz, 3H, H-4); ^{13}C NMR (101 MHz, CDCl$_3$, HSQC): δ 164.5 (C=O, oxazolidinone), 153.8 (C=O,

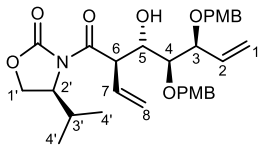
amide), 146.0 (C-2'), 121.6 (C-1'), 63.1 (C-1), 58.2 (C-2), 28.2 (C-3), 18.1 (C-3'), 17.6, 14.3 (C-4); HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{10}H_{16}NO_3$ 198.1125; Found 198.1122.

Preparation of dibutylboron triflate.

Following modified literature procedures,[55] a flame-dried round-bottom flask under argon atmosphere was filled with *n*-BuLi (2.5 M in hexanes; 720 mL, 1.8 mol, 3.0 eq.). In a separate flask, $BF_3{\cdot}OEt_2$ (74 mL, 600 mmol, 1.0 eq.) was dissolved in dry Et_2O (400 mL) and the solution was cannulated into a dropping funnel. While stirring, the solution of $BF_3{\cdot}OEt_2$ was carefully added to the *n*-BuLi at allowing the reaction mixture to slowly warm up to a gentle boil. Reflux continued for another 2 hours. The mixture was cooled to room temperature and carefully quenched with 3 M HCl (400 mL) followed by the addition of water (400 mL). The organic layer was separated and transferred to a round-bottom flask containing anhydrous Na_2SO_4 after which the supernatant was transferred to a second round bottom flask and solvents were removed under reduced pressure yielding crude tri-*n*-butylborane. Vacuum distillation of the crude (bp 50 °C, 3.0 mbar) yielded tri-*n*-butylborane as a colorless oil (72 gr, 393 mmol, 66%) and stored under protective atmosphere.

According to modified literature procedures,[40] the freshly prepared tri-*n*-butylborane was placed in an oil bath while kept under argon atmosphere. While stirring vigorously, trifluoromethanesulfonic acid (34.5 mL, 393 mmol, 1.0 eq.) was added dropwise while closely monitoring of the temperature. Subsequently, the reaction mixture was heated to 50 °C for an hour after which the reaction mixture was cooled to room temperature. Vacuum distillation of the crude (bp 60 °C, 2-3 mbar) yielded Bu_2BOTf as a yellowish liquid (103 gr, 374 mmol, 95%) and store at -25 °C under argon atmosphere.

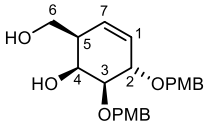
(*S*)-3-[(2*S*,3*S*,4*S*,5*S*)-4,5-Di-*O*-(4-methoxybenzyl)-3-hydroxy-2-vinyl-hept-6-enoyl]-4-isopropyl-oxazolidin-2-one (61).



Compound **60** (2.5 g, 12 mmol, 1.8 eq.) was dissolved in anhydrous DCM (21 mL, 0.60 M) and 3 Å molecular sieve rods were added to the solution. Freshly prepared Bu_2BOTf (1.0 M solution in DCM; 12 mL, 12 mmol, 1.8 eq.) was added at -78°C and after 10 min. Et_3N (1.9 mL, 14 mmol, 2.0 eq.) was added. The reaction mixture was stirred for 1 h at -78°C and 15 min. at 0°C. Compound **28** (2.5 g, 6.9 mmol), dissolved in anhydrous DCM (12 mL, 0.6 M), was added to the reaction mixture at -78°C. The reaction mixture was stirred for 2 h while allowing the reaction mixture to warm up to -30°C and was kept at this temperature overnight. Upon full conversion on TLC (R_f 0.4 (3:7, EtOAc:pentane v:v)), the reaction was quenched with a pH 7.4 aq. phosphate buffer and H_2O_2 (30% w/w in H_2O). The mixture was diluted with sat. aq. $NaHCO_3$, the organic layer was separated, the aqueous layer was extracted thrice with DCM and the combined organic layers were washed with sat. aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (10:90 EtOAc:pentane → 40:60 EtOAc:pentane) yielded the title compound **61** (3.7 g, 6.7 mmol, 97%). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.25 – 7.21 (m, 4H, CH_{arom}), 6.87 – 6.83 (m, 4H, CH_{arom}), 6.01 (ddd, *J* = 17.2, 10.6, 7.1 Hz, 1H, H-2), 5.90 (ddd, *J* = 17.2, 10.2, 8.9 Hz, 1H, H-7), 5.41 – 5.38 (m, 2H, H-1, H-8), 5.37 (ddd, *J* = 3.5, 1.6, 1.0 Hz, 1H, H-1), 5.28 (dd, *J* = 10.2, 1.5 Hz, 1H, H-8), 4.96

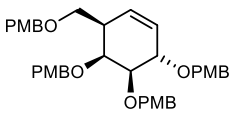
(dd, *J* = 8.9, 7.0 Hz, 1H, H-6), 4.59 (m, 2H, C*H*H PMB, C*H*H PMB), 4.43 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.41 – 4.38 (m, 1H, H-5), 4.34 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.23 (dddd, *J* = 7.1, 4.0, 1.1, 1.1 Hz, 1H, H-3), 4.08 (ddd, *J* = 8.6, 3.9, 3.1 Hz, 1H, H-2'), 3.91 (dd, *J* = 8.9, 3.1 Hz, 1H, H-1'), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.51 (dd, *J* = 8.3, 3.9 Hz, 1H, H-4), 3.45 (dd, *J* = 8.8, 8.8 Hz, 1H, H-1'), 3.36 (d, *J* = 2.3 Hz, 1H, 5-OH), 2.23 (pd, *J* = 7.0, 3.8 Hz, 1H, H-3'), 0.79 (d, *J* = 7.1 Hz, 3H, H-4'), 0.74 (d, *J* = 6.9 Hz, 3H, H-4'); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 172.8 (C=O, oxazolidinone), 159.4, 159.3 ($C_{q\text{-}arom}$), 153.6 (C=O, amide), 134.7 (C-2), 133.6 (C-7), 130.3, 130.0 ($C_{q\text{-}arom}$), 129.7, 129.2 (CH_{arom}), 120.6 (C-8), 119.1 (C-1), 113.9, 113.8 (CH_{arom}), 81.5 (C-4), 79.6 (C-3), 72.8, 70.9 (CH_2 PMB), 70.8 (C-5), 62.6 (C-1'), 58.1 (C-3'), 55.5, 55.4 (OMe), 50.1 (C-6), 28.2 (C-2'), 17.9, 14.6 (C-4'); HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{31}H_{39}NNaO_8$ 576.2568; Found 576.2561.

2,3-Di-*O*-(4-methoxybenzyl)-4-*epi*-cyclophellitol alkene (62).



Compound **61** (3.7 g, 6.7 mmol) was dissolved in THF:H_2O (9:1, 93 mL, 0.07 M). $LiBH_4$ (2.0 M solution in THF; 8.7 mL, 17 mmol, 2.6 eq.) was added on ice. The reaction mixture was stirred for 30 min. at 0 °C and 1 h at room temperature. Upon full conversion on TLC (R_f 0.3 (EtOAc:pentane, 6:4 v:v)), the reaction was quenched with 2.0 M aq. NaOH (100 mL). The mixture was diluted with sat. aq. $NaHCO_3$, the organic layer was separated, the aqueous layer was extracted thrice with EtOAc and the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20:80 EtOAc:pentane → 45:55 EtOAc:pentane) yielded the crude intermediate.
The crude intermediate was dissolved in anhydrous DCM (34 mL, 0.20 M). 2nd generation Grubbs catalyst (0.11 g, 0.13 mmol, 0.02 eq.) was added. The reaction mixture was purged with N_2 for 10 min. and stirred for 24 h at 40 °C. A second portion of 2nd generation Grubbs catalyst (0.11 g, 0.13 mmol, 0.02 eq.) was added and the reaction mixture was purged with N_2 for 10 min. and stirred overnight at 40 °C. Upon full conversion on TLC (R_f 0.4 (EtOAc:pentane, 8:2 v:v)), the reaction was concentrated *in vacuo*. Flash column chromatography (65:35 EtOAc:pentane → 90:10 EtOAc:pentane) yielded the title compound **62** (1.8 g, 4.4 mmol, 66% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.31 – 7.25 (m, 4H, CH_{arom}), 6.89 – 6.81 (m, 4H, CH_{arom}), 5.79 (ddd, *J* = 10.2, 2.6, 2.6 Hz, 1H, H-7), 5.53 – 5.47 (m, 1H, H-1), 4.66 – 4.56 (m, 4H, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.26 (m, 2H, H-2, H-4), 3.77 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.75 – 3.73 (m, 2H, H-6), 3.59 (dd, *J* = 7.7, 2.2 Hz, 1H, H-3), 3.27 – 3.15 (m, 2H, 4-OH, 6-OH), 2.40 (dddd, *J* = 6.4, 3.3, 2.9, 2.9 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.1, 130.7, 130.2 ($C_{q\text{-}arom}$), 129.5, 129.4 (CH_{arom}), 127.6 (C-7), 126.7 (C-1), 113.8, 113.7 (CH_{arom}), 81.6 (C-3), 76.5 (C-2), 71.9, 71.8 (CH_2 PMB), 69.8 (C-4), 63.4 (C-6), 55.2 (OMe), 42.1 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{28}NaO_6$ 423.1778; Found 423.1771.

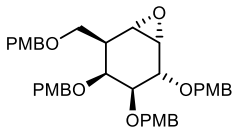
4-*Epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl)- cyclophellitol alkene (63).

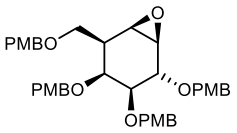


Compound **63** (2.0 g, 5.0 mmol) was co-evaporated with toluene twice and dissolved in DMF (10 mL, 0.5 M). Subsequently, TBAI (37 mg, 0.1 mmol, 0.02 eq.), PMBCl (2.7 mL, 20 mmol, 4.0 eq.) and NaH (60 wt.% dispersion in mineral oil; 0.8 g, 20 mmol, 4.0 eq.) were added on ice. The reaction mixture was kept stirring at 0°C for 30 min. after which the reaction mixture was

heated to 45 °C for 16 hours. Upon full conversion was observed (R_f 0.5 (EtOAc:pentane, 2:8 v:v)), the reaction mixture was cooled to 0°C, quenched with MeOH and concentrated *in vacuo*. The crude intermediate was dissolved in Et_2O and diluted with sat. aq. $NaHCO_3$. The organic layer was separated, the aqueous layer was extracted thrice with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (5:95 EtOAc:pentane → 25:75 EtOAc:pentane) yielded the title compound **63** as a yellow oil (2.4 g, 3.7 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.19 (m, 8H, CH_{arom}), 6.94 – 6.80 (m, 8H, CH_{arom}), 5.75 (ddd, *J* = 10.1, 2.6, 2.6 Hz, 1H, H-7), 5.47 (d, *J* = 10.2 Hz, 1H, H-1), 4.85 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.73 – 4.61 (m, 4H, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.58 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.46 – 4.38 (m, 3H, C*H*H PMB, CH*H* PMB, H-2), 4.15 (d, *J* = 2.2 Hz, 1H, H-4), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.71 (dd, *J* = 7.9, 1.8 Hz, 1H, H-3), 3.56 (dd, *J* = 8.7, 8.7 Hz, 1H, H-6), 3.45 (dd, *J* = 8.8, 6.4 Hz, 1H, H-6), 2.66 (ddd, *J* = 6.0, 6.0, 3.0 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.2, 159.1, 159.1, 131.4, 131.1, 131.0, 130.4 ($C_{q\text{-}arom}$), 129.6, 129.5, 129.5, 129.2 (CH_{arom}), 128.7 (C-7), 127.7 (C-1), 114.2, 114.1, 113.9, 113.8, 113.8, 113.7 (CH_{arom}), 83.1 (C-3), 77.4 (C-2), 74.9 (C-4), 73.7, 73.0, 72.1, 71.9 (CH_2 PMB), 70.1 (C-6), 55.4, 55.4, 55.3 (OMe), 42.0 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{39}H_{44}NaO_8$ 663.2934; Found 663.2943.

1,4,7-*Epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl) cyclophellitol (64) and 4-*epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl) cyclophellitol (65).



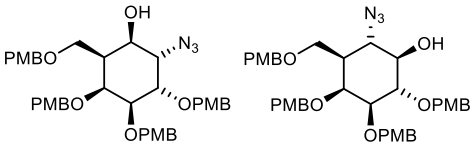


Compound **63** (0.94 g, 1.5 mmol) was dissolved in anhydrous DCM (15 mL, 0.1 M). Subsequently, $NaHCO_3$ (1.2 g, 15 mmol, 10 eq.) and *m*-CPBA (0.64 g, 3.7 mmol, 2.5 eq.) were added. The reaction was stirred under N_2 atmosphere at 5 °C for 3 days. Upon partial conversion was observed (R_f 0.5 and 0.3 for **64** and **65** respectively (EtOAc:pentane, 3:7, v:v)), the reaction was quenched with sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were subsequently washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (dry loading, 15:85 EtOAc:pentane → 25:75 EtOAc:pentane) yielded **64** (66 mg, 0.1 mmol, 7%), **65** (0.41 g, 0.63 mmol, 43%) and starting material (0.18 g, 0.28 mmol, 19%), 69% brsm.

Analytical data for α-epoxide **64**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.37 – 7.10 (m, 8H, CH_{arom}), 6.91 – 6.77 (m, 8H, CH_{arom}), 4.81 – 4.71 (m, 3H, C*H*H PMB, C*H*H PMB, CH*H* PMB), 4.62 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.59 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.47 – 4.38 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.19 (dd, *J* = 8.5, 2.5 Hz, 1H, H-2), 3.85 (ddd, *J* = 3.3, 1.5, 1.5 Hz, 1H, H-4), 3.80 – 3.80 (m, 9H, OMe), 3.79 (s, 3H, OMe), 3.56 (dd, *J* = 8.6, 1.4 Hz, 1H, H-3), 3.54 – 3.51 (m, 2H, H-6), 3.31 (dd, *J* = 3.9, 2.5 Hz, 1H, H-1), 2.91 (dd, *J* = 4.0, 1.5 Hz, 1H, H-7), 2.24 (ddd, *J* = 7.9, 3.4 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 159.2, 159.2, 131.1, 131.0, 131.0, 130.2 ($C_{q\text{-}arom}$), 129.7, 129.6, 129.6, 129.3, 114.0, 113.8, 113.8, 113.7 (CH_{arom}), 81.0 (C-3), 76.5 (C-2), 75.5 (C-4), 74.0, 73.1, 72.8, 72.5 (CH_2 PMB), 68.5 (C-6), 55.5, 55.4 (OMe), 55.4 (C-1), 54.6 (C-7), 41.0 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{44}NaO_9$ 679.2878; Found 679.2884.

Analytical data for β-epoxide **65**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.35 – 7.17 (m, 8H, CH_{arom}), 6.95 – 6.78 (m, 8H, CH_{arom}), 4.79 – 4.68 (m, 3H, C*H*H PMB, C*H*H PMB, CH*H* PMB), 4.66 – 4.59 (m, 2H, C*H*H PMB, CH*H* PMB), 4.51 (d, *J* = 11.7 Hz, 1H, CH*H* PMB), 4.45 – 4.37 (m, 2H, C*H*H PMB, CH*H* PMB), 4.09 (d, *J* = 8.7 Hz, 1H, H-2), 3.88 (dd, *J* = 1.7, 1.7 Hz, 1H, H-4), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.67 (dd, *J* = 9.0, 6.9 Hz, 1H, H-6), 3.57 (dd, *J* = 9.0, 7.3 Hz, 1H, H-6), 3.41 (dd, *J* = 8.8, 2.2 Hz, 1H, H-3), 3.21 (d, *J* = 3.8 Hz, 1H, H-1), 3.16 (dd, *J* = 3.0, 3.0 Hz, 1H, H-7), 2.31 – 2.22 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 159.3, 159.2, 159.1, 131.1, 130.8, 130.4, 130.3 ($C_{q\text{-}arom}$), 129.6, 129.6, 129.2, 113.9, 113.9, 113.8, 113.6 (CH_{arom}), 82.4 (C-3), 76.0 (C-2), 73.9, 73.2, 73.1 (CH_2 PMB), 72.5 (C-4), 72.4 (CH_2 PMB), 68.8 (C-6), 55.4, 55.3, 55.3 (OMe), 54.7 (C-1), 52.6 (C-7), 40.4 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{44}NaO_9$ 679.2878; Found 679.2880.

4-*Epi*-1-(*S*)-azido-2,3,4,6-tetra-*O*-(4-methoxybenzyl)-7-(*R*)-ol cyclophellitol alkane (66) and 4-*Epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl)-7-(*S*)-azido-1-(*R*)-ol cyclophellitol alkane (67).



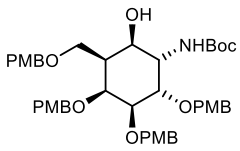
Epoxide **65** (3.9 g, 5.9 mmol) was dissolved in anhydrous DMF (59 mL, 0.1 M). Subsequently NaN_3 (7.6 g, 0.12 mol, 20 eq.) were added. The reaction was stirred under N_2 atmosphere at 140 °C for 16 hours. Upon full conversion was observed (R_f 0.5 and 0.45 for **66** and **67** respectively (EtOAc:pentane, 3:7, v:v)) the reaction was allowed to cool to room temperature and diluted with sat. aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were washed with brine. The organic layers were subsequently dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (15:85 EtOAc:pentane → 25:75 EtOAc:pentane) yielded regioisomer **66** (1.9 g, 2.7 mmol, 45%) and regioisomer **67** (1.4 g, 2.0 mmol, 34%) in an overall yield of 79%.

Analytical data for **66**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.38 – 7.18 (m, 6H, CH_{arom}), 7.13 – 7.04 (m, 2H, CH_{arom}), 6.93 – 6.73 (m, 8H, CH_{arom}), 4.84 (d, *J* = 10.5 Hz, 1H, C*H*H PMB), 4.77 – 4.60 (m, 4H, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.42 (d, *J* = 11.5 Hz, 1H, C*H*H PMB), 4.37 – 4.31 (m, 2H, C*H*H PMB, CH*H* PMB), 4.22 (dd, *J* = 9.9, 3.5 Hz, 1H, H-3), 4.18 (s, 1H, H-4), 4.03 (d, *J* = 3.7 Hz, 1H, H-1), 3.91 (d, *J* = 10.0 Hz, 1H, 7-OH), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.77 – 3.74 (m, 1H, H-7) 3.70 (dd, *J* = 10.0, 2.5 Hz, 1H, H-2), 3.62 (dd, *J* = 9.2, 9.2 Hz, 1H, H-6), 3.50 (dd, *J* = 7.4, 7.4 Hz, 1H, H-6), 2.02 – 1.92 (m, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 159.4, 159.3, 159.2, 131.0, 130.5, 130.2 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.5, 129.2, 128.8, 113.9, 113.9, 113.9 (CH_{arom}), 80.6 (C-2), 78.0 (C-4), 76.4 (C-3), 75.5, 73.3, 73.1, 73.0 (CH_2 PMB), 71.8 (C-7), 67.6 (C-6), 65.0 (C-1), 55.4, 55.4 (OMe), 38.7 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{45}NaO_9$ 722.3054; Found 722.3057.

Analytical data for **67**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.37 – 7.09 (m, 8H, CH_{arom}), 6.92 – 6.80 (m, 8H, CH_{arom}), 4.92 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.88 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.69 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.64 – 4.56 (m, 2H, CH*H* PMB, CH*H* PMB), 4.47 – 4.32 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.16 (dd, *J* = 2.2, 2.2 Hz, 1H, H-4), 3.83 – 3.78 (m, 13H, OMe, OMe, OMe, OMe, H-2), 3.62 (dd, *J* = 8.7, 4.0 Hz, 1H, H-6), 3.55 (dd, *J* = 10.2, 8.8 Hz, 1H, H-6), 3.47 (ddd, *J* = 9.2, 9.2, 2.2 Hz, 1H, H-1), 3.44 – 3.34 (m, 2H, H-3, H-7), 2.50 (d, *J* = 2.3 Hz, 1H, 1-OH), 1.61

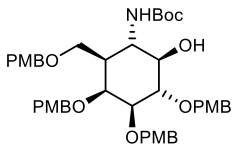
(dddd, *J* = 10.0, 10.0, 4.0, 2.2 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 159.4, 159.3, 159.2, 131.2, 130.7, 130.5 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.4, 129.2, 114.1, 114.0, 113.9, 113.7 (CH_{arom}), 83.5 (C-3), 80.9 (C-2), 77.0 (C-1), 75.2, 74.8 (CH_2 PMB), 73.3 (C-4), 73.2, 72.3 (CH_2 PMB), 67.5 (C-6), 61.7 (C-7), 55.4, 55.4 (OMe), 42.4 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{45}NaO_9$ 722.3054; Found 722.3058.

4-*Epi*-1-(*S*)-(*N*-(tert-butoxycarbonyl)-2,3,4,6-tetra-*O*-(4-methoxybenzyl)-7-(*R*)-ol cyclophellitol alkane (68).



Azide **66** (1.9 g, 2.7 mmol) was dissolved in a 1:1 solution of THF and aq. 1.0 M NaOH (27 mL, 0.1 M). Subsequently triphenylphosphine (2.8 g, 11 mmol, 4.0 eq.) was added and the reaction was stirred vigorously overnight at room temperature. Upon full conversion of the starting material was observed, the reaction was diluted with sat. aq. $NaHCO_3$ and EtOAc. The aqueous phase was separated and subsequently extracted with EtOAc (3x), the organic layers were then washed with brine. The brine layer was extracted once with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude amine was dissolved in anhydrous DCM (13.5 mL, 0.2 M) and cooled on ice. While stirring, Et_3N (1.9 mL, 13.5 mmol, 5.0 eq.) and subsequently Boc_2O (0.93 mL, 4.1 mmol, 1.5 eq.) were added. The flask was flushed with N_2 and the reaction was stirred at room temperature for 16 hours until full conversion was observed (R_f 0.5 (EtOAc:pentane, 4:6, v:v)). The reaction was quenched with sat. aq. NH_4Cl and the aqueous layer separated. Subsequently, the aqueous layer was extracted with EtOAc (3x), and the combined organic layers were washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 30:70 EtOAc:pentane) yielded **68** as a white, brittle foam (2.0 g, 2.6 mmol, 96% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.31 – 7.04 (m, 8H, CH_{arom}), 6.91 – 6.74 (m, 8H, CH_{arom}), δ 4.89 – 4.81 (m, 1H, C*H*H PMB), 4.79 – 4.72 (m, 2H, C*H*H PMB, CH*H* PMB), 4.64 – 4.57 (m, 2H, C*H*H PMB, CH*H* PMB), 4.55 – 4.48 (m, 1H, CH*H* PMB), 4.43 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.37 – 4.30 (m, 1H, CH*H* PMB), 4.28 – 4.18 (m, 3H, H-1, H-3, H-4), 4.05 (s, 1H, H-7), 3.93 – 3.87 (m, 2H, 1-NH, 7-OH), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.77 – 3.76 (m, 7H, OMe, OMe, H-6), 3.54 (s, 1H, H-6), 3.43 (s, 1H, H-2), 1.95 (s, 1H, H-5), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.2, 159.1 ($C_{q\text{-}arom}$), 156.2 (C=O), 130.9, 130.4, 130.2 ($C_{q\text{-}arom}$), 129.7, 129.6, 129.0, 113.8, 113.8, 113.7 (CH_{arom}), 86.9 ($C(CH_3)_3$), 80.4 (C-2), 77.5 (C-3/C-4), 75.5 (CH_2 PMB), 74.4 (C-3/C-4), 73.2, 73.0, 71.5 (CH_2 PMB), 71.3 (C-7), 68.0 (C-6), 55.3, 55.2, 54.2 (OMe), 45.4 (C-1), 38.6 (C-5), 28.4 ($C(CH_3)_3$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{44}H_{55}NNaO_{11}$ 796.3673; Found 796.3675.

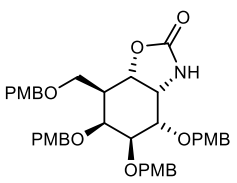
4-*Epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl)-7-(*S*)-(*N*-(*tert*-butoxycarbonyl)-1-(*R*)-ol cyclophellitol alkane (69).



Azide **67** (1.4 g, 2.0 mmol) was dissolved in a 1:1 solution of THF and aq. 1.0 M NaOH (20 mL, 0.1 M). Subsequently triphenylphosphine (2.1 g, 8.0 mmol, 4.0 eq.) was added and the reaction was stirred vigorously overnight at room temperature. Upon full conversion of the starting material was observed, the reaction was diluted with sat. aq. $NaHCO_3$

and EtOAc. The aqueous phase was separated and subsequently extracted with EtOAc (3x), the organic layers were then washed with brine. The brine layer was extracted once with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude amine was dissolved in anhydrous DCM (10 mL, 0.2 M) and cooled on ice. While stirring, Et_3N (1.4 mL, 10 mmol, 5.0 eq.) and subsequently Boc_2O (0.69 mL, 3.0 mmol, 1.5 eq.) were added. The flask was flushed with N_2 and the reaction was stirred at room temperature for 16 hours until full conversion was observed (R_f 0.3 (EtOAc:pentane, 4:6, v:v)). The reaction was quenched with sat. aq. NH_4Cl and the aqueous layer separated. Subsequently, the aqueous layer was extracted with EtOAc (3x), and the combined organic layers were washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (10:90 EtOAc:pentane → 40:60 EtOAc:pentane) yielded **69** as a white, brittle foam (1.5 g, 1.9 mmol, 95% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.33 – 7.13 (m, 8H, CH_{arom}), 6.91 – 6.77 (m, 8H, CH_{arom}), 4.91 – 4.82 (m, 2H, C*H*H PMB, C*H*H PMB), 4.76 – 4.69 (m, 2H, 7-NH, CH*H* PMB), 4.68 – 4.59 (m, 2H, C*H*H PMB, CH*H* PMB), 4.43 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.37 – 4.28 (m, 2H, C*H*H PMB, CH*H* PMB), 4.06 (s, 1H, H-4), 3.88 – 3.82 (m, 1H, H-2), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.71 – 3.67 (m, 1H, H-7), 3.55 – 3.45 (m, 2H, H-6), 3.36 (ddd, *J* = 11.6, 5.8, 5.8 Hz, 2H, H-1, H-3), 3.08 (s, 1H, 1-OH), 1.72 – 1.64 (m, 1H, H-5), 1.42 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HH-COSY, HSQC): δ 159.4, 159.3, 159.2, 159.1 ($C_{q\text{-}arom}$), 157.0 (C=O), 131.3, 131.2, 130.8, 130.2 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.4, 129.4, 129.1, 113.9, 113.9, 113.6 (CH_{arom}), 83.5 (C-1/C-3), 81.9 (C-2), 79.8 ($C(CH_3)_3$), 77.2 (C-1/C-3), 75.2, 74.4 (CH_2 PMB), 74.1 (C-4), 73.1, 72.5 (CH_2 PMB), 69.0 (C-6), 55.3, 55.3 (OMe), 52.5 (C-7), 43.1 (C-5), 28.4 ($C(CH_3)_3$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{44}H_{55}NNaO_{11}$ 796.3673; Found 796.3676.

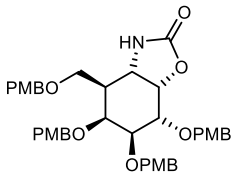
4-*Epi*-1,7-(*S*,*S*)-(*N*,*O*)-carbamate-2,3,4,6-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (21).



Compound **68** (2.0 g, 2.6 mmol) was co-evaporated with toluene, dissolved in anhydrous $CHCl_3$ (26 mL, 0.1 M) and cooled on ice. Subsequently Me-imidazole (2.1 mL, 26 mmol, 10 eq.), Et_3N (1.8 mL, 13 mmol, 5.0 eq.) and MsCl (1.0 mL, 13 mmol, 5.0 eq.) were added. The reaction was flushed with N_2 and stirred overnight at room temperature. Upon full conversion (R_f 0.6 (EtOAc:pentane, 3:7, v:v)) the reaction was diluted with EtOAc and washed with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous DMF (87 mL, 0.03 M), flushed with argon gas and stirred at 130 °C overnight. Upon full conversion (R_f 0.3 (EtOAc:pentane, 1:1, v:v)) the reaction was cooled to room temperature and concentrated to a fifth of its original volume. The residue was diluted with EtOAc and washed with H_2O and consequently brine. The aqueous layers were back-extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (20:80 EtOAc:pentane → 60:40 EtOAc:pentane) yielded carbamate **21** as a brittle foam (1.2 g, 1.7 mmol, 65% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.35 – 7.05 (m, 8H, CH_{arom}), 6.92 – 6.74 (m, 8H, CH_{arom}), 5.37 (s, 1H, 1-NH), 4.78 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.75 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.68 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.64 (d, *J* =

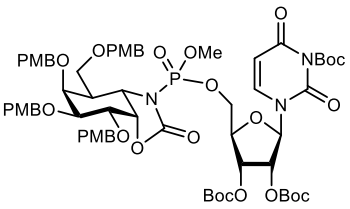
11.2 Hz, 1H, CH*H* PMB), 4.57 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.42 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.36 (d, *J* = 10.8 Hz, 1H, CH*H* PMB), 4.31 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.19 – 4.14 (m, 2H, H-4, H-7), 4.11 (dd, *J* = 6.0, 6.0 Hz, 1H, H-1), 3.99 (dd, *J* = 9.5, 5.1 Hz, 1H, H-2), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 – 3.77 (m, 6H, OMe, OMe), 3.68 (dd, *J* = 9.6, 1.8 Hz, 1H, H-3), 3.60 – 3.52 (m, 2H, H-6), 2.05 (dddd, *J* = 9.6, 9.6, 4.6, 1.9 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.5, 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 158.5 (C=O), 130.8, 130.6, 130.3, 130.1 ($C_{q\text{-}arom}$), 129.7, 129.6, 129.2, 114.0, 113.9, 113.9, 113.7 (CH_{arom}), 81.2 (C-3), 75.6 (C-7), 75.5 (C-2), 74.4, 73.8 (CH_2 PMB), 73.1 (C-4), 73.0, 72.5 (CH_2 PMB), 67.1 (C-6), 55.5 (C-1), 55.3, 55.3, 55.3 (OMe), 43.4 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{40}H_{45}NNaO_{10}$ 722.2941; Found 722.2945.

4-*Epi*-1,7-(*S*,*S*)-(*O*,*N*)-carbamate-2,3,4,6-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (23).



Compound **69** (1.5 g, 2.0 mmol) was co-evaporated with toluene, dissolved in anhydrous $CHCl_3$ (20 mL, 0.1 M) and cooled on ice. Subsequently Me-imidazole (1.6 mL, 20 mmol, 10 eq.), Et_3N (1.4 mL, 10 mmol, 5.0 eq.) and MsCl (0.8 mL, 10 mmol, 5.0 eq.) were added. The reaction was flushed with N_2 and stirred overnight at room temperature. Upon full conversion was observed(R_f 0.6 (EtOAc:pentane, 3:7, v:v)), the reaction was diluted with EtOAc and washed with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous DMF (65 mL, 0.03 M), flushed with argon gas and stirred at 130 °C overnight. Upon full conversion (R_f 0.2 (EtOAc:pentane, 1:1, v:v)) the reaction was cooled to room temperature and concentrated to a fifth of its original volume. The residue was diluted with EtOAc and washed with H_2O and consequently brine. The aqueous layers were back-extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (30:70 EtOAc:pentane → 60:40 EtOAc:pentane) yielded carbamate **23** (0.82 g, 1.2 mmol, 59% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.38 – 7.06 (m, 8H, CH_{arom}), 6.95 – 6.79 (m, 8H, CH_{arom}), 5.48 (s, 1H, 7-NH), 4.82 – 4.69 (m, 5H, C*H*H PMB, C*H*H PMB, C*H*H PMB, CH*H* PMB, H-1), 4.63 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.39 – 4.34 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.13 (dd, *J* = 9.6, 4.5 Hz, 1H, H-2), 3.84 (s, 3H, OMe), 3.83 – 3.83 (m, 6H, OMe, OMe), 3.82 (s, 3H, OMe), 3.75 (dd, *J* = 9.6, 2.1 Hz, 1H, H-3), 3.72 (dd, *J* = 2.1, 2.1 Hz, 1H, H-4), 3.56 (dd, *J* = 9.4, 6.0 Hz, 1H, H-7), 3.48 (dd, *J* = 9.8, 8.8 Hz, 1H, H-6), 3.39 (dd, *J* = 8.8, 5.1 Hz, 1H, H-6), 1.88 (dddd, *J* = 9.7, 9.7, 5.1, 2.0 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.4, 159.4, 159.3 ($C_{q\text{-}arom}$), 159.1 (C=O), 130.7, 130.5, 130.4 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.6, 129.3, 114.1, 113.9, 113.8, 113.8 (CH_{arom}), 80.6 (C-3), 77.1 (C-1), 75.0 (C-4), 74.8 (C-2), 74.0, 73.4, 73.3 (CH_2 PMB), 72.6 (C-6), 55.4, 55.4, 55.3 (OMe, C-7), 43.9 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{40}H_{45}NNaO_{10}$ 722.2941; Found 722.2943.

4''-*Epi*-1'',7''-(*S*,*S*)-(*O*,*N*-(3-*N*-(*tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxy carbonyl)uridinyl))-carbamate-2'',3'',4'',6''-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (70).



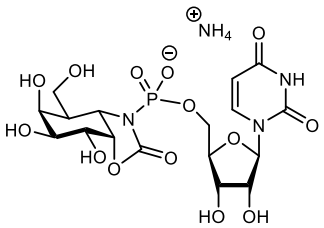
Compound **70** was prepared according to general procedure A using cyclic carbamate **23** (0.14 g, 0.2 mmol), 15-crown-5 ether (0.2 mL, 1.0 mmol, 5.0 eq.) and NaH (60 wt% dispersion in mineral oil; 12 mg, 0.3 mmol, 1.5 eq.) in anhydrous THF (1.0 mL, 0.2 M); and H-phosphonate **48** (0.25 g, 0.4 mmol, 2.0 eq.), dry DiPEA (0.21 mL, 1.2 mmol, 6.0 eq.) and $BrCCl_3$ (79 µL, 0.8 mmol, 4.0 eq.) in anhydrous DCM (1.3 mL, 0.3 M). Flash column chromatography of the crude product (20:80 EtOAc:pentane → 60:40 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **70** as a pale-yellow oil and as a mixture of P(V) diastereomers (84 mg, 64 µmol, 32%) and starting material (32 mg, 46 µmol, 23%), 55% brsm.

Data for first P(V) diastereomer: R_f 0.6 (EtOAc:pentane, 1:1 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.69 (d, *J* = 8.3 Hz, 1H, H-6), 7.32 – 7.29 (m, 4H, CH_{arom}), 7.25 – 7.22 (m, 2H, CH_{arom}), 7.14 – 7.10 (m, 2H, CH_{arom}), 6.92 – 6.82 (m, 8H, CH_{arom}), 6.17 (d, *J* = 6.1 Hz, 1H, H-1'), 5.91 (d, *J* = 8.2 Hz, 1H, H-5), 5.28 (dd, *J* = 5.4, 4.2 Hz, 1H, H-3'), 5.13 (dd, *J* = 5.8, 5.8 Hz, 1H, H-2'), 4.83 – 4.64 (m, 6H, H-1'', C*H*H PMB, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.45 – 4.30 (m, 5H, H-4', H-5', C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.27 – 4.13 (m, 2H, H-5', H-2''), 4.01 – 3.94 (m, 1H, H-7''), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.78 – 3.67 (m, 5H, P(O)OMe, H-4'', H-6''), 3.57 (dd, *J* = 9.8, 9.8 Hz, 1H, H-6''), 2.01 – 1.93 (m, 1H, H-5''), 1.61 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.5, 159.3, 159.3 ($C_{q\text{-}arom}$), 154.7 (d, $^2J_{C,P}$ = 7.5 Hz, C=O cyclic carbamate), 152.1 (C=O carbamate), 152.0 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.4 (C-6), 130.7, 130.7, 130.1 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.2, 114.0, 113.9, 113.9, 113.7 (CH_{arom}), 103.4 (C-5), 86.9 (*C*$(CH_3)_3$), 86.1 (C-1'), 83.8, 83.7 (*C*$(CH_3)_3$), 80.3 (C-4''), 80.0 (d, $^3J_{C,P}$ = 7.8 Hz, C-4'), 79.3 (d, $^3J_{C,P}$ = 6.6 Hz, C-1''), 74.5 (C-2'), 74.4 (CH_2 PMB), 74.2 (C-3''), 73.5 (C-2''), 73.1, 73.1, 73.0 (CH_2 PMB), 71.7 (C-3'), 66.9 (d, $^3J_{C,P}$ = 6.1 Hz, C-5'), 66.7 (C-6''), 57.6 (d, $^3J_{C,P}$ = 4.4 Hz, C-7''), 55.4 (OMe), 55.1 (d, $^2J_{C,P}$ = 6.5 Hz, P(O)OMe), 44.5 (C-5''), 27.7, 27.7, 27.5 (C(*C*$H_3)_3$).

Data for second P(V) diastereomer: R_f 0.3 (EtOAc:pentane, 1:1 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.67 (d, *J* = 8.3 Hz, 1H, H-6), 7.34 – 7.20 (m, 6H, CH_{arom}), 7.17 – 7.08 (m, 2H, CH_{arom}), 6.94 – 6.79 (m, 8H, CH_{arom}), 6.16 (d, *J* = 6.1 Hz, 1H, H-1'), 5.82 (dd, *J* = 8.3, 0.4 Hz, 1H, H-5), 5.26 (dd, *J* = 5.5, 3.8 Hz, 1H, H-3'), 5.19 (dd, *J* = 5.8, 5.8 Hz, 1H, H-2'), 4.83 – 4.65 (m, 6H, H-1'', C*H*H PMB, C*H*H PMB, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.44 – 4.30 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.28 – 4.13 (m, 4H, H-4', H-5', H-5', H-2''), 4.01 – 3.93 (m, 1H, H-7''), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 – 3.67 (m, 5H, P(O)OMe, H-4'', H-6''), 3.58 (dd, *J* = 9.8 Hz, 1H, H-6''), 2.12 – 2.06 (m, 1H, H-5''), 1.60 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3 (C=O uracil), 159.5, 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 154.6 (d, $^2J_{C,P}$ = 7.3 Hz, C=O cyclic carbamate), 152.1 (C=O carbamate), 151.9 (C=O uracil), 148.7, 147.6 (C=O carbonate), 139.6 (C-6), 130.8, 130.7, 130.3, 130.1 ($C_{q\text{-}arom}$), 129.9, 129.8, 129.7, 129.2, 113.9, 113.9, 113.9, 113.7 (CH_{arom}), 103.1 (C-5), 86.8 (*C*$(CH_3)_3$), 86.3 (C-1'), 83.6, 83.6 (*C*$(CH_3)_3$), 80.5 (C-4''), 80.0 (d, $^3J_{C,P}$ = 8.2 Hz, C-4'), 79.3 (d, $^3J_{C,P}$ = 5.7 Hz, C-1''), 74.5 (CH_2 PMB), 74.4

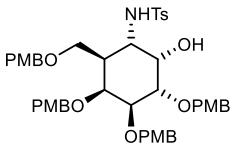
(C-2'), 74.2 (C-3''), 73.7 (C-2''), 73.1, 73.1, 73.0 (CH_2 PMB), 72.1 (C-3'), 66.9 (C-6''), 66.5 (d, $^3J_{C,P}$ = 5.9 Hz, C-5'), 57.7 (d, $^3J_{C,P}$ = 4.4 Hz, C-7''), 55.4 (OMe), 54.7 (d, $^2J_{C,P}$ = 5.9 Hz, P(O)OMe), 44.2 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{65}H_{82}N_3NaO_{24}P$ 1342.4924; Found 1342.4920.

4''-*Epi*-1'',7''-(*S*,*S*)-(*N*,*O*-(5'-*O*-phosphoryluridinyl))-carbamate cyclophellitol alkane (16).



Compound **16** was prepared according to general procedure B using **70** (84 mg, 64 μmol), TES (0.10 mL, 0.64 mmol, 10 eq.) and TFA in DCM (30% v:v, 1.4 mL, 0.05 M). The reaction mixture was stirred at 5 °C for 24 h, after which full conversion was observed on TLC (R_f 0.5 MeOH:DCM, 3:7 v:v). Pyridine (20:1 pyridine:TFA, 5.0 mL, 62 mmol) was added and the reaction mixture was stirred overnight at room temperature. Upon full conversion was observed on TLC (R_f 0.3 (H_2O:MeCN, 1:9 v:v)) and ^{31}P NMR. Flash column chromatography (0:100 H_2O:ACN → 15:85 H_2O:ACN) followed by Dowex 50WX4 Na^+ ion exchange and lyophilization yielded the title compound **16** as a transparent film (21 mg, 40 μmol, 63%). ^1H NMR (850 MHz, D_2O, HH-COSY, HSQC): δ 7.91 (d, *J* = 8.1 Hz, 1H, H-6), 5.90 (d, *J* = 4.6 Hz, 1H, H-1'), 5.87 (d, *J* = 8.1 Hz, 1H, H-5), 4.86 (dd, *J* = 4.8, 4.8 Hz, 1H, H-1''), 4.30 – 4.27 (m, 2H, H-2'', H-3''), 4.22 (dddd, *J* = 5.0, 2.6, 2.6, 2.6 Hz, 1H, H-4'), 4.17 – 4.11 (m, 3H, H-5', H-4''), 4.07 (dd, *J* = 10.4, 4.3 Hz, 1H, H-2''), 3.98 (dd, *J* = 11.5, 3.9 Hz, 1H, H-6''), 3.95 (ddd, *J* = 10.4, 5.4, 2.2 Hz, 1H, H-7''), 3.74 (dd, *J* = 10.4, 2.6 Hz, 1H, H-3''), 3.69 (dd, *J* = 11.5, 9.9 Hz, 1H, H-6''), 1.87 (dddd, *J* = 10.1, 10.1, 3.9, 2.2 Hz, 1H, H-5''); ^{13}C NMR (214 MHz, D_2O, HSQC): δ 167.2 (C=O uracil), 158.9 (d, *J* = 7.7 Hz, C=O carbamate), 152.7(C=O uracil), 142.8 (C-6), 103.3 (C-5), 89.5 (C-1'), 83.8 (d, *J* = 9.4 Hz, C-4'), 81.2 (d, *J* = 5.7 Hz, C-1''), 74.7 (C-2'/C-3'), 71.9 (C-3''), 70.4 (C-2'/C-3'), 69.5 (C-4''), 68.2 (C-2'), 65.7 (d, *J* = 5.3 Hz, C-5'), 59.9 (C-6''), 57.9 (d, *J* = 2.5 Hz, C-7''), 46.3 (C-5''); ^{31}P NMR (162 MHz, D_2O) δ -5.59; HRMS (ESI) m/z: $[M + H]^+$ Calcd. for $C_{17}H_{28}N_4O_{14}P$ 543.1340; Found 543.1345.

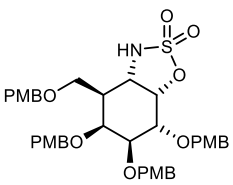
4-*Epi*-2,3,4,6-tetra-*O*-(4-methoxybenzyl)-7-(*S*)-(*p*-toluenesulfonamido)-1-(*S*)-ol cyclophellitol alkane (71).



Compound **23** (0.62 g, 0.9 mmol) was dissolved in EtOH (14 mL, 0.02 M) followed by the addition of aq. NaOH (3.0 M, 3.6 mL, 11 mmol, 12 eq.). The reaction mixture was heated to 70 °C and stirred for 2 hours after which full conversion was observed (R_f 0.3 (MeOH:DCM, 1:9, v:v)). The reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous THF (9.0 mL, 0.1 M). The reaction mixture was cooled on ice followed by the addition of Et_3N (0.49 mL, 3.6 mmol, 4.0 eq.) and TsCl (0.22 g, 1.2 mmol, 1.3 eq.). Stirring at this temperature continued for 1 hour after which full conversion was observed (R_f 0.6 (EtOAc:pentane, 1:1, v:v)). The reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (20:80 EtOAc:pentane → 70:30 EtOAc:pentane) yielded **71** (0.52 g, 0.63 mmol, 70% over two steps). ^1H

NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.70 (d, *J* = 8.3 Hz, 2H, CH_{arom}), 7.29 – 7.06 (m, 10H, CH_{arom}), 6.89 – 6.79 (m, 8H, CH_{arom}), 5.26 (d, *J* = 9.5 Hz, 1H, 7-NH), 4.77 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.62 – 4.54 (m, 3H, C*H*H PMB, C*H*H PMB, CH*H* PMB), 4.43 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.36 – 4.27 (m, 2H, C*H*H PMB, CH*H* PMB), 4.17 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.02 (dd, *J* = 2.3, 2.3 Hz, 1H, H-4), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.74 – 3.70 (m, 2H, H-1, H-2), 3.59 (dd, *J* = 9.4, 2.4 Hz, 1H, H-3), 3.47 – 3.34 (m, 2H, H-6, H-7) 3.26 (dd, *J* = 9.2, 9.2 Hz, 1H, H-6), 2.50 (d, *J* = 1.8 Hz, 1H, 1-OH), 2.44 (s, 3H, Me Ts), 2.07 (dddd, *J* = 11.4, 9.2, 4.5, 2.0 Hz, 1H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 159.3, 159.1, 159.1, 143.4, 138.2, 131.4, 131.0, 130.4, 130.2 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.6, 129.5, 129.5, 129.4, 129.1, 127.2, 113.9, 113.9, 113.8, 113.6 (CH_{arom}), 80.1 (C-3), 78.2 (C-1/C-2), 74.6 (CH_2 PMB), 74.1 (C-4), 73.0, 72.6, 72.6 (CH_2 PMB), 69.5 (C-1/C-2), 68.4 (C-6), 55.4 (OMe), 52.3 (C-7), 40.3 (C-5), 21.7 (Me Ts); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{46}H_{53}NNaO_{11}S$ 850.3237; Found 850.3240.

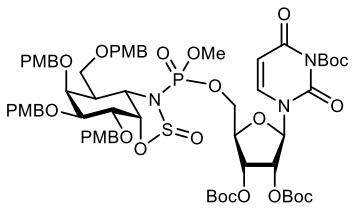
4-*Epi*-1,7-(*S,S*)-(*O,N*)-sulfamidate-2,3,4,6-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (24).



Compound **71** (0.52 g, 0.63 mmol) was dissolved in anhydrous DCM (6.3 mL, 0.1 M) and kept under inert atmosphere. Et_3N (0.35 mL, 2.5 mmol, 4.0 eq.) was added and the reaction mixture was cooled to -78 °C followed by the dropwise addition of SO_2Cl_2 (61 µL, 0.76 mmol, 1.2 eq.). The reaction was allowed to attain to 0 °C over the course of 2 hours after which full conversion was observed (R_f 0.6 (EtOAc:pentane, 3:7, v:v)). The reaction was quenched with sat. aq. NH_4Cl at -78 °C and subsequently diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. In a separate flask, naphthalene (0.97 g, 7.6 mmol, 12 eq.) was dissolved in anhydrous THF (12.5 mL, 0.05 M) followed by the addition of sodium metal (0.15 g, 6.3 mmol, 10 eq.). The mixture was sonicated for 15 min. at room temperature before being cooled to -78 °C. The crude intermediate was co-evaporated thrice with toluene, dissolved in anhydrous THF (1 mL) and added dropwise to the Na-naphthalene solution. The reaction mixture was stirred for 1 hour at -78 °C. Upon full conversion on TLC (R_f 0.2 (EtOAc:pentane, 3:7, v:v)), the reaction was quenched with sat. aq. NH_4Cl at -78 °C. The mixture was diluted with sat. aq. $NaHCO_3$, the organic layer was separated, the aqueous layer was extracted thrice with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (30:70 EtOAc:pentane → 70:30 EtOAc:pentane) yielded **24** (0.34 g, 0.47 mmol, 74% over two steps). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.05 (m, 8H, CH_{arom}), 6.95 – 6.79 (m, 8H, CH_{arom}), 5.43 (d, *J* = 3.1 Hz, 1H, 7-NH), 5.00 (dd, *J* = 4.0, 4.0 Hz, 1H, H-1), 4.80 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.77 – 4.72 (m, 3H, C*H*H PMB, C*H*H PMB, CH*H* PMB), 4.65 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.43 – 4.35 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.13 (dd, *J* = 9.4, 3.7 Hz, 1H, H-2), 3.92 (dd, *J* = 2.2, 2.2 Hz, 1H, H-4), 3.84 (s, 3H, OMe), 3.83 – 3.82 (m, 10H, OMe, OMe, OMe, H-3), 3.65 (ddd, *J* = 10.5, 3.5, 3.5 Hz, 1H, H-7), 3.57 (dd, *J* = 9.0, 7.7 Hz, 1H, H-6), 3.46 (dd, *J* = 9.0, 6.5 Hz, 1H, H-6), 2.37 (dddd, *J* = 10.1, 7.9, 6.4, 2.0 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.6, 159.4, 159.4, 130.5, 130.4 ($C_{q\text{-}arom}$), 129.9, 129.8, 129.7, 129.7, 129.6, 129.3, 114.1, 114.0, 114.0, 113.8 (CH_{arom}), 83.1 (C-1), 80.1 (C-3), 74.7 (C-4), 74.5 (C-2), 74.5, 73.3, 73.2,

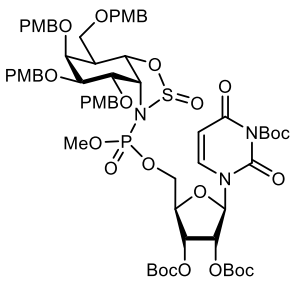
73.1 (CH_2 PMB), 70.0 (C-6), 58.6 (C-7), 55.4, 55.4 (OMe), 40.9 (C-5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{39}H_{45}NNaO_{11}S$ 758.2611; Found 758.2608.

4''-*Epi*-1'',7''-(*S*,*S*)-(*O*,*N*-(3-*N*-(*tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxy carbonyl)uridinyl))-sulfamidite-2'',3'',4'',6''-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (S2).



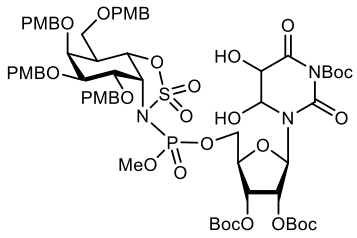
Compound **23** (70 mg, 0.1 mmol) was dissolved in EtOH (2.0 mL, 0.05 M) followed by the addition of aq. NaOH (3.0 M, 1.2 mL, 2.0 mmol, 20 eq.). The reaction mixture was heated to 80 °C and stirred for 2 hours after which full conversion was observed (R_f 0.3 (MeOH:DCM, 1:9, v:v)). The reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous $CHCl_3$ (2.0 mL, 0.05 M). The reaction mixture was cooled on ice followed by the addition of H-phosphonate **48** (93 mg, 0.15 mmol, 1.5 eq.), DiPEA (0.13 mL, 0.8 mmol, 8.0 eq.) and consequently $BrCCl_3$ (20 µL, 0.2 mmol, 2.0 eq.). Stirring continued for 15 minutes while kept on ice after which full conversion was observed (R_f 0.4 and 0.5 corresponding to both phosphor diastereomers (EtOAc:pentane, 8:2, v:v)). The reaction mixture was cooled to -40 °C followed by the addition of $SOCl_2$ (15 µL, 0.2 mmol, 2.0 eq.). Stirring continued overnight while allowing the mixture to attain to 5 °C. Upon full conversion was observed (R_f 0.3 (EtOAc:pentane, 1:1, v:v)), the reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (20:80 EtOAc:pentane → 50:50 EtOAc:pentane) yielded **S2** as a mixture of S(IV) and P(V) diastereomers (23 mg, 17 µmol, 17% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.64 (d, *J* = 8.3 Hz, 1H, H-6), 7.49 – 7.36 (m, 2H, H-6), 7.34 – 7.07 (m, 32H, CH_{arom}), 6.94 – 6.78 (m, 23H, CH_{arom}), 6.15 – 5.91 (m, 3H, H-5), 5.84 – 5.69 (m, 3H, H-1'), 5.29 – 5.08 (m, 7H, H-2', H-3'), 4.84 – 4.52 (m, 17H, H-3', CH_2 PMB, CH_2 PMB, CH_2 PMB), 4.43 – 4.10 (m, 16H, H-4', H-5', H-1'', H-2'', H-3'', H-4'', CH_2 PMB), 4.03 – 3.43 (m, 49H, H-6'', H-7'', OMe, OMe, OMe, OMe, P(O)OMe), 2.68 – 2.52 (m, 3H, H-5''), 1.65 – 1.52 (m, 27H, $C(CH_3)_3$), 1.54 – 1.40 (m, 56H, $C(CH_3)_3$, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$, HH-COSY, HSQC): δ 160.2, 160.2, 160.0 (C=O uracil), 159.5, 159.4, 159.3, 159.3, 159.2 ($C_{q\text{-}arom}$), 152.1, 152.0 (C=O cyclic carbamate), 148.6, 148.3, 147.6, 147.4 (C=O carbonate), 139.4, 139.3, 130.9, 130.8, 130.7, 130.7, 130.0, 130.0 ($C_{q\text{-}arom}$), 129.9, 129.9, 129.8, 129.7, 129.6, 129.2, 129.2, 113.9, 113.9, 113.9, 113.8 (CH_{arom}), 103.0, 102.8 (C-5), 89.0, 88.6, 88.3, 87.6 ($C(CH_3)_3$), 87.1, 87.1, 86.9, 86.4 (C-1'), 83.9, 83.8, 83.7, 83.6, 82.3, 82.2 ($C(CH_3)_3$), 80.6, 80.5, 80.2, 80.1, 79.9, 79.8, 77.5, 74.9, 74.8, 74.7, 74.6, 74.5, 74.1, 74.0, 73.8, 73.5, 73.3, 73.1, 73.1, 73.0, 72.6, 71.9, 71.5, 71.2 (C-1'', C-2', C-3', C-4', C-2'', C-3'', C-4'', CH_2 PMB, CH_2 PMB, CH_2 PMB CH_2 PMB), 66.6, 66.4, 66.1, 65.6 (C-5', C-6''), 59.4, 57.0, 55.4, 55.0, 54.9, 54.8, 54.7 (C-1'', OMe, OMe, OMe, OMe, P(O)OMe), 44.5, 43.8 (C-5''), 29.8, 28.7, 28.5, 27.7, 27.5 ($C(CH_3)_3$, $C(CH_3)_3$, $C(CH_3)_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ 2.17, 2.09, 1.87, 1.80; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{64}H_{82}N_3NaO_{24}S$ 1362.4644; Found 1362.4647.

4''-*Epi*-1'',7''-(*S*,*S*)-(*N*,*O*-(3-*N*-(*tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxy carbonyl)uridinyl))-sulfamidite-2'',3'',4'',6''-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (76).



Compound **21** (0.14 g, 0.2 mmol) was dissolved in EtOH (4.0 mL, 0.05 M) followed by the addition of aq. NaOH (3.0 M, 2.4 mL, 4.0 mmol, 20 eq.). The reaction mixture was heated to 80 °C and stirred for 2 hours after which full conversion was observed (R_f 0.3 (MeOH:DCM, 1:9, v:v)). The reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude intermediate was dissolved in anhydrous $CHCl_3$ (4.0 mL, 0.05 M). The reaction mixture was cooled on ice followed by the addition of H-phosphonate **48** (0.19 g, 0.3 mmol, 1.5 eq.), DiPEA (0.27 mL, 1.6 mmol, 8.0 eq.) and consequently $BrCCl_3$ (40 µL, 0.4 mmol, 2.0 eq.). Stirring continued for 15 minutes while kept on ice after which full conversion was observed (R_f 0.3 and 0.5 corresponding to both phosphor diastereomers of **74** (EtOAc:pentane, 8:2, v:v)). The reaction mixture was cooled to -40 °C followed by the addition of $SOCl_2$ (29 µL, 0.4 mmol, 2.0 eq.). Stirring continued overnight while allowing the mixture to attain to 5 °C. Upon full conversion was observed (R_f 0.3 (EtOAc:pentane, 1:1, v:v)), the reaction was diluted with EtOAc and washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (20:80 EtOAc:pentane → 50:50 EtOAc:pentane) yielded **76** as a mixture of P(V) diastereomers (99 mg, 74 µmol, 37% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.58 (d, *J* = 8.3 Hz, 1H, H-6), 7.52 (d, *J* = 8.3 Hz, 1H, H-6*), 7.22 – 7.03 (m, 8H, CH_{arom}), 6.90 – 6.75 (m, 9H, CH_{arom}), 6.08 (d, *J* = 5.1 Hz, 1H, H-5), 6.02 (d, *J* = 5.2 Hz, 1H, H-5*), 5.82 (m, 2H, H-1', H-1'*), 5.31 – 5.09 (m, 4H, H-2, H-3, H-2*, H-3*), 4.57 – 4.18 (m, 64H, H-4', H-5', H-7'', H-2'', H-3'', H-4'', H-4'*, H-5'*, H-7''*, H-2''*, H-3''*, H-4''*, CH_2 PMB, CH_2 PMB, CH_2 PMB, CH_2 PMB, CH_2 PMB*, CH_2 PMB*, CH_2 PMB*, CH_2 PMB*), 4.09 – 4.02 (m, 1H, H-1'', H-1''*), 3.88 – 3.68 (m, 32H, H-6'', H-6''*, OMe, OMe, OMe, OMe, P(O)Me, OMe*, OMe*, OMe*, OMe*, P(O)Me*), 3.66 – 3.59 (m, 2H, H-6'', H-6''*), 2.73 (m, 2H, H-5'', H-5''*), 1.62 – 1.56 (m, 18H, $C(CH_3)_3$, $C(CH_3)_3$*), 1.51 – 1.42 (m, 36H, $C(CH_3)_3$, $C(CH_3)_3$, $C(CH_3)_3$*, $C(CH_3)_3$*); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 160.2, 160.2 (C=O uracil), 159.4, 159.4, 159.3, 159.3, 159.3 ($C_{q\text{-}arom}$), 152.1, 152.0, 152.0, 151.9 (C=O cyclic carbamate), 148.5, 148.5, 147.6, 147.5 (C=O carbonate), 139.3, 138.9, 130.4, 130.3, 130.3, 130.2, 130.0, 130.0 ($C_{q\text{-}arom}$), 129.9, 129.9, 129.6, 129.6, 129.3, 129.2, 128.9, 128.7, 113.9, 113.8, 113.8 (CH_{arom}), 103.1, 103.0 (C-5, C-5*), 87.2, 86.9 ($C(CH_3)_3$), 86.9, 86.8 (C-1', C-1'*), 83.8, 83.8, 83.7, 83.6 ($C(CH_3)_3$), 79.8, 79.8, 79.7, 77.5, 75.9, 75.7, 75.2, 74.9, 74.7, 73.3, 72.9, 72.8, 72.7, 72.7, 72.5, 72.1, 71.7, 71.6, 71.5, 71.5 (C-2', C-3', C-4', C-7'', C-2'', C-3'', C-4'', CH_2 PMB, CH_2 PMB, CH_2 PMB CH_2 PMB), 67.1, 65.7, 65.6 (C-5', C-6''), 57.9, 57.9, 57.6, 55.4, 55.3, 54.8, 54.7, 54.6, 54.5 (C-1'', OMe, OMe, OMe, OMe, P(O)OMe) 39.7 (C-5''), 27.7, 27.5 ($C(CH_3)_3$, $C(CH_3)_3$, $C(CH_3)_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ 0.58, 0.51; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{64}H_{82}N_3NaO_{24}S$ 1362.4644; Found 1362.4649.

4''-E*pi*-1'',7''-(*O,N*-(3-*N*-(*tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxy carbonyl)-5,6-dihydroxydihydro-uridinyl))-sulfamidate-2'',3'',4'',6''-tetra-*O*-(4-methoxybenzyl) cyclophellitol alkane (77).



Compound **76** (40 mg, 30 µmol) was dissolved in a 1:1 mixture of EtOAc and acetonitrile (0.6 mL, 0.05 M) and cooled on ice. In a separate flask, $RuCl_3$ (2.0 mg, 7.5 µmol, 0.25 eq.) and $NaIO_4$ (16 mg, 75 µmol, 2.5 eq.) were dissolved in H_2O and subsequently added to the substrate solution. After stirring for 20 minutes, TLC indicated full conversion (R_f 0.2 (EtOAc:pentane, 1:1, v:v)) and the reaction was quenched with sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were subsequently washed with sat. aq. $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (30:70 EtOAc:pentane → 50:50 EtOAc:pentane) yielded **77** as a mixture of P(V) diastereomers (20 mg, 15 µmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.30 – 7.04 (m, 9H), 6.91 – 6.79 (m, 8H), 6.01 (d, *J* = 5.2 Hz, 1H), 5.48 – 5.20 (m, 2H), 4.96 (dd, *J* = 35.3, 5.2 Hz, 1H), 4.78 – 4.53 (m, 1H), 4.50 – 4.18 (m, 8H), 4.10 (dd, *J* = 6.2, 3.8 Hz, 1H), 4.05 – 3.86 (m, 3H), 3.84 – 3.74 (m, 12H), 3.72 – 3.52 (m, 2H), 3.37 (d, *J* = 5.8 Hz, 0H), 2.66 (d, *J* = 9.3 Hz, 1H), 1.59 – 1.51 (m, 7H), 1.51 – 1.38 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 167.9, 167.6, 159.5, 159.4, 159.3, 152.5, 152.2, 152.1, 149.6, 149.0, 147.4, 130.2, 129.6, 129.4, 129.0, 114.0, 113.9, 86.6, 86.4, 86.2, 83.6, 83.5, 81.7, 78.8, 76.8, 76.1, 75.6, 74.1, 73.8, 73.5, 73.2, 73.1, 72.9, 72.2, 72.0, 71.9, 71.5, 71.3, 69.5, 69.3, 68.0, 67.2, 66.3, 60.0, 59.8, 56.2, 56.1, 55.7, 55.4, 39.9, 39.8, 27.7, 27.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.82, -3.06, -3.98; HRMS (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{64}H_{84}N_3NaO_{27}PS$ 1412.4648; Found 1412.4652.

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