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

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Chapter 6

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

Introduction

Glycosyltransferases (GTs) catalyze the formation of glycosidic linkages by transferring a monosaccharide from an activated glycosyl donor to an acceptor substrate (Figure 1A).[1,2] GT acceptor substrates range from saccharides to lipids, proteins, DNA, and small molecules and GTs are therefore involved in the creation of a wide variety of complex carbohydrates, glycans, and glycoconjugates (*O*- and *N*-glycoproteins, glycolipids).[3,4] These biosynthetic products play pivotal roles in many biological processes, including cell growth and development, cell signaling, and host-pathogen interactions.[5,6] In addition, harmful pathogens manage to evade our immune system by decorating their exteriors through the action of GTs.[7,8] This, and deviations from normal glycosylation patterns commonly implicated in human disease, make GTs attractive medicinal targets in a vast variety of therapeutic areas, including, but not limited to, infection, inflammation, neuropathological disorders, and cancer.[9–11] Due to this significance, the development of GT inhibitors is a major area of interest within the fields of chemical biology and medicinal chemistry.

Universal glycoside donors utilized by GTs consist of a monosaccharide charged with an aglycon consisting of a mono- or diphosphate nucleotide, which make for a great leaving group during substitution (Figure 1B). Mammalian cells only use nine GT donor

substrates, one for each glycoside isostere incorporated by the mammalian biosynthesis machinery. Examples of mammalian donor substrates are α-UDP-Glu, β-CMP-Neu5NAc, β-GDP-Fuc and α-UDP-Gal.[12–14]

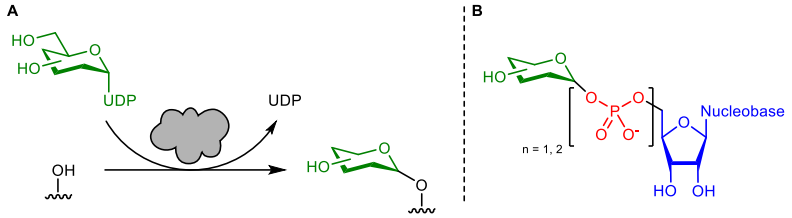


Figure 1. (A) Glycosyltransferases (GTs) catalyze glycosylation reactions with either inversion or retention of anomeric configuration of the glycosyl donor resulting in either α- or β-linkages. An α-linked UDP donor is exemplified here (B) Representation of generic glycosyltransferase donor substrate (In green = monosaccharide; in red = mono- or pyrophosphate; in blue = nucleotide).

GTs can be subdivided by the stereochemical outcome of the glycosyl transfer reaction, which can occur either with inversion or retention of the anomeric configuration with respect to the sugar donor.[15] Thus, GTs can be characterized as either inverting or retaining glycosyltransferases. These two classes of enzymes utilize different catalytic mechanisms giving rise to the different stereochemical outcomes.[1] Similar to inverting glycosidases, the itinerary of inverting GTs employ a single displacement pathway (S_N2) moving through a half-chair transition state carrying significant oxocarbenium ion character (Figure 2A). This reaction is facilitated by a carboxylate side chain in the active site (either Asp or Glu) which serves as a general base, deprotonating the hydroxyl of the acceptor substrate for direct nucleophilic displacement of the phosphate leaving group. In comparison to inverting GTs, retaining glycosyltransferases do not contain a correctly placed nucleophilic carboxylic acid residue to act as a nucleophile during catalysis.[16] Therefore, it is postulated that retaining GT's employ a front-side single displacement mechanism (Figure 2B). Here, the incoming acceptor attacks the anomeric center from the same face as the (pyro)phosphate aglycon departs (S_Ni-like). In addition, the (pyro)phosphate leaving group directly acts as an intermolecular base by deprotonating the incoming nucleophile. Also, these reactions proceed with significant oxocarbenium character. As a result, a net retention of the anomeric configuration is achieved. For this type of itinerary, the interactions between the aglycon and incoming acceptor by means of acid-base catalysis, forged by the enzymes' cavity, are crucial to facilitate this nucleophilic displacement.[17,18]

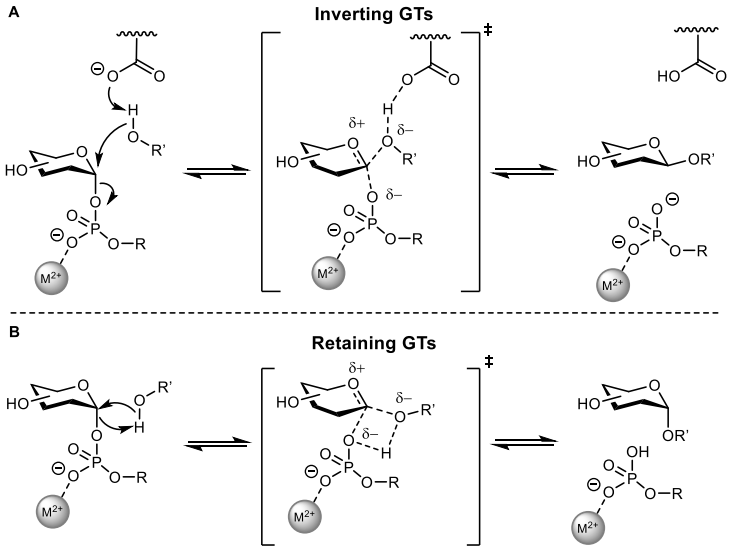


Figure 2. Proposed mechanisms for inverting and retaining metal ion-dependent glycosyltransferases. (A) Inverting GTs follow a single displacement pathway *via* an oxocarbenium ion-like transition state which leads to inversion of anomeric configuration. (B) Retaining GTs may follow a front-side single displacement (S_Ni-like) mechanism, in which the anomeric configuration of the donor substrate is retained.[1] Either phosphates of the pyrophosphate aglycon could act as an intermolecular base (here depicted with the β-phosphate).

Due to limited understanding of the reaction itineraries of glycosyltransferases, compared to that employed by glycosyl hydrolases, the rational design of GT inhibitors is complicated.[2] Design of inhibitors is further complicated by the enzymes' conformational plasticity, complex multicomponent transition states (carbohydrate donor, nucleotide, acceptor, (pyro)phosphate-chelating metal ion), weak natural substrate binding (usually in the mM range), and the limited availability of structural data.[19] Furthermore, and again in contrast to what is observed in the field of glycoside hydrolase inhibitor design (iminosugars, cyclophellitols), nature has yielded preciously little in terms of natural product GT inhibitor classes. Nevertheless, the past decades have seen some extensive systematic endeavors regarding the design and synthesis of suitable GT inhibitors.[20–24] The existing literature on the design of GT inhibitors particularly relies on donor substrate analogues, with a focus on the identification of modifications of the glycoside part of the donor.[20,25–27] These types of derivatives are highly attractive as their structural resemblance to regular sugars still allows for their recognition by biological systems while ensuring a higher stability towards endogenous carbohydrate-degrading enzymes.[28] In the context of GTs, this concept has translated into the development of a variety of carbohydrate mimetic-based GT inhibitors, mostly in the form of imino- and carbasugar nucleotide analogues.[29–31]

Due to the high degree of rotational freedom within the donor substrate, the binding mode in the enzymes' pocket diverge considerably.[32] In general, four distinct conformations have been observed, ranging from an extended, linear orientation to a "tucked under" orientation, each stabilized by different hydrogen interactions within the pocket. Adaptation of the correct conformation during binding appeared crucial for the enzymes' ability to accept donor mimetics.[32,33] For instance, during co-crystallization attempts with non-hydrolysable donor substrates as a mean to obtain insightful crystal structures.[33–36] Although the donor binding orientation of GTs is crucial for recognition, it has been ignored in contemporary studies aimed at the design of suitable inhibitors.[23,37–40] Strategically designing inhibitors to match the exact binding orientation within the binding pocket could, besides increase the binding affinity, increase the selectivity immensely, as GT's with different binding modes will show inferior binding.

The donor substrate binding orientation of several glucosyl- and galactosyl transferases have been identified. In several, the donor substrate (UDP-Glc and UDP-Gal, Figure 3A) adopts a "tucked under" conformation when bound to GTs.[32–36,41–43], Figure 3B depicts two crystal structures of UDP-Glc and UDP-Gal exhibiting this concaved orientation.

This chapter describes the design and synthesis of 8 putative GT inhibitors incorporating the above-described, distinct conformational characteristic of protein-bound donor substrates (**1** – **8**, Figure 3). In order to capitalize on the required conformational features, locking of the inhibitor molecules in the bioactive conformation was envisioned to be achieved through structure rigidification.[44,45] To this end, incorporation of a caged bicyclic scaffold, based on pyrophosphate mimetics developed by Montero *et al*.[46] and Grimes *et al*.[47] (Figure 3C), linked to a uridine monophosphate (UMP), positions the UMP below the glycoside. In this way, the concaved spatial arrangement of the GT-bound natural substrates could be mimicked.

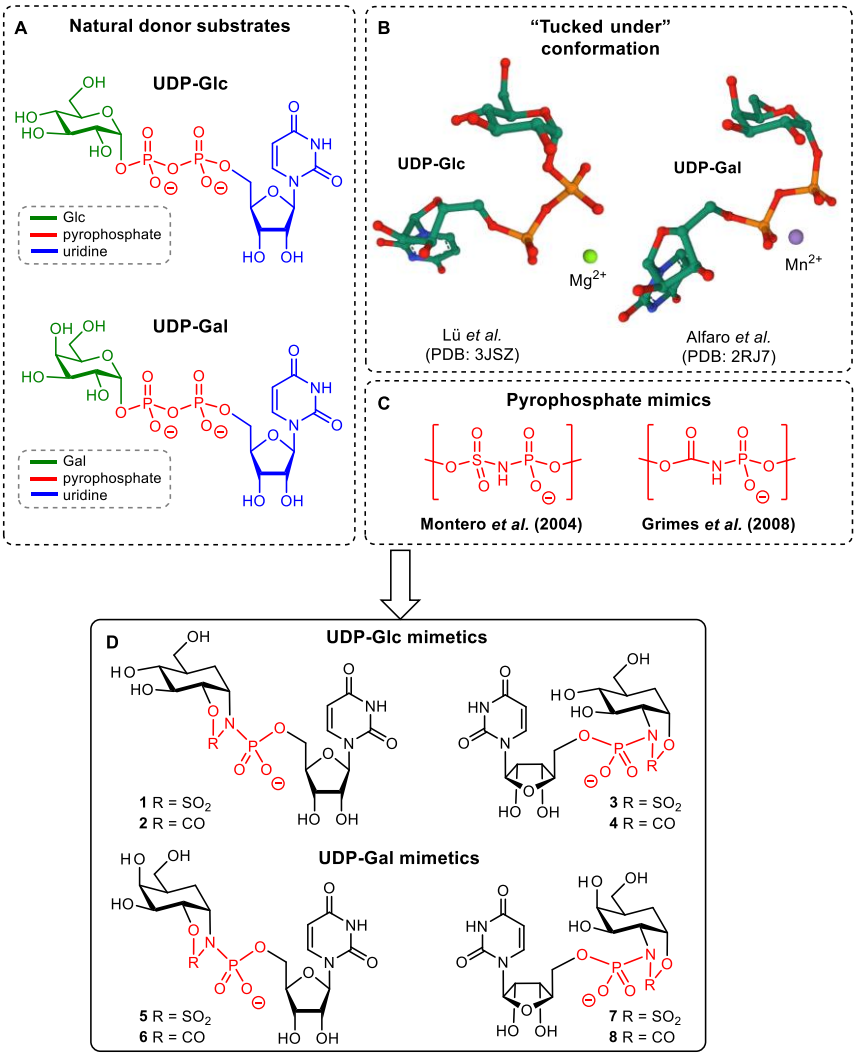


Figure 3. Overview of eight putative inhibitors proposed and synthesized in this chapter for UDP-glucosyl- and UDP galactosyl transferases, based on the binding orientation of their natural donor substrates. (A) UDP-Glc and UDP-Gal; the natural donor substrates (in green = monosaccharide; in red = pyrophosphate; in blue = nucleotide). (B) spatial orientation of UDP-Glc (left) and UDP-Gal (right), The former upon binding to glucosyltransferase Lgt1, one of three glucosylating toxins of *Legionella pneumophila*[43] and the latter upon binding to GTB/G176R, a human blood group A and B galactosyltransferase.[42] (C) *N*-sulfamidate- and *N*-carbamate phosphoramidate based pyrophosphate mimetics developed by Montero *et al*.[46] and Grimes *et al*.[47] (D) The four glucose configured and four galactose configured putative inhibitors, mimicking the tucked under donor substrate and envisioned to act on the corresponding GT's. In red the pyrophosphate mimicking entities.

From a synthetic point of view, compounds **9** – **12**, previously synthesized in chapter 3, were considered as suitable fragments ready to undergo coupling to a uridine phosphate fragment leading to the glucose configured targets (Figure 4A). In turn, the galactose configured targets were envisioned to be obtained after C-4 inversion of a carba-glucose intermediate. Although formation of the nitrogen-phosphorous linkage was considered to be a challenging transformation due to the electron depleted nature of the endocyclic nitrogen and the anticipated lability of the product, literature provides a vast array of coupling conditions (Figure 4B). Oxidative cross-coupling conditions have recently become attractive in phosphoramidate synthesis because of the mild, one-pot procedures which do not require pre-activation of a suitably protected H-phosphonate diester fragment (Figure 4B).[48–51] Alternatively, the Atherton-Todd reaction employs pre-activation of a H-phosphonate fragment *via* chlorination or bromination to allow for a subsequent nucleophilic substitution by a primary or secondary amine or amide (Figure 4B).[52–58]

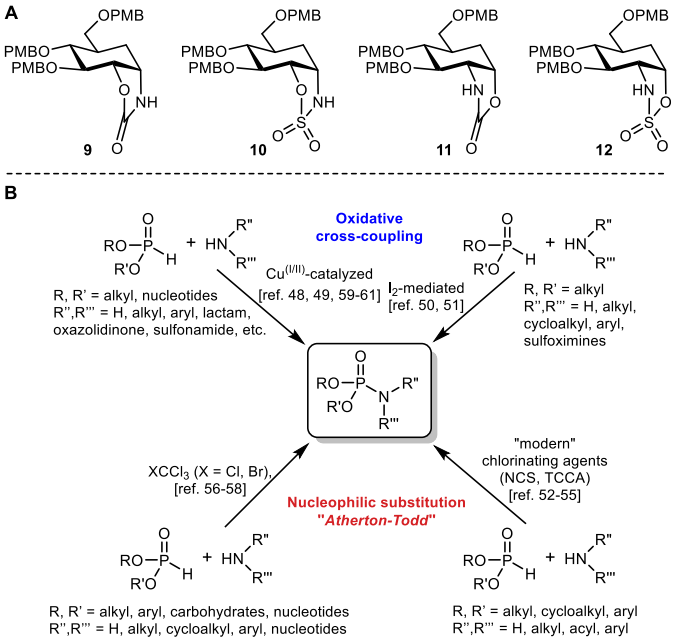
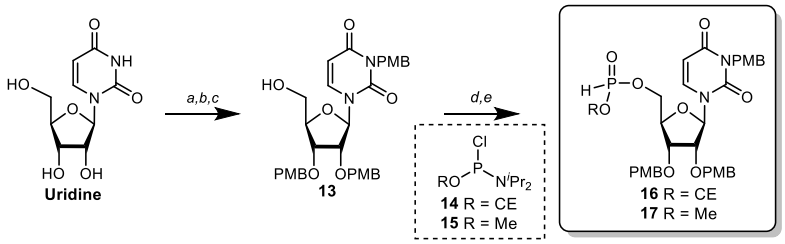


Figure 4. Formation of *N-P* linkages, envisioned to be the key transformation. (A) Four carba-glucose configured constructs previously described in chapter 3, considered to be suitable amide coupling fragments (B) Overview of most promising methods for synthesizing phosphoramidates, divided into oxidative cross-coupling reactions[48–51,59–61] (red) and Atherton-Todd type reactions[52–58] (blue).

Results and discussion

A suitably protected uridine H-phosphonate diester was advanced from commercially available uridine as follows (Scheme 1). The primary hydroxyl was regioselectively protected as a silyl ether (TBDPSCl, DMAP) allowing for a subsequent protection of the ribosyl 2'- and 3'-OH and the uracil amide with a PMB group. The PMB-protecting groups were selected to allow for a single, global deprotection step after coupling to the per-*O*-(4-methoxybenzyl)-protected carbamates and sulfamidates. Consecutive treatment with TBAF yielded intermediate **13** in 32% yield over three steps. The choice of phosphonate protecting group was anticipated to be crucial for the success of the subsequent *N*-*P* coupling and deprotection. To this end, two protecting group strategies were selected to broaden the range of compatible reaction conditions. In a two-step one-pot procedure, and depending on the commercially available phosphoramidite of choice, either the 2-cyanoethyl- or methyl- protected phosphodiesters were obtained in good to excellent yield (64% and 92%, for **16** and **17** respectively).

Scheme 1. Synthesis of PMB protected uridine H-phosphonate diester building blocks **16** and **17**.

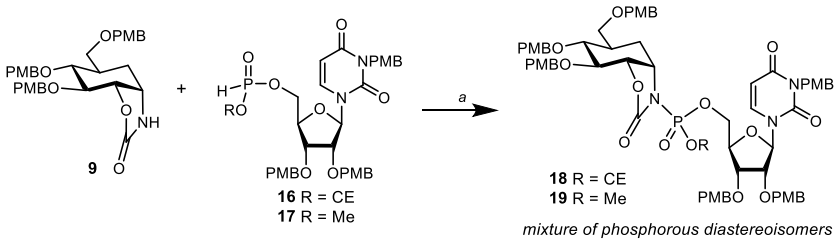


Reagents and conditions: a) TBDPSCl, DMAP, pyridine, rt, O/N; *b*) PMBCl, NaH, TBAI, DMF, 0 °C → rt, 2 days; *c*) TBAF, THF, rt, 2 h (32% over three steps); *d*) 2-cyanoethyl *N,N*-diisopropyl chlorophosphoramidite (**14**) or methyl *N,N*-diisopropyl chlorophosphoramidite (**15**), DiPEA, DCM, 0 °C, 15-30 min; *e*) ETT, H_2O, MeCN, rt, 15-30 min, 64% (**16**), 92% (**17**).

With both the H-phosphonate diester building blocks **16** and **17**, and the protected carbamates and sulfamidates in hand, *N*-*P* coupling conditions were investigated next. Preliminary coupling attempts between cyclic carbamate **9** and H-phosphonate diester **16** employing a myriad of oxidative cross-coupling reaction, either mediated by copper salts[49,59–61] or iodine[50,51], resulted in degradation of the H-phosphonate rather than product formation. No product formation was observed for H-phosphonate diester **17** when treated with identical conditions. Then attention was turned to the more classical approach to synthesize phosphoramidates by means of an Atherton-Todd reaction. Following procedures of Lowary and co-workers formation of the *N*-*P* bond was attempted *via* bromination of the H-phosphonate diester ($BrCCl_3$, DiPEA) followed by a nucleophilic substitution by carbamate **9** (Scheme 2).[58] Bromination of H-phosphonate

diester **16** indeed resulted in clean conversion into the bromophosphate intermediate according to ^{31}P NMR (two bromophosphate signals at δ = −7.05 and −7.08 ppm corresponding to P(V) diastereomers). Combining the bromophosphate with a solution of activated cyclic carbamate (KHMDS, THF) did not result in formation of the product **18**. Instead, degradation was observed, probably because of the lability of the cyanoethyl group towards the alkaline reaction conditions. However, switching to the base stable methyl-protected H-phosphonate diester **17** did result in product formation, as compound **19** was isolated as a mixture of phosphorous diastereomers in a yield of 72%. Structural elucidation *via* ^{13}C NMR confirmed product **19** indeed to be the *N*-phosphorylated product (see Appendix, Scheme S1).

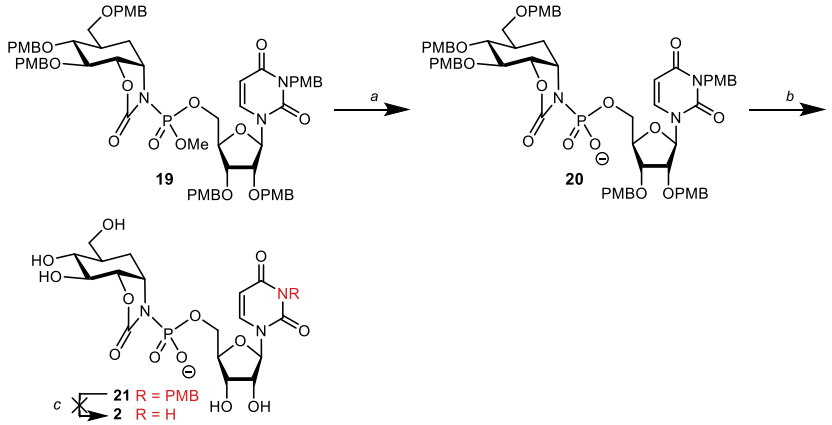
Scheme 2. Coupling attempts of PMB protected cyclic carbamate **9** and H-phosphonate diester fragments **16** or **17** employing a modified version of the Atherton-Todd reaction.



Reagents and conditions: *a*) *i.* **16** or **17**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min; *ii.* **9**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; *then* added activated **16** or **17**, 0 °C, 2 h, 72% (**19**).

With a viable synthetic approach towards compound **19**, its global deprotection was studied next. Prior to acid catalyzed removal of the PMB ether, removal of the methyl phosphate protecting group was investigated. To this end, compound **19** was subjected to a mild nucleophile (PhSH, Et_3N, MeCN, 35 °C), which resulted in clean conversion to compound **20** as judged from the observed upfield shift in ^{31}P NMR as well as disappearance of diastereomeric signals (Scheme 3).[62] Unfortunately, due to the intrinsic stability of the uracil *N*-PMB group, as a result of the electron depleted nature induced by the two adjacent electron withdrawing carbonyl functionalities, removal of this protecting group under acidic conditions proved to be difficult and compound **21** was isolated instead.

Scheme 3. Demethylation of PMB protected *N*-phosphoramidate **19** followed by attempted global PMB-deprotection.



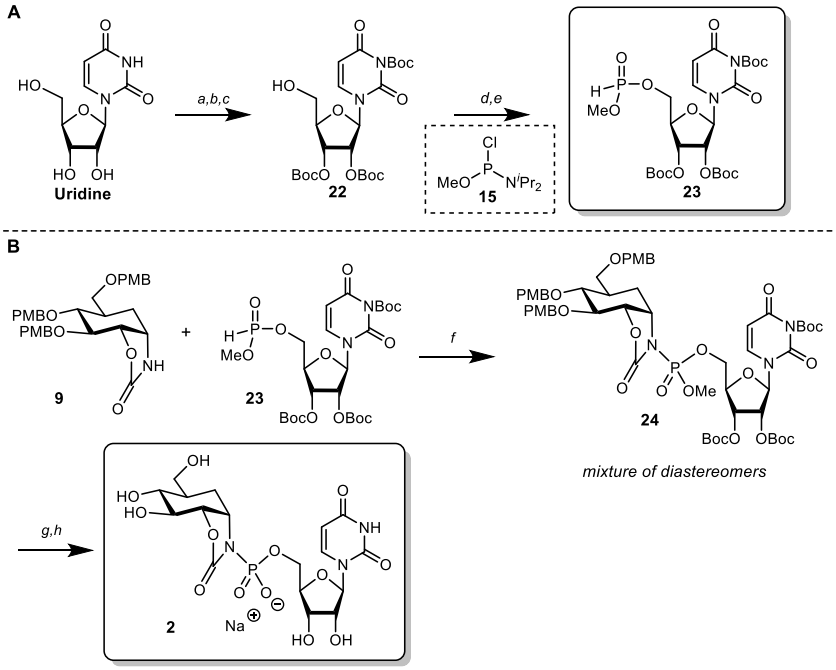
Reagents and conditions: *a*) PhSH:Et_3N:MeCN (1:2:2 v:v), 35 °C, 1 h (77%); *b*) TFA, TES, DCM, 0 °C, 16 h; *c*) Appendix Table S1.

Compound **21** was subjected to a myriad of deprotection conditions (acid, oxidative, reductive, Appendix Table S1) to obtain the target compound **2**, but none proved to be fruitful.

Prompted by the robustness of the phosphoramidate formation and its stability against acid conditions, it was hypothesized that the problematic uracil deprotection could be circumvented by the use of a different acid labile protecting group. To this end, focus was shifted to use of *tert*-butoxy carbonyl (Boc) protecting groups, since it was hypothesized the Boc protecting groups could be easily removed under the acidic conditions (20% TFA v:v) used for the PMB ether deprotection. In addition, the rate and stability of the Boc group during deprotection does not depend on the electronegativity of the adjacent heteroatom and should therefore result in clean conversion to the target compound.

Thus, commercially available uridine was protected at the 5'-OH as a TBDPS ether and subsequently, the 2'- and 3'-OH and uracil amide were protected with Boc groups (Boc_2O, DMAP, Scheme 4A). Lastly, the TBDPS ether was hydrolyzed under *aegis* of TBAF to yield compound **22** in an excellent yield of 92% over three steps. Again, in a two-step one-pot procedure, the commercially available phosphoramidite **15** was coupled to **22** and hydrolyzed affording the methyl protected H-phosphonate diester **23** in good yield (82% over two steps).

Scheme 4. Synthesis of Boc protected H-phosphonate diester **23** (A) and consequent synthesis of *N*-UMP-carba-1'',2''-(*N*,*O*)-carbamate **2** (B).

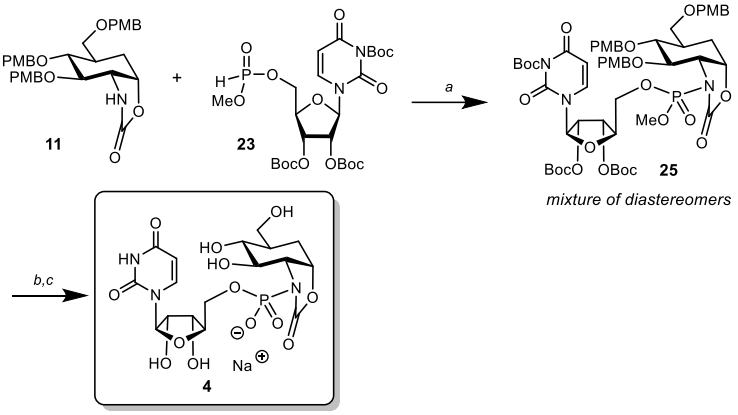


Reagents and conditions: a) TBDPSCl, DMAP, pyridine, rt, O/N; *b*) Boc_2O, Et_3N, DMAP, DCM, 0 °C → rt, 4 h; *c*) TBAF, THF, rt, O/N (92% over three steps); *d*) methyl *N*,*N*-diisopropyl chlorophosphoramidite (**15**), DiPEA, DCM, 0 °C, 15 min; *e*) ETT, H_2O, MeCN, rt, 15 min (82% over two steps); *f*) *i.* **23**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min; *ii.* **9**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; *then* added activated **23**, 0 °C, 2 h (68%); *g*) 30% TFA/DCM (v:v), TES, 5 °C, 24 h; *h*) pyridine, 5 °C, 30 min., (72%).

Treatment of **23** with bromination conditions resulted in clean conversion to the bromophosphate intermediate according to ^{31}P NMR (Scheme 4B) and its subsequent addition to activated carbamate **9** (NaH, THF) led to clean formation of compound **24**, which could be isolated as a mixture of phosphorous diastereomers in good yield (68%). Removal of the PMB and Boc groups commenced by treating **24** with a solution of 30% TFA in DCM (v:v) and triethyl silane as cation scavenger. Full removal of all acid labile protecting groups was observed after 16 hours. Interestingly, quenching of the reaction with pyridine directly resulted in demethylation of the phosphoramidate methyl ester to provide the final compound **2**, as indicated by ^{31}P NMR. In this transformation pyridine acts as a mild nucleophile removing the methyl ester to yield the *N*-methyl pyridinium salt of **2**. After Dowex Na^+ ion exchange and lyophilization the *N*-UMP-carba-1'',2''-(*N*,*O*)-carbamate target **2** was successfully obtained as a Na^+ salt in good yield (72% over two steps).

After successfully obtaining of the *N*-UMP-carbaglucose-1'',2''-(*N*,*O*)-carbamate **2**, attention was turned to the 1'',2''-(*O*,*N*)-carbamate **4** to test the robustness of the novel three step sequence methodology (Scheme 5). Using the Atherton-Todd coupling conditions, compound **11** could be efficiently *N*-phosphorylated to give compound **25** in excellent yield, again as a mixture of phosphorous diastereomers (97%). Following the optimized two-step one-pot procedure, *i.e.* acid hydrolysis followed by demethylation under *aegis* of pyridine, neatly provided the target structure. Dowex Na^+ ion exchange and lyophilization led to the *N*-UMP-carbaglucose-1'',2''-(*O*,*N*)-carbamate target **4** as its Na^+ salt in 32% yield over two steps.

Scheme 5. Synthesis of *N*-UMP-carba-1'',2''-(*O*,*N*)-carbamate **4**.

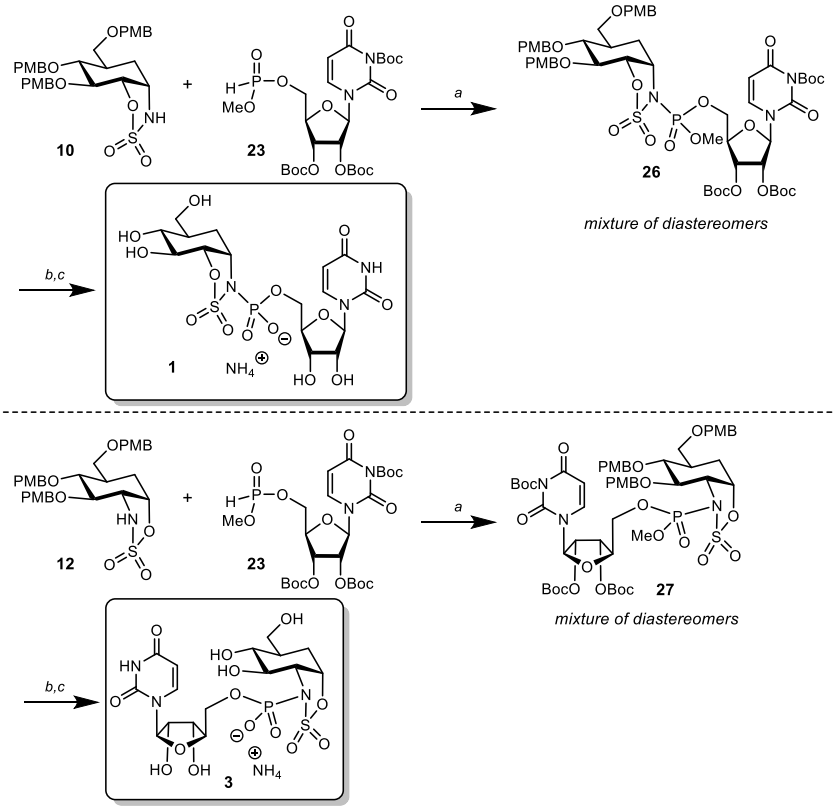


Reagents and conditions: *a*) *i.* **23**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min; *ii.* **11**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; *then* added activated **23**, 0 °C, 2 h (97%); *b*) 30% TFA/DCM (v:v), TES, 5 °C, 24 h; *c*) pyridine, 0 °C, 30 min, (32%).

To further capitalize on the newly developed methodology, the scope was expanded towards the 1,2-cyclic sulfamidates **10** and **12** (scheme 6). Thus, treating cyclic sulfamidates **10** and **12** with H-phosphonate diester **23** under the standardized Atherton-Todd conditions yielded *N*-sulfonylphosphoramidates **26** and **27** as a mixture of phosphorous diastereomers in 53% and 77% yield for **26** and **27**, respectively. Global acidic deprotection of **26** and **27** using TFA/TES proceeded smoothly, after which the reaction mixture was neutralized with pyridine. Gratifyingly, ^{31}P NMR analysis revealed clean demethylation of the methyl ester, virtually without any trace of phosphorus-based by-products. However, upon conversion of the pyridinium salt into its Na^+ congener using Dowex Na^+ ion exchange, rapid degradation of the product was observed. The *N*-sulfonylphosphoramidates, **1** and **3**, were hypothesized to be relatively base labile and susceptible to hydrolysis under the slightly alkaline nature of the Dowex resin. By switching to a NH_4^+ counter ion the degradation could be circumvented. Thus, Dowex NH_4^+ ion exchange resin, prepared by treating Dowex resin with an aqueous 0.5

M NH_4OAc solution, followed by lyophilization yielded the target compounds **1** and **3**, as their NH_4^+ salt in good yield over two steps (77% and 74%, for **1** and **3** respectively).

Scheme 6. Synthesis of *N*-UMP-carba-1'',2''-sulfamidates **1** and **3**.



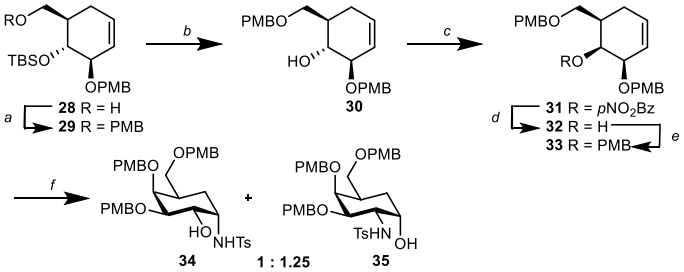
Reagents and conditions: a) *i.* **23**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min, *ii.* cyclic sulfamidate **10** or **12**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; then added activated **23**, 2 h, 0 °C, **26** (53%), **27** (77%); *b*) 30% TFA/DCM (v:v), TES-H, 0 °C, 3 h; *c*) *i.* pyridine, 0 °C → rt, 16 h; *ii.* Dowex NH_4^+ cation exchange, **1** (77% over two steps), **3** (74% over two steps).

With robust synthetic methodologies towards glucose configured carbamate-*N*-phosphoramidates and sulfamidate-*N*-phosphoramidates, attention was shifted towards the galactose configured carbasugars. To this end, compound **28**, previously synthesized in chapter 2, was considered as a suitable starting point (Scheme 7). as the orthogonality between the protecting groups in **28** should allow for the regioselective manipulation of the C-4 substituent and provide access to its *galacto*-configured counterpart.

First the primary alcohol in compound **28** was protected as a PMB ether (Scheme 7). However, standard Williamson etherification conditions (PMBCl, NaH) led to partial

cleavage of the TBS ether.[63] Acid catalyzed PMB installation (PMB-2,2,2-trichloroacetimidate, *p*-TsOH) did prove successful and yielded compound **29** in a 57% yield. Regioselective deprotection of the 4-OH proceeded smoothly under *aegis* of TBAF to yield compound **30** in 67% yield. Initially, the C-4 inversion was investigated using an oxidation-reduction strategy. Thus, the 4-OH was oxidized to the corresponding ketone and consecutive reduction using $NaBH_4$, as described by Wei *et al*., provided the C-4-alcohol as an inseparable epimeric mixture in a 4:1 ratio between D-galactal and D-glucal configuration.[64] To prevent the formation of a diastereoisomeric mixture, Mitsunobu inversion conditions (4-nitrobenzoic acid, DEAD, TPP) were employed next on alcohol **30**, yielding D-galactal configured compound **31** in quantitative yield. Transesterification of the 4-nitrobenzoate (NaOMe, MeOH) followed by protection of the 4-OH as a PMB ether under standard Williamson etherification conditions then yielded intermediate **33** in 89% yield.[63]

Scheme 7. Synthesis of galactose configured α-*cis*-amino alcohols **34** and **35**.



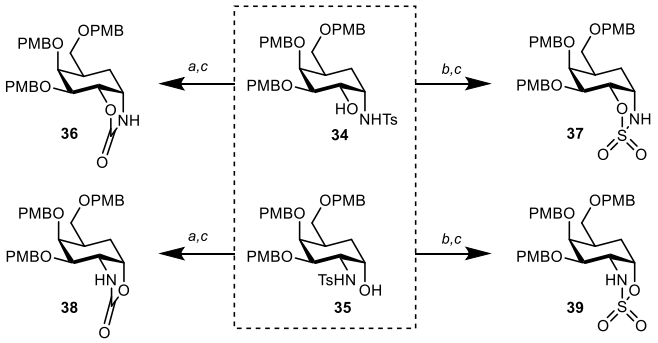
Reagents and conditions: a) PMB imidate, PPTS, DCM, rt, 16 h (57%); *b)* TBAF, THF, rt, 1 h (67%); *c)* PPh_3, *p*-nitrobenzoic acid, DEAD, THF, 60 °C, 4.5 h (*quant*.); *d)* NaOMe, DCM:MeOH (1:1 v:v), rt, 16 h (67%); *e)* PMBCl, NaH, DMF, rt, 16 h (89%); *f)* CAT·$3H_2O$, $K_2[OsO_2(OH)_4]$, TEBACl, $CHCl_3$:H_2O (1:1 v:v), 60 °C, 16 h (91%).

Next, a Sharpless amino hydroxylation stereospecifically provided the desired amino alcohols **34** and **35** in a regioisomeric ratio of 1:1.25 respectively, with an overall yield of 91%. The relative stereochemistry, *trans* with respect to the other ring substituents was anticipated based on results described in chapter 3.

With both *N*-tosylated *cis*-amino alcohols **34** and **35** in hand, the corresponding cyclic carbamates and sulfamidates **36** – **39** were prepared next (Scheme 8). Employing the methodologies described in chapter 3, both amino alcohols could be transformed in two-step procedures into their corresponding cyclic carbamates **36** and **38** and sulfamidates **37** and **39**. Treatment of **34** or **35** with triphosgene and subsequent reductive detosylation using a sodium naphthalenide solution, yielded cyclic carbamates **36** and **38** in 78% and 49% yield, respectively.[65] Alternatively, Treatment of **34** and **35** with sulfuryl chloride at -78 °C and subsequent reductive detosylation in a sodium

naphthalenide solution, yielded cyclic sulfamidates **37** and **39** in 34% and 55% yield, respectively.

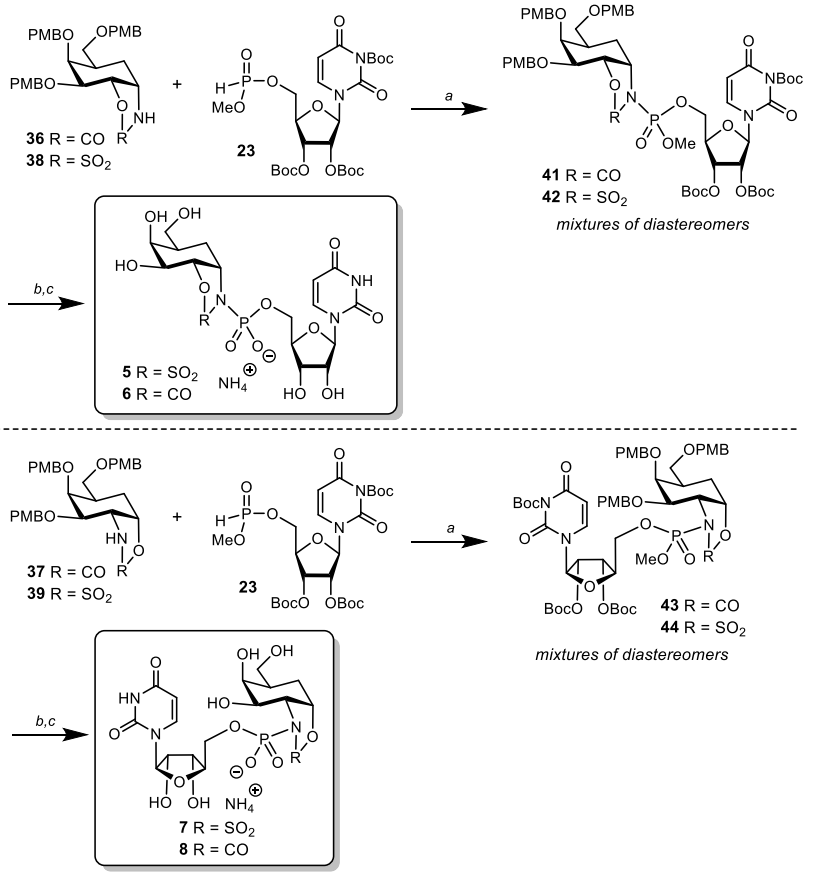
Scheme 8. Divergent synthesis towards cyclic carbamates **36** and **38** and cyclic sulfamidates **37** and **39**.



Reagents and conditions: a) triphosgene, pyridine, DCM, rt, 2 h; *b)* SO_2Cl_2, Et_3N, DCM, -78 °C → 5 °C, 2 h; *c)* naphthalene, Na, THF, -78 °C, 1 h, **36** (78%), **37** (34%), **38** (49%) and **39** (55%).

With all four coupling fragments **36** – **39** in hand, attempts were made to couple the galactose carbasugars to H-phosphonate diester **23** using the established Atherton-Todd conditions (Scheme 9). After formation of the bromophosphate, it was added to the anion of the carbamate or sulfamidate, generated using NaH in combination with 15-crown-5, to result in clean *N*-phosphorylation. The coupled products **41** – **44** were isolated as mixtures of phosphor-diastereomers in 54%, 27%, 42% and 33% yield, for **41**, **42**, **43** and **44**, respectively. All that remained now, was removal of the protecting groups in a two-step one-pot deprotection. To this end, compounds **41** – **44** were treated with a 30% TFA solution in DCM v:v with triethylsilane as a cation scavenger, which resulted in clean removal of all PMB and Boc protection groups according to ^{31}P NMR. Subsequent addition of pyridine freed the methylated P^V-phosphoramidate diesters giving rise to the four target structures, which after Dowex NH_4^+ ion exchange yielded the corresponding ammonium salts **5** – **8** in 55%, 30%, 22% and 54% yield over two steps respectively.

Scheme 9. Galactose configured target structures **5** – **8**, assembled *via N*-phosphorylation and subsequent global deprotection.



Reagents and conditions: a) i. **23**, $BrCCl_3$, DiPEA, DCM, 0 °C, 30 min, *ii.* cyclic sulfamidate or carbamates **36**, **37**, **38** or **39**, NaH, 15-crown-5, THF, 0 °C → rt, 30 min; then added activated **23**, 2 h, 0 °C, **41** (54%), **42** (27%), **43** (42%), **44** (33%); *b)* TES, TFA, DCM, 0 °C, 16 h; *c) i*. pyridine, 0 °C → rt, 16 h; *ii.* Dowex NH_4^+ cation exchange, **5** (55%), **6** (30%), **7** (22%) and **8** (54%).

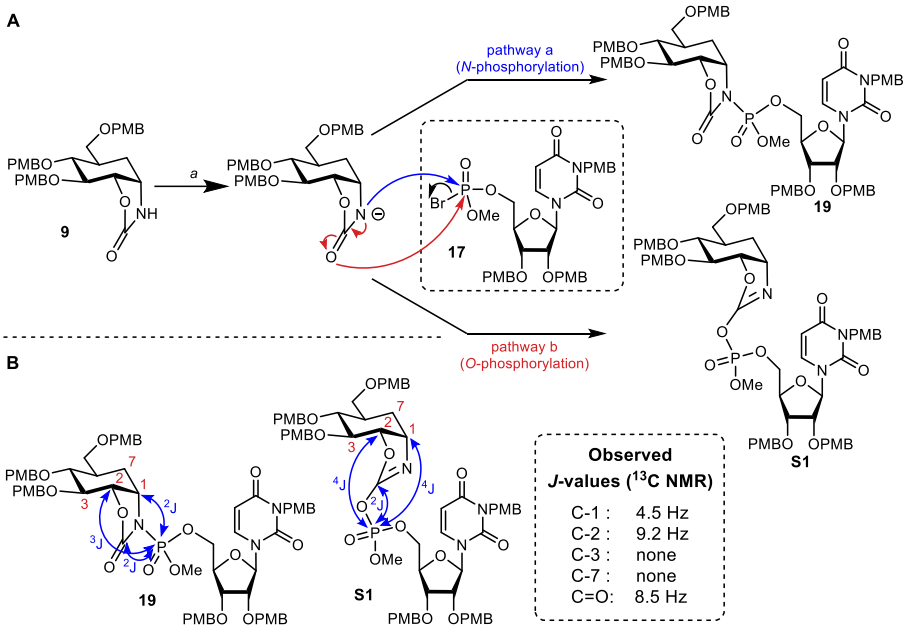
Conclusion

In conclusion, this chapter reports on the synthesis of UDP-glucose and UDP-galactose configured mimetics of high structural complexity as putative GT inhibitors. The design of these structures was based on crystallographic data, suggesting donor substrates to adopt a concaved kinked orientation upon forming a Michaelis complex with the enzyme. It was hypothesized that, by means of rigidification, the proposed structures could closely resemble the natural donor conformation in the Michaelis complexes, and therefore could act as strong enzyme binders. To this end, novel and robust methodology has been developed that allows for a divergent and efficient synthesis of targets **1** – **8**. Amongst the key transformations are the Atherton-Todd *N*-phosphorylation, providing a robust and efficient coupling between the cyclic carbamate or sulfamidate with a suitably protected H-phosphonate diester. In an efficient two-step one-pot deprotection method, the structures were successfully deprotected and isolated. The synthetic methodology described here can serve as a blueprint for future syntheses of complex phosphorylated structures. In addition, the described putative GT inhibitors can, upon screening for their inhibitory potencies in suitably designed assays, form a solid base to uncover potent and selective GT inhibitors.

Acknowledgements

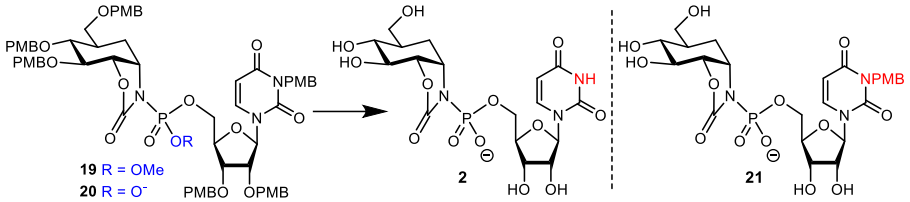
Roy Steneker and Duncan de Graaf are kindly acknowledged for their synthesis work in the context of their MSc internships. Pascal Balić is acknowledged for our insightful discussions in relation to the phosphorus chemistries.

Appendix



Scheme S4. (A) Two possible pathways under Atherton-Todd conditions, resulting either in *N*-phosphorylation or *O*-phosphorylation of cyclic carbamate **9**. (B) Structural proof the reaction merely occurs *via N*-phosphorylation (pathway I) to give desired phosphoramidate **19**, according to (^{31}P,^{13}C) *J*-values observed in the ^{13}C NMR spectrum of the isolated product.

Table S1. Attempted global deprotection of PMB protected compound **19** and **20**.



R-group	Conditions	Observations
R = Me	Pd/C, H_2, MeOH, rt, O/N	Reaction halted at compound **21** according to TLC-MS analysis
R = Me	DDQ (2.0 eq.), H_2O:DCM (1:2 v/v), 0 °C, 2 h	Degradation of starting material
R = H	HCl/HFIP (10 eq.), TES-H, DCM/HFIP (1:1 v/v), 0 °C, 30 h	Reaction halted at compound **21** according to TLC-MS analysis
R = H	20% TFA/DCM (v/v), TES-H, 0 °C, 3 h	Reaction halted at compound **21** according to TLC-MS analysis
R = H	MSA (10 eq.), TES-H, DCM, 0 °C, 1 h	Degradation of starting material
R = H	CAN (4.0 eq.), H_2O/MeCN (1:1 v/v), 3 days, 5 °C; then 65 °C, 3 h	Degradation of starting material

Synthetic procedures.

General procedure A: One-pot two-step H-phosphonate diester synthesis from protected uridine building blocks

The H-phosphonate diesters were prepared according to a modified literature procedure.[66] The protected uridine substrate was co-evaporated 3x with dry $CHCl_3$ or DCM under N_2 atmosphere and dissolved in anhydrous DCM (0.1-0.2 M). Anhydrous diisopropylethylamine (DiPEA; 2.5 eq.) was added and the solution was cooled on ice before the addition of the *N,N*-diisopropylchlorophosphoramidite (95%, 1.2 eq.). The reaction mixture was stirred for 15-30 min on ice, and after full conversion was confirmed by both TLC and ^{31}P NMR analysis (acetone-d_6 probe; $\delta \approx 150$ ppm), the mixture was concentrated to dryness under a N_2 atmosphere. The resulting crude product was redissolved in MeCN (0.05-0.1 M), after which demineralized H_2O (30 eq.) and 5-(ethylthio)-1*H*-tetrazole (ETT activator, 0.25 M in MeCN; 1.5-3.0 eq.) were added. The reaction mixture was stirred at room temperature for 15-30 minutes. After full conversion was confirmed by both TLC and ^{31}P NMR analysis (acetone-d_6 probe; ^1H gated decoupled: $\delta \approx$ 10-13 ppm; ^1H coupled: $\delta \approx$ 8-20 ppm and $^1J_{P,H} \approx$ 700-725 Hz), the reaction was quenched by the addition of a sat. aq. $NaHCO_3$ solution. The mixture was extracted with EtOAc (3x), after which the combined organic layers were washed once with a 1.0 M aq. HCl solution, once with sat. aq. $NaHCO_3$, and once with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography of the crude material (SiO_2, EtOAc in pentane) yielded the H-phosphonate diester as a mixture of P(V) diastereomers.

General procedure B: Carbamylation and *N*-detosylation of *N*-Ts protected 1,2-*cis* amino-alcohols

The *N*-tosyl protected cyclic carbamates were prepared according to a modified literature procedure.[67] 1,2-*cis* amino-alcohol was co-evaporated with toluene, dissolved in anhydrous DCM (0.10 M) and cooled on ice. Pyridine (4.5 eq.) and triphosgene (0.60 eq.) were added and the ice bath was removed after 10 min. The reaction mixture was stirred for 2 h at room temperature. Upon full conversion on TLC, the reaction was quenched 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*. Subsequently, a second flask was prepared with a glass stirring bar, in which naphthalene (12 eq.) was dissolved in anhydrous THF (0.05 M). Na (10 eq.) was added to this solution. This mixture was sonicated for 15 min. at room temperature and stirred at room temperature, before being cooled to -78°C. The crude intermediate was co-evaporated thrice with toluene, dissolved in anhydrous THF and added dropwise to the Na-naphthalenide solution. The reaction mixture was stirred for 0.5-1 h at -78°C. Upon full conversion on TLC, 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 (SiO_2, EtOAc in pentane) yielded the products.

General procedure C: Sulfamidation and *N*-detosylation of *N*-Ts protected 1,2-*cis* amino-alcohols

The *N*-tosyl protected cyclic sulfamidates were prepared according to a modified literature procedure.[68] 1,2-*cis* amino-alcohol substrate was co-evaporated with toluene and dissolved in anhydrous DCM (0.10 M). Et_3N (4.0 eq.) was added and the reaction mixture was cooled to -78°C. SO_2Cl_2 (1.3 eq.) was added dropwise. The reaction mixture was stirred for 2 h while allowing the reaction mixture to warm up from -78 °C to 0 °C. Upon full conversion on TLC, the reaction was quenched 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* at room temperature. Subsequently, a second flask was prepared with a glass stirring bar, in which naphthalene (12 eq.) was dissolved in anhydrous THF (0.05 M). Na (10 eq.) was added to this solution. This mixture was sonicated for 15 min. at room temperature and stirred at room temperature, before being cooled to -78°C. The crude intermediate was co-evaporated thrice with toluene, dissolved in anhydrous THF and added dropwise to the Na-naphthalene solution. The reaction mixture was stirred for 0.5-1 h at -78°C. Upon full conversion on TLC, 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 (SiO_2, EtOAc in pentane) yielded the products.

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

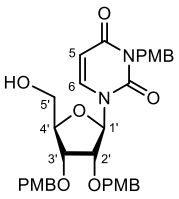
Per-*O*-(4-methoxybenzyl) cyclic carbamate or sulfamidate was co-evaporated with anhydrous $CHCl_3$ and added to an oven-dried round-bottom flask. The flask was connected to a Schlenk line and subjected to three vacuum-N_2 backfill cycles before dissolving in anhydrous THF (0.2-0.3 M). The solution was 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 diester (2.0 eq.) and also put under a N_2 atmosphere using Schlenk setup before 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 bromophosphonate 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 bromophosphonate 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 E: 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 *N*-UMP-carba-1'',2''-cyclic carbamates or sulfamidate target compounds as their NH_4^+ or Na^+ salts.

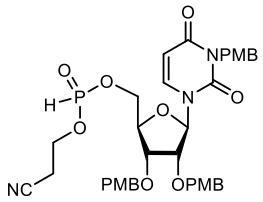
3-*N*-(4-Methoxybenzyl)-2',3'-di-*O*-(4-methoxybenzyl)uridine (13).



Uridine (3.66 gr, 15 mmol) was dissolved in pyridine (18 mL, 0.8 M). 4-Dimethylaminopyridine (DMAP; 183 mg, 1.5 mmol, 0.1 eq.) and *tert*-butyldiphenylchlorosilane (TBDPSCl; 4.3 mL, 16.6 mmol, 1.1 eq.) were added and the reaction mixture was stirred overnight under N_2 atmosphere according to literature procedure.[69] Upon full conversion (R_f 0.65 (MeOH:DCM, 1:9 v:v)), the reaction was quenched by the addition of MeOH, diluted with sat. aq. $NaHCO_3$ and brine and extracted with DCM (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product (colorless oil) was co-evaporated twice with toluene, dissolved in DMF (50 mL, 0.3 M) and cooled on ice. PMBCl (17 mL, 128 mmol, 8.5 eq.) was added followed by the addition of NaH (60 wt% dispersion in mineral oil; 5.1 gr, 128 mmol, 8.5 eq.) and TBAI (2.8 gr, 7.6 mmol, 0.5 eq.) while stirring on ice. The reaction mixture was slowly warmed to room temperature and stirred for 42 h. Upon full conversion (R_f 0.5 (EtOAc:pentane, 3:7 v:v)), the reaction mixture was carefully quenched using a sat. aq. $NaHCO_3$ solution while stirring on ice. The reaction mixture was extracted with EtOAc (3x), after which the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (dark-brown oil) was dissolved in THF (80 mL), TBAF (1.0 M in THF; 20 mL, 20 mmol, 1.35 eq.) was added and the reaction mixture was stirred for 2 h. After full conversion was observed (R_f 0.15 (EtOAc:pentane, 1:1 v:v)), the mixture was diluted with sat. aq. $NaHCO_3$ solution and extracted with EtOAc (3x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography of the crude material (SiO_2, 50:50 EtOAc:pentane → 100:0 EtOAc:pentane)

followed by recrystallization from EtOAc/pentane yielded title compound **13** as a yellow solid (2.9 gr, 4.8 mmol, 32% over three steps). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.49 – 7.45 (m, 2H, CH_{arom}), 7.42 (d, *J* = 8.1 Hz, 1H, H-6), 7.22 – 7.17 (m, 4H, CH_{arom}), 6.89 – 6.81 (m, 4H, CH_{arom}), 6.78 – 6.73 (m, 2H, CH_{arom}), 5.71 (d, *J* = 3.8 Hz, 1H, H-1'), 5.65 (d, *J* = 8.1 Hz, 1H, H-5), 5.04 (d, *J* = 13.6 Hz, 1H, NC*H*H PMB), 4.95 (d, *J* = 13.6 Hz, 1H, NCH*H* PMB), 4.71 (d, *J* = 12.0 Hz, 1H, C*H*H PMB), 4.57 (d, *J* = 12.0 Hz, 1H, CH*H* PMB), 4.50 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.34 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.24 – 4.17 (m, 2H, H-2', H-4'), 4.01 (dd, *J* = 5.5, 5.5 Hz, 1H, H-3'), 3.93 (ddd, *J* = 12.6, 2.6, 2.6 Hz, 1H, H-5'), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.67 (ddd, *J* = 12.3, 7.1, 2.2 Hz, 1H, H-5'), 2.50 (dd, *J* = 6.9, 3.6 Hz, 1H, 5'-OH); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 162.6 (C=O uracil), 159.7, 159.6, 159.3 ($C_{q\text{-}arom}$), 150.8 (C=O uracil), 139.5 (C-6), 131.1, 130.3 (CH_{arom}), 129.7 ($C_{q\text{-}arom}$), 129.6 (CH_{arom}), 129.4, 129.1 ($C_{q\text{-}arom}$), 114.0, 113.9, 113.8 (CH_{arom}), 102.0 (C-5), 92.4 (C-1'), 83.4 (C-4'), 77.7 (C-2'), 74.6 (C-3'), 72.2, 71.8 (CH_2 PMB), 61.6 (C-5'), 55.4, 55.4 (OMe), 43.6 (NCH_2 PMB). ^{1}H and ^{13}C NMR are consistent with literature data.[70] HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{33}H_{36}N_2O_9Na$ 627.2319, found 627.2313.

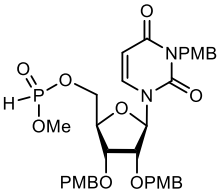
3-*N*-(4-Methoxybenzyl)-2',3'-di-*O*-(4-methoxybenzyl)uridine 2-cyanoethyl H-phosphonate (16).



Compound **16** was prepared according to **general procedure A** using **13** (1.2 gr, 1.9 mmol), 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite **14** (95%, 0.55 mL, 2.3 mmol, 1.2 eq.) and dry DiPEA (0.4 mL, 2.3 mmol, 1.2 eq.) in anhydrous DCM (20 mL, 0.1 M) in step 1; and ETT activator (0.25 M in MeCN; 23.2 mL, 5.8 mmol, 3.0 eq.), demineralized H_2O (1.1 mL, 61 mmol, 32 eq.) in MeCN (9.0 mL, 0.06 M) in step 2. Flash column chromatography of the crude product (SiO_2; 50:50 EtOAc:pentane → 80:20 EtOAc:pentane) yielded title compound **16** as a yellow oil (887 mg, 1.23 mmol, 64% over two steps). R_f 0.4 (EtOAc); The NMR data showed the presence of two P(V) diastereomers in a 1:1 ratio. Data for diastereomeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.74 (d, $^{1}J_{H,P}$ = 722.3 Hz, 1H, PH), 7.76 – 7.43 (m, 4H, CH_{arom}, CH_{arom}*), 7.31 (d, *J* = 8.2 Hz, 1H, H-6), 7.30 (d, *J* = 8.1 Hz, 1H, H-6*), 7.26 – 7.15 (m, 8H, CH_{arom}, CH_{arom}*), 6.90 – 6.82 (m, 8H, CH_{arom}, CH_{arom}*), 6.80 – 6.75 (m, 4H, CH_{arom}, CH_{arom}*), 5.92 (d, $^{1}J_{H,P}$ = 720.3 Hz, 1H, PH*), 5.92 (m, 1H, H-1'), 5.89 (d, *J* = 2.1 Hz, 1H, H-1'*), 5.71 (d, *J* = 8.1 Hz, 1H, H-5), 5.71 (d, *J* = 8.1 Hz, 1H, H-5*), 5.12 – 4.99 (m, 4H, NC*H*H PMB, NCH*H* PMB, NC*H*H PMB*, NCH*H* PMB*), 4.78 – 4.63 (m, 4H, C*H*H PMB, CH*H* PMB, C*H*H PMB*, CH*H* PMB*), 4.45 – 4.16 (m, 14H, H-4', H-4'*, H-5', H-5'*, C*H*H PMB, CH*H* PMB, C*H*H PMB*, CH*H* PMB*, CH_2CH_2CN, CH_2CH_2CN*), 3.98 – 3.93 (m, 2H, H-2', H-2'*), 3.85 (dd, *J* = 8.0, 5.3 Hz, 1H, H-3'), 3.81 – 3.77 (m, 19H, H-3'*, OMe, OMe, OMe, OMe*, OMe*, OMe*), 2.72 (t, *J* = 6.2 Hz, 2H, CH_2CH_2CN), 2.68 (t, *J* = 6.1 Hz, 2H, CH_2CH_2CN*); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 162.5, 162.5 (C=O uracil, C=O uracil*), 159.7, 159.7, 159.7, 159.3 ($C_{q\text{-}arom}$, $C_{q\text{-}arom}$*), 150.7, 150.7 (C=O uracil, C=O uracil*), 137.6 (C-6), 137.3 (C-6*), 131.0, 131.0, 130.5, 130.5, 129.7, 129.7 (CH_{arom}, CH_{arom}*), 129.2, 129.1, 129.1, 129.0 ($C_{q\text{-}arom}$, $C_{q\text{-}arom}$*), 114.1, 114.0, 113.8 (CH_{arom}, CH_{arom}*), 102.2 (C-5), 102.2 (C-5*), 90.8 (C-1'*) 90.5 (C-1'), 80.1 (d, $^{3}J_{C,P}$ = 6.6 Hz, C-4'), 80.0 (d, $^{3}J_{C,P}$ = 6.4 Hz, C-4'*), 77.5 (C-2'), 77.4 (C-2'*), 74.2 (C-3'), 74.2 (C-3'*), 72.1, 72.1, 71.6, 71.5 (CH_2 PMB, CH_2 PMB*), 64.4 (d, $^{2}J_{C,P}$ = 6.0 Hz, C-5'), 64.3 (d, $^{2}J_{C,P}$ = 5.9 Hz, C-5'*), 60.3 (d, $^{3}J_{C,P}$ = 5.3 Hz, CH_2CH_2CN), 60.2 (d, $^{3}J_{C,P}$ = 5.5 Hz, CH_2CH_2CN), 55.5, 55.4, 55.4 (OMe, OMe*), 43.7, 43.7 (NCH_2 PMB, NCH_2 PMB*), 20.1 (d, $^{2}J_{C,P}$ = 6.2 Hz, CH_2CH_2CN), 20.1 (d, $^{2}J_{C,P}$

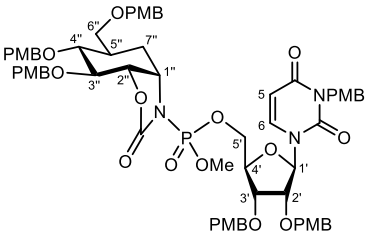
= 6.5 Hz, *C*H_2CH_2CN); ^{31}P NMR (162 MHz, $CDCl_3$, ^1H coupled): δ 9.31 ($^1J_{P,H}$ = 721.8 Hz; $^3J_{P,H}$ = 8.8 Hz), 8.69 ($^1J_{P,H}$ = 722.6 Hz; $^3J_{P,H}$ = 8.5 Hz); HRMS (ESI) m/z: [M+Na^+] calcd for $C_{36}H_{40}N_3O_{11}PNa$ 744.2298, found 744.2293.

3-*N*-(4-Methoxybenzyl)-2',3'-di-*O*-(4-methoxybenzyl)uridine methyl H-phosphonate (17).



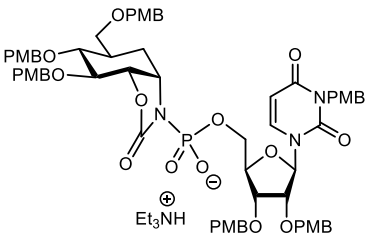
Compound **17** was prepared according to general procedure A, using **13** (4.6 gr, 7.6 mmol), *N,N*-diisopropylmethylphosphonamidic chloride **15** (95%, 1.9 mL, 9.3 mmol) and dry DiPEA (3.3 mL, 18.9 mmol, 2.5 eq.) in anhydrous DCM (40 mL, 0.2 M) in step 1; and ETT activator (0.25 M in MeCN; 92 mL, 23 mmol, 3.0 eq.), demineralized H_2O (4.1 mL, 230 mmol, 30 eq.) in MeCN (35 mL, 0.06 M) in step 2. Purification of the crude product by flash column chromatography (SiO_2; 60:40 EtOAc:pentane → 90:10 EtOAc:pentane) obtained title compound **17** as a colorless oil (4.8 gr, 7.0 mmol, 92% over two steps). R_f 0.35 (EtOAc); The NMR data showed the presence of two P(V) diastereomers in a 1:1 ratio. Data for diastereomeric mixture: ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.65 (d, $^1J_{H,P}$ = 706.6 Hz, 1H, PH), 7.55 – 7.44 (m, 4H, CH_{arom}, CH_{arom}*), 7.41 (d, *J* = 8.2 Hz, 1H, H-6), 7.41 (d, *J* = 8.2 Hz, 1H, H-6*), 7.26 – 7.23 (m, 4H, CH_{arom}, CH_{arom}*), 7.20 – 7.12 (m, 4H, CH_{arom}, CH_{arom}*), 6.90 – 6.80 (m, 8H, CH_{arom}, CH_{arom}*), 6.80 – 6.74 (m, 4H, CH_{arom}, CH_{arom}*), 5.96 (d, *J* = 2.0 Hz, 1H, H-1'), 5.93 (d, *J* = 2.0 Hz, 1H, H-1'*), 5.83 (d, $^1J_{H,P}$ = 708.2 Hz, 1H, PH*), 5.68 (d, *J* = 8.2 Hz, 1H, H-5), 5.68 (d, *J* = 8.1 Hz, 1H, H-5*), 5.12 – 4.99 (m, 4H, NC*H* PMB, NCH*H* PMB, NC*H*H PMB*, NCH*H* PMB*), 4.78 – 4.67 (m, 4H, C*H*H PMB, C*H*H PMB*, CH*H* PMB, CH*H* PMB*), 4.42 – 4.28 (m, 6H, H-4', H-4'*, H-5', H-5'*, C*H*H PMB, C*H*H PMB*), 4.26 – 4.16 (m, 4H, H-5', H-5'*, CH*H* PMB, CH*H* PMB*), 3.94 – 3.89 (m, 2H, H-2', H-2'*), 3.84 (dd, *J* = 7.9, 5.1 Hz, 1H, H-3'), 3.79 – 3.78 (m, 13H, H-3'*, OMe, OMe, OMe*, OMe*), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe*), 3.74 (d, $^3J_{H,P}$ = 12.0 Hz, 3H, P(O)OMe), 3.72 (d, $^3J_{H,P}$ = 11.9 Hz, 3H, P(O)OMe*); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 162.5, 162.5 (C=O uracil, C=O uracil*), 159.7, 159.7, 159.6, 159.3 ($C_{q\text{-}arom}$, $C_{q\text{-}arom}$*), 150.7, 150.7 (C=O uracil, C=O uracil*), 137.4 (C-6), 137.2 (C-6*), 131.0, 131.0, 130.5, 129.6, 129.6 (CH_{arom}, CH_{arom}*), 129.2, 129.1, 129.1, 129.1 ($C_{q\text{-}arom}$, $C_{q\text{-}arom}$*), 114.0, 113.9, 113.8 (CH_{arom}, CH_{arom}*), 102.0, 102.0 (C-5, C-5*), 90.2 (C-1'*), 90.0 (C-1'), 80.2 (d, $^3J_{C,P}$ = 6.2 Hz, C-4'), 80.2 (d, $^3J_{C,P}$ = 6.6 Hz, C-4'*), 77.5, 77.5 (C-2', C-2'*), 74.1 (C-3'), 74.0 (C-3'*), 72.2, 72.1, 71.4, 71.3 (CH_2 PMB, CH_2 PMB*), 63.8 (d, $^2J_{C,P}$ = 6.2 Hz, C-5'), 63.6 (d, $^2J_{C,P}$ = 6.2 Hz, C-5'*), 55.4, 55.4, 55.4 (OMe PMB, OMe PMB*), 52.4, 52.4 (P(O)OMe, P(O)OMe*), 43.6, 43.6 (NCH_2 PMB, NCH_2 PMB*); ^{31}P NMR (162 MHz, $CDCl_3$, ^1H coupled): δ 10.56 ($^1J_{P,H}$ = 707.1 Hz), 10.06 ($^1J_{P,H}$ = 705.6 Hz); HRMS (ESI) m/z: [M+Na^+] calcd for $C_{34}H_{39}N_2O_{11}PNa$ 705.2189, found 705.2184.

1'',2''-(*N*-(3-*N*-(4-Methoxybenzyl)-5'-*O*-methylphosphinyl-2',3'-di-*O*-(4-methoxybenzyl)uridinyl),*O*)-carbamate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucopyranoside (19).



Compound **19** was prepared according to general procedure D using cyclic carbamate **9** (294 mg, 0.52 mmol), 15-crown-5 ether (0.52 mL, 2.6 mmol, 5.0 eq.) and NaH (60 wt% dispersion in mineral oil; 31.2 mg, 0.78 mmol, 1.5 eq.) in anhydrous THF (2.6 mL, 0.2 M); and H-phosphonate **17** (705 mg, 1.03 mmol, 2.0 eq.), dry DiPEA (0.54 mL, 3.1 mmol, 6.0 eq.) and $BrCCl_3$ (0.2 mL, 2.0 mmol, 3.9 eq.) in anhydrous DCM (3.4 mL, 0.3 M). Purification of the crude product by flash column chromatography (SiO_2; 50:50 EtOAc:pentane → 90:10 EtOAc:pentane) yielded title compound **19** as a yellow oil and a mixture of P(V) diastereomers (465 mg, 0.37 mmol, 72%). Data for first P(V) diastereomer: R_f 0.55 and 0.7 (EtOAc:pentane, 9:1 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.50 (d, *J* = 8.1 Hz, 1H, H-6), 7.51 – 7.48 (m, 2H, CH_{arom}), 7.24 – 7.10 (m, 10H, CH_{arom}), 6.88 – 6.77 (m, 10H, CH_{arom}), 6.73 – 6.68 (m, 2H, CH_{arom}), 6.05 (d, *J* = 2.8 Hz, 1H, H-1'), 5.68 (d, *J* = 8.1 Hz, 1H, H-5), 5.09 – 5.01 (m, 2H, NC*H*H PMB, NCH*H* PMB), 4.68 – 4.65 (m, 3H, H-2'', C*H*H PMB, CH*H* PMB), 4.62 – 4.52 (m, 3H, C*H*H PMB, CH*H* PMB, C*H*H PMB), 4.49 – 4.41 (m, 1H, H-1''), 4.40 (ddd, *J* = 11.6, 4.4, 2.2 Hz, 1H, H-5'), 4.34 – 4.19 (m, 6H, H-5', CH*H* PMB, C*H*H PMB, CH*H* PMB, C*H*H PMB, CH*H* PMB), 4.20 – 4.13 (m, 1H, H-4'), 3.95 (dd, *J* = 7.1, 5.0 Hz, 1H, H-3'), 3.86 (dd, *J* = 5.1, 2.8 Hz, 1H, H-2'), 3.82 – 3.73 (m, 22H, H-3'', OMe, OMe, OMe, OMe, OMe, OMe, P(O)OMe), 3.45 (dd, *J* = 7.7, 6.2 Hz, 1H, H-4''), 3.33 (dd, *J* = 8.9, 3.5 Hz, 1H, H-6''), 3.29 (dd, *J* = 8.9, 4.8 Hz, 1H, H-6''), 2.13 (ddd, *J* = 13.6, 5.0, 5.0 Hz, 1H, H-7''), 1.97 – 1.85 (m, 2H, H-5, H-7''); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 162.6 (C=O uracil), 159.6, 159.6, 159.4, 159.4, 159.3, 159.2 ($C_{q\text{-}arom}$), 155.0 (d, $J_{C,P}$ = 8.5 Hz, C=O carbamate), 150.9 (C=O uracil), 137.5 (C-6), 131.0, 130.4 (CH_{arom}), 130.3, 130.3 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.8, 129.7 ($C_{q\text{-}arom}$), 129.6, 129.5, 129.4 (CH_{arom}), 129.3, 129.3 ($C_{q\text{-}arom}$), 114.0, 113.9, 113.9, 113.9, 113.8, 113.8 (CH_{arom}), 102.0 (C-5), 88.9 (C-1'), 80.3 (d, $^3J_{C,P}$ = 9.1 Hz, C-4'), 78.7 (C-3''), 78.5 (d, $^3J_{C,P}$ = 9.2 Hz, C-2''), 78.1 (C-2'), 76.1 (C-4''), 74.6 (C-3'), 73.0, 73.0, 73.0, 72.2, 71.3 (CH_2 PMB), 71.0 (C-6''), 65.7 (d, $^2J_{C,P}$ = 5.3 Hz, C-5'), 55.4 (d, $^2J_{C,P}$ = 4.5 Hz, C-1''), 55.4 (OMe), 54.7 (d, $^2J_{C,P}$ = 5.7 Hz, P(O)OMe), 43.6 (NCH_2 PMB), 36.9 (C-5''), 28.0 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ –1.60; HRMS (ESI) m/z: [M+Na^+] calcd for $C_{66}H_{74}N_3O_{19}PNa$ 1266.4552, found 1266.4546.

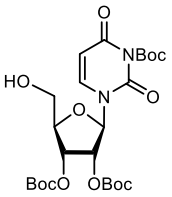
1'',2''-(*N*-(3-*N*-(4-Methoxybenzyl)-5'-*O*-phosphoryl-2',3'-di-*O*-(4-methoxybenzyl)uridinyl),*O*)-carbamate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucopyranoside (20).



Compound **19** (79 mg, 64 μmol) was dissolved in a mixture of PhSH:Et_3N:MeCN (1:2:2 v:v, 0.6 mL, 0.1 M) and the reaction mixture was stirred at 35 °C according to a literature procedure.[62] After 1 h, ^{31}P NMR analysis (acetone-d_6 probe) indicated full demethylation of the starting material. The mixture was diluted with water, extracted with EtOAc (3x), after which the combined organic layers were washed with brine, dried over

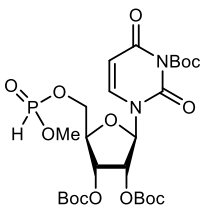
Na_2SO_4, filtered, and concentrated *in vacuo*. Flash column chromatography of (SiO_2, 0→10% MeOH/DCM) yielded title compound **20** as a colorless oil (61 mg, 49 μmol, 77%). Unfortunately, due to the amphiphilic nature of the demethylated compound, no interpretable ^1H or ^{13}C NMR spectra could be obtained. R_f 0.6 (MeOH:DCM, 1:9 v:v); ^{31}P NMR (121 MHz, acetone-d_6 probe): δ –7.68; HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{65}H_{72}N_3O_{19}PNa$ 1252.4395, found 1252.4390.

3-*N*-(*Tert*-butoxycarbonyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridine (22).



To a stirred solution of uridine (4.9 g, 20 mmol) in pyridine (25 mL, 0.8 M) were added DMAP (0.25 g, 2.0 mmol, 0.1 eq.) and TBDPSCl (6.3 mL, 24 mmol, 1.2 eq.). The reaction mixture was stirred overnight under N_2 atmosphere according to a literature procedure.[69] Upon full conversion was observed (R_f 0.65 (MeOH:DCM, 1:9 v:v)), the reaction was quenched by the addition of MeOH, diluted with sat. aq. $NaHCO_3$ and brine and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product (colorless oil) was co-evaporated twice with toluene and dissolved in DCM (100 mL, 0.2 M). Et_3N (17 mL, 120 mmol, 6.0 eq.) and DMAP (0.74 g, 6.0 mmol, 0.3 eq.) were added and the mixture was cooled on ice. Boc_2O (26.5 g, 120 mmol, 6.0 eq.) was added and the ice bath was removed after 5 minutes, after which the resulting reaction mixture was stirred at room temperature for 4 h. Upon full conversion was observed (R_f 0.8 (EtOAc:pentane, 1:1 v:v)), the reaction was concentrated to dryness. The crude product (yellow oily liquid) was dissolved in THF (75 mL), TBAF (1.0 M in THF; 80 mL, 80 mmol, 4.0 eq.) was added and the solution was stirred overnight. Upon full conversion (R_f 0.15 (EtOAc:pentane, 3:7 v:v), the reaction mixture was diluted with sat. aq. $NaHCO_3$ and brine and extracted with EtOAc (3x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography of the crude product (SiO_2, 30:70 EtOAc:pentane → 60:40 EtOAc:pentane) yielded title compound **22** as a white brittle foam (10.1 g, 18.6 mmol, 92% over three steps). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.60 (d, *J* = 8.2 Hz, 1H, H-6), 5.91 (d, *J* = 5.7 Hz, 1H, H-1'), 5.78 (d, *J* = 8.2 Hz, 1H, H-5), 5.41 (dd, *J* = 5.5, 5.5 Hz, 1H, H-2'), 5.34 (dd, *J* = 5.4, 3.9 Hz, 1H, H-3'), 4.28 (ddd, *J* = 4.1, 2.2, 2.2 Hz, 1H, H-4'), 3.97 (dd, *J* = 12.2, 2.1 Hz, 1H, H-5'), 3.84 (d, *J* = 12.3 Hz, 1H, H-5'), 2.52 (bs, 1H, OH-5'), 1.60 (s, 9H, $C(CH_3)_3$), 1.49 (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), 152.5 (C=O carbamate), 152.1 (C=O uracil), 148.6, 147.5 (C=O carbonate), 140.6 (C-6), 102.9 (C-5), 89.5 (C-1'), 87.2, 83.8, 83.6 ($C(CH_3)_3$), 82.9 (C-4'), 75.0 (C-2'), 72.9 (C-3'), 61.9 (C-5'), 27.8, 27.8, 27.6 ($C(CH_3)_3$). HRMS (ESI) m/z: [M+Na]$^+$ Calcd. for $C_{24}H_{36}N_2NaO_{12}$ 567.2160; Found 567.2156.

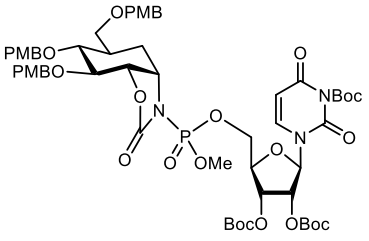
3-*N*-(*Tert*-butoxycarbonyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridine methyl H-phosphonate (23).



Compound **23** was prepared according to general procedure A using **22** (7.1 g, 13 mmol), *N,N*-diisopropylmethylphosphonamidic chloride **15** (95%, 3.2 mL, 15.7 mmol, 1.2 eq.) and dry DiPEA (5.6 mL, 32 mmol, 2.5 eq.) in anhydrous DCM (65 mL, 0.2 M) in step 1; and ETT activator (0.25 M in MeCN; 78 mL, 19.5 mmol, 1.5 eq.), demineralized H_2O (7.0 mL, 390 mol, 30 eq.) in MeCN (52 mL, 0.1 M) in step 2. Flash column chromatography of the crude product (SiO_2, 50:50 EtOAc:pentane →

100:0 EtOAc:pentane) yielded title compound **23** as a white brittle foam (6.6 g, 10.6 mmol, 82% over two steps). R_f 0.35 (EtOAc:pentane, 8:2 v:v); The NMR data showed the presence of two P(V) diastereomers in a 1:1 ratio. Data for diastereomeric mixture: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.60 (d, $^1J_{H,P}$ = 710.6 Hz, 1H, PH), 7.47 (d, *J* = 5.9 Hz, 1H, H-6), 7.45 (d, *J* = 5.9 Hz, 1H, H-6*), 6.90 (d, *J* = 713.2 Hz, 1H, PH), 6.89 (d, *J* = 709.5 Hz, 1H, PH*), 5.99 (s, 1H, H-1'), 5.93 (d, *J* = 4.5 Hz, 1H, H-1'*), 5.82 (d, *J* = 8.1 Hz, 1H, H-5), 5.79 (d, *J* = 8.2 Hz, 1H, H-5*), 5.37 – 5.14 (m, 4H, H-2', H-2'*, H-3', H-3'*), 4.49 – 4.17 (m, 6H, H-4', H-4'*, H-5', H-5'*), 3.84 (d, *J* = 12.0 Hz, 3H, P(O)OMe), 3.81 (d, *J* = 12.0 Hz, 3H, P(O)OMe*), 1.60 (s, 18H, $C(CH_3)_3$, $C(CH_3)_3$*), 1.50 (s, 18H, $C(CH_3)_3$, $C(CH_3)_3$*), 1.48 (s, 18H, $C(CH_3)_3$, $C(CH_3)_3$*); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.2, 160.2 (C=O uracil, C=O uracil*), 152.2 (C=O carbamate/ C=O carbamate*), 152.2 (C=O uracil/ C=O uracil*), 152.1 (C=O carbamate/C=O carbamate*), 152.1 (C=O uracil/C=O uracil*), 148.4, 148.4 (C=O carbonate/C=O carbonate*), 147.4, 147.4 (C=O carbonate/C=O carbonate*), 139.8, 139.4 (C-6, C-6*), 103.0 (C-5, C-5*), 89.0, 88.4 (C-1', C-1'*), 87.1 ($C(CH_3)_3$, $C(CH_3)_3$*), 84.0, 84.0, 83.9, 83.9 ($C(CH_3)_3$, $C(CH_3)_3$, $C(CH_3)_3$*, $C(CH_3)_3$*), 80.0 (d, *J* = 1.6 Hz), 80.0 (d, *J* = 5.8 Hz) (C-4', C-4'*), 74.8, 74.8 (C-2', C-2'*), 71.7, 71.5 (C-3', C-3'*), 64.1 (d, *J* = 5.3 Hz), 63.9 (d, *J* = 5.6 Hz) (C-5', C-5'*), 52.7 (d, *J* = 5,7 Hz), 52.6 (d, *J* = 5.8 Hz) (P(O)OMe, P(O)OMe*), 27.7 ($C(CH_3)_3$, ($C(CH_3)_3$*), 27.7 ($C(CH_3)_3$, ($C(CH_3)_3$*), 27.6 ($C(CH_3)_3$, ($C(CH_3)_3$*); ^{31}P NMR (202 MHz, $CDCl_3$, ^{1}H coupled): δ 10.63 ($^1J_{P,H}$ = 709.4 Hz), 10.02 ($^1J_{P,H}$ = 713.4 Hz). HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{39}N_2NaO_{14}P$ 645.2031; Found 645.2023.

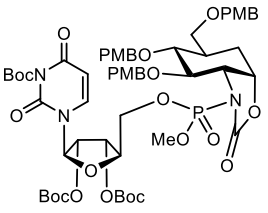
1'',2''-(*N*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridinyl),*O*)-carbamate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-*α*-D-glucopyranoside (24).



Compound **24** was prepared according to general procedure D using cyclic carbamate **9** (0.39 g, 0.69 mmol), 15-crown-5 ether (0.68 mL, 3.4 mmol, 5.0 eq.) and NaH (60 wt% dispersion in mineral oil; 41 mg, 1.0 mmol, 1.5 eq.) in anhydrous THF (3.4 mL, 0.2 M); and H-phosphonate **23** (0.86 g, 1.4 mmol, 2.0 eq.), dry DiPEA (0.72 mL, 4.1 mmol, 6.0 eq.) and $BrCCl_3$ (0.27 mL, 2.7 mmol, 3.9 eq.) in anhydrous DCM (4.6 mL, 0.3 M). Purification of the crude material by flash column chromatography (SiO_2; 30:70 EtOAc:pentane → 80:20 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **24** as a yellow oil and a mixture of P(V) diastereomers (0.56 g, 0.47 mmol, 68%).
Data for first P(V) diastereomer: R_f 0.75 (EtOAc:pentane, 8:2 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.73 (d, *J* = 8.3 Hz, 1H, H-6), 7.25 – 7.13 (m, 6H, CH_{arom}), 6.90 – 6.81 (m, 6H, CH_{arom}), 6.16 (d, *J* = 5.8 Hz, 1H, H-1'), 5.87 (d, *J* = 8.2 Hz, 1H, H-5), 5.29 (dd, *J* = 5.5, 4.4 Hz, 1H, H-3'), 5.15 (dd, *J* = 5.6, 5.6 Hz, 1H, H-2'), 4.69 (dd, *J* = 8.3, 5.3 Hz, 1H, H-2''), 4.65 – 4.56 (m, 3H, C*H*H PMB, CH*H* PMB, C*H*H PMB), 4.52 – 4.42 (m, 2H, H-1'', H-5'), 4.42 – 4.26 (m, 5H, H-4', H-5', CH*H* PMB, C*H*H PMB, CH*H* PMB), 3.83 (dd, *J* = 5.7, 5.7 Hz, 1H, H-3''), 3.81 – 3.76 (m, 12H, OMe, OMe, OMe, P(O)OMe), 3.48 (dd, *J* = 8.0, 6.1 Hz, 1H, H-4''), 3.38 (qd, *J* = 8.9, 4.4 Hz, 2H, H-6''), 2.23 (ddd, *J* = 14.9, 5.4, 5.4 Hz, 1H, H-7''), 1.98 (dddd, *J* = 12.9, 8.7, 4.8, 4.8 Hz, 1H, H-5''), 1.90 (ddd, *J* = 13.9, 9.2, 4.4 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126

MHz, $CDCl_3$, HSQC): δ 160.4 (C=O uracil), 159.6, 159.5, 159.3 ($C_{q\text{-}arom}$), 155.2 (d, $^2J_{C,P}$ = 8.3 Hz, C=O cyclic carbamate), 152.2 (C=O carbamate), 152.0 (C=O uracil), 148.8, 147.7 (C=O carbonate), 139.5 (C-6), 130.4, 130.4 ($C_{q\text{-}arom}$), 129.8 (CH_{arom}), 129.8 ($C_{q\text{-}arom}$), 129.7, 129.5, 114.1, 113.9, 113.9 (CH_{arom}), 103.3 (C-5), 86.9 ($C(CH_3)_3$), 86.3 (C-1'), 83.8, 83.7 ($C(CH_3)_3$), 80.0 (d, $^3J_{C,P}$ = 7.8 Hz, C-4'), 78.8 (C-3''), 78.5 (d, $^3J_{C,P}$ = 9.4 Hz, C-2''), 76.5 (C-4''), 74.7 (C-2'), 73.0, 73.0 (CH_2 PMB), 71.8 (C-3'), 70.9 (C-6''), 67.0 (d, $^2J_{C,P}$ = 5.9 Hz, C-5'), 55.5 (d, $^2J_{C,P}$ = 4.9 Hz, C-1''), 55.4, 55.4, 55.4 (OMe), 54.8 (d, $^2J_{C,P}$ = 5.8 Hz, P(O)OMe), 36.7 (C-5''), 27.8 (C-7''), 27.8, 27.8, 27.6 (C(CH_3)$_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ −2.15; HRMS (ESI) m/z: [M+Na^+] calcd for $C_{57}H_{74}N_3O_{22}PNa$ 1206.4399, found 1206.4394.
Data for second P(V) diastereomer: R_f 0.65 (EtOAc:pentane, 8:2 v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.65 (d, *J* = 8.3 Hz, 1H, H-6), 7.25 – 7.12 (m, 6H, CH_{arom}), 6.90 – 6.78 (m, 6H, CH_{arom}), 6.12 (d, *J* = 5.9 Hz, 1H, H-1'), 5.82 (d, *J* = 8.2 Hz, 1H, H-5), 5.25 (dd, *J* = 5.6, 4.2 Hz, 1H, H-3'), 5.14 (dd, *J* = 5.7, 5.7 Hz, 1H, H-2'), 4.71 – 4.63 (m, 1H, H-2''), 4.63 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.59 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.48 (ddd, *J* = 7.6, 7.6, 4.3 Hz, 1H, H-1''), 4.40 – 4.30 (m, 5H, H-5', C*H*H PMB, CH*H* PMB, C*H*H PMB), 4.25 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.20 (dddd, *J* = 4.3, 4.3, 2.4, 2.4 Hz, 1H, H-4'), 3.89 – 3.82 (m, 4H, H-3'', P(O)OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.49 (dd, *J* = 7.4, 7.4 Hz, 1H, H-4''), 3.42 – 3.31 (m, 2H, H-6''), 2.26 – 2.15 (m, 1H, H-7''), 1.99 (dddd, *J* = 17.6, 7.2, 3.9, 3.9 Hz, 1H, H-5''), 1.94 – 1.90 (m, 1H, H-7''), 1.58 (s, 9H, C(CH_3)$_3$), 1.47 (s, 9H, C(CH_3)$_3$), 1.44 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.5, 159.4, 159.3 ($C_{q\text{-}arom}$), 155.0 (d, $^2J_{C,P}$ = 8.7 Hz, C=O cyclic carbamate), 152.1 (C=O carbamate), 151.9 (C=O uracil), 148.7, 147.6 (C=O carbonate), 139.4 (C-6), 130.5, 130.4, 129.9 ($C_{q\text{-}arom}$), 129.8, 129.6, 129.5, 114.0, 113.9, 113.8 (CH_{arom}), 103.1 (C-5), 86.9 ($C(CH_3)_3$), 86.5 (C-1'), 83.7, 83.6 ($C(CH_3)_3$), 80.0 (d, $^3J_{C,P}$ = 8.7 Hz, C-4'), 79.6 (C-3''), 79.2 (d, $^3J_{C,P}$ = 9.3 Hz, C-2''), 76.0 (C-4''), 74.7 (C-2'), 73.2, 72.9 (CH_2 PMB), 72.0 (C-3'), 71.0 (C-6''), 66.4 (d, $^2J_{C,P}$ = 5.5 Hz, C-5'), 55.6 (d, $^2J_{C,P}$ = 4.9 Hz, C-1''), 55.4, 55.4, 55.4 (OMe), 55.0 (d, $^2J_{C,P}$ = 6.0 Hz, P(O)OMe), 37.1 (C-5''), 28.0 (C-7''), 27.7, 27.7, 27.5 (C(CH_3)$_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ −1.47; HRMS (ESI) m/z: [M+Na^+] calcd for $C_{57}H_{74}N_3O_{22}PNa$ 1206.4399, found 1206.4394.

1'',2''-(*O*,*N*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridinyl))-carbamate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-glucopyranoside (25).

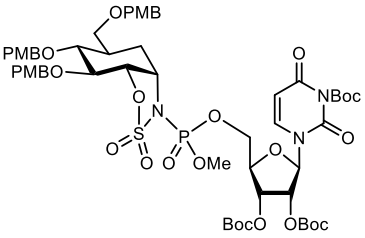


Compound **25** was prepared according to general procedure D using cyclic carbamate **11** (0.29 g, 0.51 mmol), 15-crown-5 ether (0.5 mL, 2.5 mmol, 5.0 eq.) and NaH (60 wt% dispersion in mineral oil; 31 mg, 0.76 mmol, 1.5 eq.) in anhydrous THF (2.5 mL, 0.2 M); and H-phosphonate **23** (0.67 g, 1.1 mmol, 2.0 eq.), dry DiPEA (0.57 mL, 3.3 mmol, 6.0 eq.) and $BrCCl_3$ (0.21 mL, 2.1 mmol, 4.0 eq.) in anhydrous DCM (3.6 mL, 0.3 M). Flash column chromatography of the crude product (SiO_2; 40:60 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **25** as a pale-yellow oil and as a mixture of P(V) diastereomers (0.59 g, 0.50 mmol, 97%).
Data for first P(V) diastereomer: R_f 0.6 (EtOAc:pentane, 7:3 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.56 (d, *J* = 8.3 Hz, 1H, H-6), 7.26 – 7.19 (m, 4H, CH_{arom}), 7.12 – 7.07 (m, 2H, CH_{arom}), 6.87 – 6.78 (m, 6H, CH_{arom}), 6.16 (d, *J* = 6.4 Hz, 1H, H-1'), 5.82 (d, *J* = 8.0 Hz, 1H, H-5), 5.35 (dd, *J* =

5.4, 3.4 Hz, 1H, H-3'), 5.06 (dd, *J* = 6.4, 5.3 Hz, 1H, H-2'), 4.93 (ddd, *J* = 7.8, 2.8, 2.8 Hz, 1H, H-1''), 4.67 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.60 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.48 – 4.37 (m, 5H, H-2'', C*H*H PMB, CH*H* PMB, C*H*H PMB, CH*H* PMB), 4.23 (ddd, *J* = 11.4, 4.4, 1.8 Hz, 1H, H-5'), 4.18 (dddd, *J* = 3.6, 3.6, 2.0, 2.0 Hz, 1H, H-4'), 4.15 (ddd, *J* = 11.3, 5.3, 2.4 Hz, 1H, H-5'), 3.95 (dd, *J* = 4.5, 4.5 Hz, 1H, H-3''), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.67 – 3.61 (m, 4H, H-4'', P(O)OMe), 3.48 (dd, *J* = 9.1, 5.0 Hz, 1H, H-6''), 3.37 (dd, *J* = 9.1, 5.1 Hz, 1H, H-6''), 2.18 – 2.09 (m, 2H, H-5'', H-7''), 1.87 (ddd, *J* = 16.4, 13.7, 3.1 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.2 (C=O uracil), 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 155.7 (d, $^2J_{C,P}$ = 8.8 Hz, C=O cyclic carbamate), 152.3 (C=O carbamate), 152.2 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.2 (C-6), 130.4, 130.3, 130.1 ($C_{q\text{-}arom}$), 129.7, 129.5, 129.5, 113.9, 113.8 (CH_{arom}), 103.4 (C-5), 87.0 ($C(CH_3)_3$), 85.7 (C-1'), 83.8, 83.6 ($C(CH_3)_3$), 80.2 (d, $^3J_{C,P}$ = 8.9 Hz, C-4'), 78.1 (C-3''), 77.1 (C-4''), 75.7 (d, $^3J_{C,P}$ = 8.7 Hz, C-1''), 74.8 (C-2'), 72.8, 72.7, 72.2 (CH_2 PMB), 72.2 (C-3'), 71.1 (C-6''), 66.3 (d, $^2J_{C,P}$ = 4.9 Hz, C-5'), 58.5 (d, $^2J_{C,P}$ = 3.9 Hz, C-2''), 55.5 (d, $^2J_{C,P}$ = 5.7 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 34.8 (C-5''), 27.8, 27.7, 27.5 ($C(CH_3)_3$), 26.4 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ −0.55; HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{57}H_{74}N_3O_{22}PNa$ 1206.4399, found 1206.4394.

Data for second P(V) diastereomer: R_f 0.5 (EtOAc:pentane, 7:3 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.73 (d, *J* = 8.3 Hz, 1H, H-6), 7.23 – 7.19 (m, 4H, CH_{arom}), 7.10 – 7.05 (m, 2H, CH_{arom}), 6.87 – 6.83 (m, 4H, CH_{arom}), 6.79 – 6.75 (m, 2H, CH_{arom}), 6.09 (d, *J* = 6.3 Hz, 1H, H-1'), 5.86 (d, *J* = 8.1 Hz, 1H, H-5), 5.17 (dd, *J* = 5.2, 3.4 Hz, 1H, H-3'), 5.04 (dd, *J* = 6.3, 5.2 Hz, 1H, H-2'), 4.92 (ddd, *J* = 8.3, 2.8, 2.8 Hz, 1H, H-1''), 4.60 – 4.51 (m, 2H, C*H*H PMB, CH*H* PMB), 4.43 – 4.29 (m, 5H, H-2'', C*H*H PMB, CH*H* PMB, C*H*H PMB, CH*H* PMB), 4.09 (ddd, *J* = 11.8, 3.7, 1.9 Hz, 1H, H-5'), 4.05 (dd, *J* = 3.3, 3.3 Hz, 1H, H-3''), 3.95 (ddd, *J* = 11.8, 5.7, 2.4 Hz, 1H, H-5'), 3.89 – 3.84 (m, 4H, H-4', P(O)OMe), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.64 (ddd, *J* = 6.1, 4.5, 2.3 Hz, 1H, H-4''), 3.45 (dd, *J* = 9.1, 5.1 Hz, 1H, H-6''), 3.36 (dd, *J* = 9.1, 5.7 Hz, 1H, H-6''), 2.19 – 2.06 (m, 2H, H-5'', H-7''), 1.84 (ddd, *J* = 15.3, 12.6, 2.9 Hz, 1H, H-7''), 1.58 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.5 (C=O uracil), 159.4, 159.3 ($C_{q\text{-}arom}$), 155.4 (d, $^2J_{C,P}$ = 8.2 Hz, C=O cyclic carbamate), 152.2 (C=O carbamate), 152.0 (C=O uracil), 148.8, 147.8 (C=O carbonate), 139.5 (C-6), 130.4, 130.1, 129.9 ($C_{q\text{-}arom}$), 129.8, 129.6, 129.4, 113.9, 113.9, 113.9 (CH_{arom}), 103.3 (C-5), 86.8 ($C(CH_3)_3$), 85.6 (C-1'), 83.6, 83.5 ($C(CH_3)_3$), 80.0 (d, $^3J_{C,P}$ = 9.3 Hz, C-4'), 76.5 (C-3''), 76.4 (C-4''), 75.0 (C-2'), 75.0 (d, $^3J_{C,P}$ = 8.7 Hz, C-1''), 72.8 (CH_2 PMB), 72.4 (C-3'), 72.2, 71.6 (CH_2 PMB), 71.5 (C-6''), 66.5 (d, $^2J_{C,P}$ = 5.1 Hz, C-5'), 57.5 (d, $^2J_{C,P}$ = 4.4 Hz, C-2''), 55.4, 55.4, 55.4 (OMe), 55.1 (d, $^2J_{C,P}$ = 5.9 Hz, P(O)OMe), 34.1 (C-5''), 27.8, 27.7, 27.6 ($C(CH_3)_3$), 26.1 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ −1.45; HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{57}H_{74}N_3O_{22}PNa$ 1206.4399, found 1206.4393.

1'',2''-(*N*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl) uridinyl),*O*)-sulfamidate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-*α*-D-glucopyranoside (26).



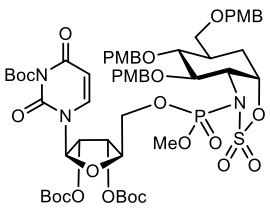
Compound **26** was prepared according to general procedure D using cyclic sulfamidate **10** (305 mg, 0.51 mmol), 15-crown-5 ether (0.50 mL, 2.52 mmol, 4.9 mmol) and NaH (60 wt% dispersion in mineral oil; 30.5 mg, 0.76 mmol, 1.5 eq.) in anhydrous THF (2.5 mL, 0.2 M); and H-phosphonate **23** (685 mg, 1.1 mmol, 2.2 eq.), dry DiPEA (0.58 mL, 3.33 mmol, 6.5 eq.) and $BrCCl_3$ (0.22 mL, 2.2 mmol, 4.3 eq.) in anhydrous DCM (3.6 mL, 0.3 M). Purification of the crude material by flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography obtained title compound **26** as a yellow oil (which solidified upon standing) and as a mixture of P(V) diastereomers (330 mg, 0.27 mmol, 53%).

Data for first P(V) diastereomer: R_f 0.6 (EtOAc:pentane, 6:4 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.58 (d, *J* = 8.3 Hz, 1H, H-6), 7.29 – 7.26 (m, 2H, CH_{arom}), 7.22 – 7.17 (m, 2H, CH_{arom}), 7.14 – 7.11 (m, 2H, CH_{arom}), 6.89 – 6.82 (m, 6H, CH_{arom}), 6.11 (d, *J* = 5.4 Hz, 1H, H-1'), 5.83 (d, *J* = 8.2 Hz, 1H, H-5), 5.26 (dd, *J* = 5.6, 4.7 Hz, 1H, H-3'), 5.16 (dd, *J* = 5.5, 5.5 Hz, 1H, H-2'), 4.78 (ddd, *J* = 7.1, 5.8, 1.1 Hz, 1H, H-2''), 4.76 – 4.67 (m, 2H, C*H*H PMB, CH*H* PMB), 4.53 – 4.43 (m, 3H, H-1'', H-5'), 4.43 – 4.35 (m, 3H, C*H*H PMB, CH*H* PMB, C*H*H PMB), 4.33 (ddd, *J* = 5.2, 2.6, 2.6 Hz, 1H, H-4'), 4.29 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.13 (dd, *J* = 8.6, 7.2 Hz, 1H, H-3''), 3.92 (d, $^3J_{H,P}$ = 11.8 Hz, 3H, P(O)OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.59 (dd, *J* = 9.1, 4.1 Hz, 1H, H-6''), 3.48 (dd, *J* = 9.6, 8.7 Hz, 1H, H-4''), 3.39 (dd, *J* = 9.1, 3.0 Hz, 1H, H-6''), 2.45 (ddd, *J* = 15.3, 4.7, 4.7 Hz, 1H, H-7''), 2.11 – 2.01 (m, 1H, H-5''), 1.91 (ddd, *J* = 14.4, 10.0, 4.1 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.5, 159.4, 159.4 ($C_{q\text{-}arom}$), 152.1 (C=O carbamate), 152.0 (C=O uracil), 148.6, 147.6 (C=O carbonate), 139.3 (C-6), 130.4, 130.3, 129.9 ($C_{q\text{-}arom}$), 129.8, 129.8, 129.5, 114.0, 113.9, 113.9 (CH_{arom}), 103.2 (C-5), 87.0 ($C(CH_3)_3$), 86.9 (C-1'), 85.5 (d, $^3J_{C,P}$ = 9.4 Hz, C-2''), 83.8, 83.8 ($C(CH_3)_3$), 80.6 (C-3''), 79.9 (d, $^3J_{C,P}$ = 7.6 Hz, C-4'), 77.0 (C-4''), 74.8 (C-2'), 74.6, 74.5, 73.0 (CH_2 PMB), 71.6 (C-3'), 69.3 (C-6''), 67.2 (d, $^2J_{C,P}$ = 5.6 Hz, C-5'), 59.3 (d, $^2J_{C,P}$ = 3.3 Hz, C-1''), 55.9 (d, $^2J_{C,P}$ = 5.7 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 36.9 (C-5''), 27.7, 27.7, 27.6 ($C(CH_3)_3$), 27.4 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ −3.18; HRMS (ESI) m/z: [M+Na$^+$] calcd for $C_{56}H_{74}N_3O_{23}PSNa$ 1242.4069, found 1242.4064.

Data for second P(V) diastereomer: R_f 0.5 (EtOAc:pentane, 6:4 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.47 (d, *J* = 8.3 Hz, 1H, H-6), 7.29 – 7.11 (m, 6H, CH_{arom}), 6.89 – 6.82 (m, 6H, CH_{arom}), 6.03 (d, *J* = 4.8 Hz, 1H, H-1'), 5.79 (d, *J* = 8.2 Hz, 1H, H-5), 5.26 (dd, *J* = 5.5, 5.5 Hz, 1H, H-3'), 5.21 (dd, *J* = 5.7, 4.8 Hz, 1H, H-2'), 4.79 (dd, *J* = 6.5, 6.5 Hz, 1H, H-2''), 4.73 – 4.65 (m, 2H, C*H*H PMB, CH*H* PMB), 4.51 (ddd, *J* = 7.2, 3.6, 1.6 Hz, 1H, H-1''), 4.47 (ddd, *J* = 11.5, 5.4, 2.3 Hz, 1H, H-5'), 4.41 – 4.34 (m, 4H, H-5', C*H*H PMB, CH*H* PMB, C*H*H PMB), 4.30 (dd, *J* = 5.3, 2.8 Hz, 1H, H-4'), 4.27 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.11 (dd, *J* = 8.5, 7.0 Hz, 1H, H-3''), 3.90 (d, $^3J_{H,P}$ = 11.9 Hz, 3H, P(O)OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.51 (dd, *J* = 8.9, 4.3 Hz, 1H, H-6''), 3.46 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4''), 3.41 (dd, *J* = 9.2, 3.1 Hz, 1H, H-6''), 2.40 (ddd, *J* = 15.2, 5.1, 5.1 Hz, 1H, H-7''), 2.11 – 2.03 (m, 1H, H-5''), 1.89 (ddd, *J* = 14.5, 9.1, 3.9 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$),

1.48 (s, 9H, C(CH_3)$_3$), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.2 (C=O uracil), 159.6, 159.4, 159.4 ($C_{q\text{-}arom}$), 152.0 (C=O carbamate), 151.9 (C=O uracil), 148.5, 147.5 (C=O carbonate), 139.5 (C-6), 130.4, 130.3, 129.9 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.5, 114.0, 113.9, 113.9 (CH_{arom}), 103.0 (C-5), 87.9 (C-1'), 87.1 (*C*(CH_3)$_3$), 85.1 (d, $^3J_{C,P}$ = 9.4 Hz, C-2''), 83.8, 83.7 (*C*(CH_3)$_3$), 80.5 (C-3''), 79.5 (d, $^3J_{C,P}$ = 8.7 Hz, C-4'), 76.7 (C-4''), 74.8 (C-2'), 74.6, 74.3, 73.0 (CH_2 PMB), 71.5 (C-3'), 69.5 (C-6''), 66.5 (d, $^2J_{C,P}$ = 4.8 Hz, C-5'), 59.2 (d, $^2J_{C,P}$ = 3.0 Hz, C-1''), 55.8 (d, $^2J_{C,P}$ = 5.7 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 37.1 (C-5''), 27.7, 27.7, 27.6 (C(*C*H_3)$_3$), 27.5 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ −2.82; HRMS (ESI) m/z: [M+Na^+] calcd for $C_{56}H_{74}N_3O_{23}PSNa$ 1242.4069, found 1242.4064.

1'',2''-(*O*,*N*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl) uridinyl))-sulfamidate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-*α*-D-glucopyranoside (27).

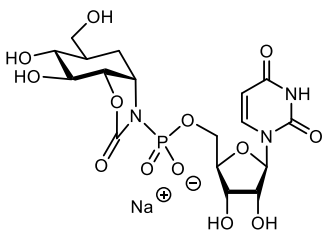


Compound **27** was prepared according to general procedure D using cyclic sulfamidate **12** (0.57 g, 0.94 mmol), 15-crown-5 ether (0.93 mL, 4.7 mmol, 5.0 mmol) and NaH (60 wt% dispersion in mineral oil; 57 g, 1.4 mmol, 1.5 eq.) in anhydrous THF (3.1 mL, 0.3 M); and H-phosphonate **23** (1.2 g, 1.9 mmol, 2.0 eq.), dry DiPEA (0.99 mL, 5.7 mmol, 6.0 eq.) and $BrCCl_3$ (0.22 mL, 2.2 mmol, 4.3 eq.) in anhydrous DCM (4.7 mL, 0.4 M). Flash column chromatography of the crude product (SiO_2, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded title compound **27** as a white brittle foam and as a mixture of P(V) diastereomers (880 mg, 0.72 mmol, 77%).

Data for first P(V) diastereomer: R_f 0.45 (EtOAc:pentane, 1:1 v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.57 (d, *J* = 8.3 Hz, 1H, H-6), 7.41 – 7.34 (m, 2H, CH_{arom}), 7.22 – 7.15 (m, 2H, CH_{arom}), 7.13 – 7.06 (m, 2H, CH_{arom}), 6.89 – 6.79 (m, 6H, CH_{arom}), 6.22 (d, *J* = 6.6 Hz, 1H, H-1'), 5.84 (d, *J* = 8.3 Hz, 1H, H-5), 5.34 (dd, *J* = 5.2, 3.2 Hz, 1H, H-3'), 5.23 (ddd, *J* = 2.8, 2.8 2.3 Hz, 1H, H-1''), 5.05 (dd, *J* = 6.6, 5.2 Hz, 1H, H-2'), 4.91 (d, *J* = 10.4 Hz, 1H, C*H*H PMB), 4.82 (d, *J* = 10.3 Hz, 1H, CH*H* PMB), 4.75 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.45 (d, *J* = 10.6 Hz, 1H, CH*H* PMB), 4.37 (s, 2H, C*H*H PMB, CH*H* PMB), 4.35 – 4.26 (m, 3H, H-2'', H-5'), 4.22 (dddd, *J* = 3.8, 3.8, 2.0, 2.0 Hz, 1H, H-4'), 4.05 (dd, *J* = 9.3, 9.3 Hz, 1H, H-3''), 3.88 (d, $^3J_{H,P}$ = 11.8 Hz, 3H, P(O)OMe), 3.79 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.70 (dd, *J* = 9.2, 3.6 Hz, 1H, H-6''), 3.50 (dd, *J* = 9.7, 9.7 Hz, 1H, H-4''), 3.38 (dd, *J* = 9.1, 2.2 Hz, 1H, H-6''), 2.29 – 2.23 (m, 1H, H-7''), 2.12 – 1.99 (m, 2H, H-5'', H-7''), 1.59 (s, 9H, C(CH_3)$_3$), 1.48 (s, 9H, C(CH_3)$_3$), 1.43 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.2 (C=O uracil), 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 152.3 (C=O carbamate), 152.3 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.0 (C-6), 130.5, 130.4, 130.3 ($C_{q\text{-}arom}$), 129.5, 129.4, 129.4, 113.9, 113.9 (CH_{arom}), 103.5 (C-5), 87.1 (*C*(CH_3)$_3$), 85.2 (C-1'), 84.7 (d, $^3J_{C,P}$ = 3.7 Hz, C-1''), 83.9, 83.7 (*C*(CH_3)$_3$), 82.2 (C-3''), 79.9 (d, $^3J_{C,P}$ = 9.6 Hz, C-4'), 79.3 (C-4''), 75.9 (CH_2 PMB), 74.9 (C-2'), 74.8, 72.9 (CH_2 PMB), 72.1 (C-3'), 68.3 (C-6''), 66.9 (d, $^2J_{C,P}$ = 5.3 Hz, C-5'), 66.4, 66.4 (d, $^2J_{C,P}$ = 1.9 Hz, C-2''), 56.0 (d, $^2J_{C,P}$ = 5.7 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 37.1 (C-5''), 27.9 (C-7''), 27.8, 27.7, 27.6 (C(*C*H_3)$_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ −0.82; HRMS (ESI) m/z: [M+Na^+] calcd for $C_{56}H_{74}N_3O_{23}PSNa$ 1242.4069, found 1242.4064.

Data for second P(V) diastereomer: R_f 0.3 (EtOAc:pentane, 1:1 v:v); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.3 Hz, 1H, H-6), 7.33 – 7.29 (m, 2H, CH_{arom}), 7.22 – 7.19 (m, 2H, CH_{arom}), 7.07 – 7.04 (m, 2H, CH_{arom}), 6.87 – 6.78 (m, 6H, CH_{arom}), 6.13 (d, *J* = 6.3 Hz, 1H, H-1'), 5.85 (d, *J* = 8.2 Hz, 1H, H-5), 5.24 (dd, *J* = 5.4, 3.8 Hz, 1H, H-3'), 5.14 (ddd, *J* = 3.0, 3.0, 2.9 Hz, 1H, H-1''), 5.04 (dd, *J* = 6.3, 5.4 Hz, 1H, H-2'), 4.98 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.73 (d, *J* = 10.8 Hz, 1H, CH*H* PMB), 4.72 (d, *J* = 10.5 Hz, 1H, C*H*H PMB), 4.46 (d, *J* = 10.5 Hz, 1H, CH*H* PMB), 4.41 – 4.36 (m, 2H, C*H*H PMB, CH*H* PMB), 4.20 (dd, *J* = 5.5, 3.8 Hz, 1H, H-2''), 4.20 – 4.13 (m, 2H, H-5'), 4.11 (dddd, *J* = 2.9, 2.9, 2.9, 2.9 Hz, 1H, H-4'), 4.02 (dd, *J* = 9.3, 9.3 Hz, 1H, H-3''), 3.82 (d, $^3J_{H,P}$ = 11.8 Hz, 3H, P(O)OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.73 (dd, *J* = 9.1, 3.8 Hz, 1H, H-6''), 3.52 (dd, *J* = 9.9, 9.9 Hz, 1H, H-4''), 3.38 (dd, *J* = 9.2, 2.4 Hz, 1H, H-6''), 2.26 (ddd, *J* = 15.5, 2.7, 2.7 Hz, 1H, H-7''), 2.11 – 2.04 (m, 1H, H-5''), 2.00 (ddd, *J* = 15.9, 12.8, 3.1 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.4, 159.2 ($C_{q\text{-}arom}$), 152.2 (C=O carbamate), 152.1 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.2 (C-6), 130.5, 130.3, 130.2 ($C_{q\text{-}arom}$), 129.5, 129.5, 129.0, 114.0, 113.9, 113.9 (CH_{arom}), 103.5 (C-5), 87.0 ($C(CH_3)_3$), 85.8 (C-1'), 84.1 (d, $^3J_{C,P}$ = 3.9 Hz, C-1''), 83.8, 83.7 ($C(CH_3)_3$), 81.9 (C-3''), 79.7 (d, $^3J_{C,P}$ = 8.3 Hz, C-4'), 79.5 (C-4''), 75.2, 74.8 (CH_2 PMB), 74.7 (C-2'), 73.0 (CH_2 PMB), 71.9 (C-3'), 68.2 (C-6''), 66.9 (d, $^2J_{C,P}$ = 5.8 Hz, C-5'), 66.4 (d, $^2J_{C,P}$ = 0.9 Hz, C-2''), 56.0, 56.0 (d, $^2J_{C,P}$ = 5.9 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 37.1 (C-5''), 28.1 (C-7''), 27.8, 27.7, 27.6 ($C(CH_3)_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ −2.08; HRMS (ESI) m/z: [M+Na^+] calcd for $C_{56}H_{74}N_3O_{23}PSNa$ 1242.4069, found 1242.4064.

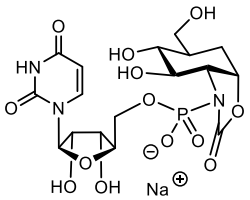
1'',2''-(*N*-(5'-*O*-Phosphoryluridinyl),*O*)-carbamate-carba-*α*-D-glucopyranoside (2).



Compound **2** was prepared according to general procedure E using **24** (81 mg, 69 μmol), TES (0.11 mL, 0.69 mmol, 10 eq.) and TFA (0.51 mL, 6.7 mmol, 30% v:v) in DCM (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 0.25 MeOH:DCM, 2:8 v:v) and pyridine (10.8 mL, 134 mmol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at 35°C, before full conversion was observed on TLC (R_f 0.25 (H_2O:MeCN, 1:9 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 12:88 H_2O:ACN) followed by Dowex 50WX4 Na^+ ion exchange and lyophilization yielded the title compound **2** as a colorless transparent film (16.8 mg, 31.6 μmol, 72%). R_f 0.25 (H_2O:MeCN, 1:9 v:v); ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 7.94 (d, *J* = 8.1 Hz, 1H, H-6), 5.95 (d, *J* = 4.7 Hz, 1H, H-1'), 5.92 (d, *J* = 8.1 Hz, 1H, H-5), 4.55 (dd, *J* = 7.6, 7.6 Hz, 1H, H-2''), 4.37 (ddd, *J* = 7.4, 7.1, 3.7 Hz, 1H, H-1''), 4.34 (dd, *J* = 5.0, 5.0 Hz, 1H, H-2'), 4.31 (dd, *J* = 4.9, 4.9 Hz, 1H, H-3'), 4.25 (dddd, *J* = 4.9, 2.6, 2.6, 2.6 Hz, 1H, H-4'), 4.23 – 4.11 (m, 2H, H-5'), 3.79 (dd, *J* = 9.5, 7.3 Hz, 1H, H-3''), 3.70 (dd, *J* = 11.4, 3.7 Hz, 1H, H-6''), 3.66 (dd, *J* = 11.4, 5.4 Hz, 1H, H-6''), 3.39 (dd, *J* = 9.0, 9.0 Hz, 1H, H-4''), 2.35 (qd, *J* = 8.6, 6.4 Hz, 1H, H-7''), 1.88 – 1.77 (m, 2H, H-5'', H-7''); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 166.7 (C=O uracil), 158.7 (d, $^2J_{C,P}$ = 8.5 Hz, C=O carbamate), 152.1 (C=O uracil), 141.8 (C-6), 102.5 (C-5), 88.8 (C-1'), 83.0 (d, $^3J_{C,P}$ = 9.0 Hz, C-4'), 79.8 (d, $^3J_{C,P}$ = 8.1 Hz, C-2''), 74.5 (C-3''), 73.8 (C-2'), 69.9 (C-4''), 69.6 (C-3'), 64.7 (d, $^2J_{C,P}$ = 5.4 Hz,

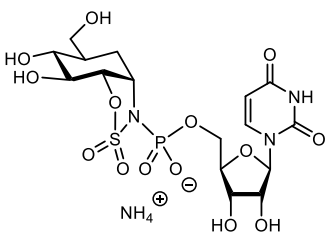
C-5'), 62.3 (C-6''), 56.0 (d, $^{2}J_{C,P}$ = 3.5 Hz, C-1''), 39.3 (C-5''), 26.2 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ −5.58; HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{17}H_{24}N_3O_{13}PNa$ 532.0944, found 532.0939.

1'',2''-(*O*,*N*-(5'-*O*-Phosphoryluridinyl))-carbamate-carba-*α*-D-glucopyranoside (4).



Compound **4** was prepared according to general procedure E using **25** (473 mg, 0.4 mmol), TES (0.63 mL, 4.0 mmol, 10 eq.) and TFA (2.8 mL, 36.8 mmol, 30% v:v) in DCM (4.6 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 0.2 MeOH:DCM, 2:8 v:v) and pyridine (29 mL, 368 mmol, 10:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at 35°C, before full conversion was observed on TLC (R_f 0.2 (H_2O:MeCN, 1:9 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 12:88 H_2O:ACN) followed by Dowex 50WX4 Na^+ ion exchange and lyophilization yielded the title compound **4** as a colorless transparent film (67.5 mg, 0.13 mmol, 32% over two steps). ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 7.94 (d, *J* = 8.2 Hz, 1H, H-6), 5.97 (d, *J* = 4.9 Hz, 1H, H-1'), 5.95 (d, *J* = 8.0 Hz, 1H, H-5), 4.86 (m, 1H, H-1''), 4.39 (dd, *J* = 5.0, 5.0 Hz, 1H, H-2'), 4.33 (dd, *J* = 4.9, 4.9 Hz, 1H, H-3'), 4.28 (ddd, *J* = 5.9, 2.1, 2.1 Hz, 1H, H-4'), 4.26 (dd, *J* = 4.2, 2.3 Hz, 1H, H-5'), 4.25 – 4.18 (m, 1H, H-5'), 4.03 (ddd, *J* = 7.9, 6.3, 1.8 Hz, 1H, H-2''), 3.78 (dd, *J* = 11.4, 3.6 Hz, 1H, H-6''), 3.72 (dd, *J* = 11.4, 5.6 Hz, 1H, H-6''), 3.66 (dd, *J* = 9.5, 7.8 Hz, 1H, H-3''), 3.38 (dd, *J* = 10.0, 10.0 Hz, 1H, H-4''), 2.30 (d, *J* = 15.3 Hz, 1H, H-7''), 1.82 (dddd, *J* = 16.0, 10.0, 3.3, 3.3 Hz, 1H, H-5''), 1.73 (ddd, *J* = 16.3, 13.0, 3.8 Hz, 1H, H-7''); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 166.2 (C=O amide), 158.5 (d, $^{2}J_{C,P}$ = 8.1 Hz, C=O carbamate), 151.8 (C=O amide), 142.0 (C-6), 102.6 (C-5), 88.9 (C-1'), 82.9 (d, $^{3}J_{C,P}$ = 9.1 Hz, C-4'), 78.1 (C-3''), 77.4 (d, $^{3}J_{C,P}$ = 6.7 Hz, C-1''), 73.7 (C-2'), 71.2 (C-4''), 69.7 (C-3'), 65.1 (d, $^{2}J_{C,P}$ = 5.5 Hz, C-5'), 63.6 (d, $^{2}J_{C,P}$ = 3.2 Hz, C-2''), 61.8 (C-6''), 37.5 (C-5''), 27.0 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ −4.88; HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{17}H_{24}N_3O_{13}PNa$ 532.0944, found 532.0939.

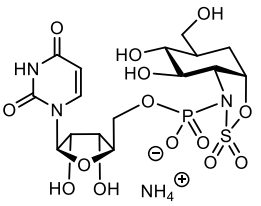
1'',2''-(*N*-(5'-*O*-Phosphoryluridinyl),*O*)-sulfamidate-carba-*α*-D-glucopyranoside (1).



Compound **1** was prepared according to general procedure E using protected *N*-sulfonylphosphoramidate **26** (78 mg, 64 μmol), TFA (0.39 mL, 5.1 mmol, 30% v:v), TES (0.10 mL, 0.63 mmol, 9.8 eq.) in anhydrous DCM (0.8 mL, 0.05 M). The reaction mixture was stirred for 3 h at 0°C, before full conversion was observed on TLC (R_f 0.1 (MeOH:DCM, 2:8 v:v)) and pyridine (8.2 mL, 101 mmol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at room temperature, before full conversion was observed on TLC (R_f 0.2 (H_2O:ACN, 1:9 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 12:88 H_2O:ACN) followed by NH_4^+-Dowex® 50WX4 ion exchange and lyophilization yielded the title compound **1** as a colorless transparent film (27.7 mg, 49.3 μmol, 77% over two steps). ^{1}H NMR (500 MHz, D_2O, HH-COSY): δ 7.91 (d, *J* = 8.1 Hz, 1H, H-6), 5.96 (d, *J* = 4.0 Hz, 1H, H-1'), 5.94 (d, *J* = 7.8 Hz, 1H, H-5), 4.76 (dd, *J* = 8.8, 5.7 Hz, 1H, H-2''), 4.49 (ddd, *J* = 6.0, 3.3, 3.3 Hz, 1H, H-1''), 4.36 (dd, *J* = 4.9, 4.9 Hz, 1H, H-2'), 4.32 (dd, *J* = 5.0, 5.0 Hz, 1H, H-3'), 4.30 – 4.23 (m, 3H, H-4', H-5'),

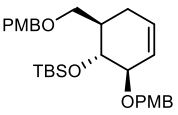
4.02 (dd, *J* = 9.8, 8.6 Hz, 1H, H-3''), 3.76 (dd, *J* = 11.5, 4.7 Hz, 1H, H-6''), 3.62 (dd, *J* = 11.5, 3.3 Hz, 1H, H-6''), 3.41 (dd, *J* = 10.1, 10.1 Hz, 1H, H-4''), 2.46 (ddd, *J* = 15.4, 3.2, 3.2 Hz, 1H, H-7''), 1.86 (dddd, *J* = 13.5, 10.6, 3.8, 3.8 Hz, 1H, H-5''), 1.77 (ddd, *J* = 15.9, 12.3, 3.8 Hz, 1H, H-7''); ^{13}C NMR (126 MHz, D_2O, HH-COSY, HSQC): δ 166.2, 151.8 (C=O uracil), 141.8 (C-6), 102.6 (C-5), 89.0 (C-1'), 85.4 (d, $^3J_{C,P}$ = 8.5 Hz, C-2''), 82.7 (d, $^3J_{C,P}$ = 8.5 Hz, C-4'), 73.8 (C-3'') 73.6 (C-2'), 70.6 (C-4''), 69.4 (C-3'), 65.1 (d, $^2J_{C,P}$ = 5.6 Hz, C-5'), 61.2 (C-6''), 58.9 (d, $^2J_{C,P}$ = 1.4 Hz, C-1''), 38.0 (C-5''), 25.9 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ −7.77; HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{16}H_{28}N_4O_{14}PS$ 563.1055, found 563.1055.

1'',2''-(*O*,*N*-(5'-*O*-Phosphoryluridinyl))-sulfamidate-carba-*α*-D-glucopyranoside (3).



Compound **3** was prepared according to general procedure E using protected *N*-sulfonylphosphoramidate **27** (70 mg, 57 μmol), TFA (0.35 mL, 4.6 mmol, 30% v:v), TES (91 μL, 66 mg, 0.57 mmol, 10.0 eq.) in anhydrous DCM (0.70 mL, 0.05 M). The reaction mixture was stirred for 3 h at 0°C, before full conversion was observed on TLC (R_f 0.1 (MeOH:DCM, 2:8 v:v)) and pyridine (7.4 mL, 92 mmol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at room temperature, before full conversion was observed on TLC (R_f 0.25 (H_2O:ACN, 1:9 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, distilled DCM then 0:100 H_2O:ACN → 15:85 H_2O:ACN) followed by NH_4^+-Dowex® 50WX4 ion exchange and lyophilization yielded the title compound **3** as a colorless transparent film (23.9 mg, 42.5 μmol, 74% over two steps). ^{1}H NMR (500 MHz, D_2O, HH-COSY, HSQC): δ 7.87 (d, *J* = 8.1 Hz, 1H, H-6), 5.96 (d, *J* = 4.3 Hz, 1H, H-1'), 5.95 (d, *J* = 8.1 Hz, 1H, H-5), 5.22 (ddd, *J* = 4.6, 2.8, 2.8 Hz, 1H, H-1''), 4.40 – 4.35 (m, 2H, H-2', H-3'), 4.33 – 4.21 (m, 3H, H-4', H-5'), 3.99 (ddd, *J* = 8.4, 4.1, 4.1 Hz, 1H, H-2''), 3.88 (dd, *J* = 9.7, 8.5 Hz, 1H, H-3''), 3.76 (dd, *J* = 11.4, 3.6 Hz, 1H, H-6''), 3.71 (dd, *J* = 11.4, 5.6 Hz, 1H, H-6''), 3.35 (dd, *J* = 10.7, 9.6 Hz, 1H, H-4''), 2.36 (ddd, *J* = 16.0, 3.0, 3.0 Hz, 1H, H-7''), 1.88 (dddd, *J* = 13.9, 13.9, 6.1, 3.5 Hz, 1H, H-5''), 1.76 (ddd, *J* = 16.2, 13.1, 3.2 Hz, 1H, H-7''); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 166.2, 151.8 (C=O uracil), 141.9 (C-6), 102.8 (C-5), 89.0 (C-1'), 82.7 (d, $^3J_{C,P}$ = 9.0 Hz, C-4'), 82.6 (d, $^3J_{C,P}$ = 5.6 Hz, C-1''), 76.1 (C-3''), 73.5 (C-2'), 71.2 (C-4''), 69.4 (C-3'), 66.5 (d, $^2J_{C,P}$ = 2.2 Hz, C-2''), 65.0 (d, $^2J_{C,P}$ = 5.7 Hz, C-5'), 61.3 (C-6''), 37.3 (C-5''), 27.1 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ −6.76; HRMS (ESI) m/z: [M+H$^+$] calcd for $C_{16}H_{28}N_4O_{14}PS$ 563.1055, found 563.1055.

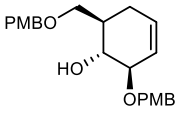
3,6-Di-*O*-(4-methoxybenzyl)-4-*O*-*tert*-butyldimethylsilyl-carba-D-glucal (29).



Compound **28** (1.9 g, 5.0 mmol) was dissolved in DCM (50 mL, 0.10 M). 4-methoxybenzyl-2,2,2-trichloroacetimidate (3.5 g, 13 mmol, 2.5 eq.) and PPTS (0.63 g, 2.5 mmol, 0.50 eq.) were added. The reaction mixture was stirred overnight at room temperature. Upon full conversion on TLC (R_f 0.7 (EtOAc:pentane, 1:9 v:v)), the reaction was quenched 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 1.0 M aq. HCl and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, dry loading on Celite, 3:97 Et_2O:pentane → 20:80 Et_2O:pentane) yielded the title compound **29** (1.4 g, 2.9 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$,

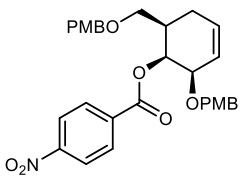
HH-COSY, HSQC): δ 7.30 – 7.23 (m, 4H, CH_{arom}), 6.91 – 6.85 (m, 4H, CH_{arom}), 5.81 – 5.71 (m, 1H, H-1), 5.65 (dddd, *J* = 10.1, 2.4, 2.3, 1.4 Hz, 1H, H-2), 4.55 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.51 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.47 (d, *J* = 11.7 Hz, 1H, C*H*H PMB), 4.40 (d, *J* = 11.6 Hz, 1H, CH*H* PMB), 3.86 (ddd, *J* = 4.6, 3.0, 1.3 Hz, 1H, H-3), 3.82 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.77 (dd, *J* = 9.1, 6.4 Hz, 1H, H-4), 3.64 (dd, *J* = 9.0, 3.4 Hz, 1H, H-6), 3.45 (dd, *J* = 9.0, 7.3 Hz, 1H, H-6), 2.39 – 2.24 (m, 1H, H-7), 2.12 – 1.99 (m, 2H, H-5, H-7), 0.89 (s, 9H, $C(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.2, 159.1, 131.0, 131.0 ($C_{q\text{-}arom}$), 129.4, 129.2 (CH_{arom}), 128.6 (C-1), 125.5 (C-2), 113.8, 113.8 (CH_{arom}), 80.9 (C-3), 72.8 (CH_2 PMB), 72.5 (C-4), 71.1 (C-6), 70.7 (CH_2 PMB), 55.4, 55.4 (OMe), 40.6 (C-5), 28.3 (C-7), 26.2 ($C(CH_3)_3$), 18.4 ($C(CH_3)_3$), -3.8, -4.7 ($SiCH_3$); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{42}NaO_5Si$ 521.2694; Found 521.2691.

3,6-Di-*O*-(4-methoxybenzyl)-carba-D-glucal (30).



Compound **29** (7.0 g, 14 mmol) was dissolved in THF (0.14 L, 0.10 M). TBAF (1.0 M solution in THF; 42 mL, 42 mmol, 3.0 eq.) was added. The reaction mixture was stirred for 1 h at room temperature. Upon full conversion on TLC (R_f 0.25 (EtOAc:pentane, 2:8 v:v)), the reaction was quenched 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 (SiO_2, 20:80 EtOAc:pentane → 40:60 EtOAc:pentane) yielded the title compound **30** (3.6 g, 9.5 mmol, 67%). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.40 – 7.19 (m, 4H, CH_{arom}), 6.94 – 6.85 (m, 4H, CH_{arom}), 5.72 (dddd, *J* = 10.1, 4.3, 2.0, 2.0 Hz, 1H, H-2), 5.69 – 5.64 (m, 1H, H-1), 4.68 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.63 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.54 – 4.42 (m, 2H, C*H*H PMB, CH*H* PMB), 4.05 – 3.95 (m, 1H, H-3), 3.82 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.75 (ddd, *J* = 10.9, 7.6, 1.7 Hz, 1H, H-4), 3.64 (dd, *J* = 9.3, 6.0 Hz, 1H, H-6), 3.59 (dd, *J* = 9.3, 5.2 Hz, 1H, H-6), 3.26 (d, *J* = 1.8 Hz, 1H, 4-OH), 2.23 – 2.13 (m, 1H, H-7), 2.07 (dddd, *J* = 10.9, 10.9, 5.5, 5.5 Hz, 1H, H-5), 2.02 – 1.90 (m, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.3, 131.0, 130.2 ($C_{q\text{-}arom}$), 129.5, 129.3 (CH_{arom}), 127.9 (C-2), 126.3 (C-1), 113.9, 113.9 (CH_{arom}), 80.9 (C-3), 74.6 (C-4), 73.1, 72.5 (CH_2 PMB), 71.2 (C-6), 55.4 (OMe), 39.0 (C-5), 28.5 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{28}NaO_5$ 407.1829; Found 407.1824.

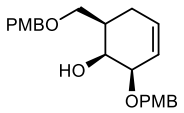
3,6-Di-*O*-(4-methoxybenzyl)-4-*O*-(4-nitrobenzoate)-carba-D-glucal (31).



Compound **30** (1.7 g, 4.5 mmol) was dissolved in anhydrous THF (45 mL, 0.10 M). PPh_3 (3.5 g, 13 mmol, 3.0 eq.), *p*-nitrobenzoic acid (2.2 g, 13 mmol, 3.0 eq.) and DEAD (2.1 mL, 13 mmol, 3.0 eq.) were added. The reaction mixture was stirred for 4.5 h at 60°C. Upon full conversion on TLC (R_f 0.45 (EtOAc:pentane, 2:8 v:v)), the reaction was quenched 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 (SiO_2, dry loading on Celite, 10:90 Et_2O:pentane → 30:70 Et_2O:pentane) yielded the title compound **31** (2.3 g, 4.4 mmol, 98%). ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 8.26 – 8.19 (m, 2H, CH_{arom}), 8.13 – 8.09 (m, 2H, CH_{arom}), 7.23 – 7.19 (m, 4H, CH_{arom}), 6.83 – 6.76 (m, 4H, CH_{arom}), 6.04 – 5.99 (m, 1H, H-4), 5.91 – 5.83 (m, 1H, H-1), 5.64 – 5.57 (m, 1H, H-2), 4.72 (d, *J* = 11.4 Hz, 1H,

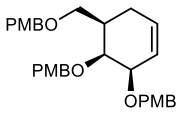
C*H*H PMB), 4.45 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.42 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.38 (d, *J* = 11.5 Hz, 1H, CH*H* PMB), 4.18 – 4.15 (m, 1H, H-3), 3.76 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.37 (s, 1H, H-6), 3.36 (s, 1H, H-6), 2.28 (dddd, *J* = 12.8, 12.8, 6.9, 1.4 Hz, 1H, H-7), 2.15 (ddddd, *J* = 17.9, 6.3, 4.3, 1.9, 1.9 Hz, 1H, H-5), 2.05 (dddd, *J* = 17.5, 11.0, 3.0, 3.0 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 164.6, 159.3, 159.3, 150.5, 136.2 ($C_{q\text{-}arom}$), 130.9 (CH_{arom}), 130.3, 130.1 ($C_{q\text{-}arom}$), 129.6, 129.5 (CH_{arom}), 127.8 (C-1), 127.1 (C-2), 123.5, 113.9, 113.8 (CH_{arom}), 74.3 (C-3), 73.2, 70.8 (CH_2 PMB), 70.3 (C-6), 68.1 (C-4), 55.4, 55.3 (OMe), 37.0 (C-5), 24.8 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{31}NNaO_8$ 556.1942; Found 556.1938.

3,6-Di-*O*-(4-methoxybenzyl)-carba-D-galactal (32).



Compound **31** (2.3 g, 4.4 mmol) was dissolved in DCM:MeOH (1:1, 88 mL, 0.05 M). NaOMe (0.94 g, 4.4 mmol, 4.0 eq.) was added on ice and the ice bath was removed after 5 min. The reaction mixture was stirred overnight at room temperature. Upon full conversion on TLC (R_f 0.2 (EtOAc:pentane, 2:8 v:v)), the reaction was quenched 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 (SiO_2, 10:90 EtOAc:pentane → 40:60 EtOAc:pentane) yielded the title compound **32** (1.1 g, 3.0 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.36 – 7.25 (m, 4H, CH_{arom}), 6.95 – 6.87 (m, 4H, CH_{arom}), 5.86 – 5.80 (m, 1H, H-1), 5.56 (ddd, *J* = 10.2, 1.8, 1.8 Hz, 1H, H-2), 4.66 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.56 (d, *J* = 11.4 Hz, 1H, CH*H* PMB), 4.53 (d, *J* = 11.5 Hz, 1H, C*H*H PMB), 4.46 (d, *J* = 11.5 Hz, 1H, CH*H* PMB), 4.29 (ddd, *J* = 3.9, 2.2 Hz, 1H, H-3), 4.04 (ddd, *J* = 4.1, 2.1, 2.1 Hz, 1H, H-4), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.66 (dd, *J* = 9.0, 7.7 Hz, 1H, H-6), 3.46 (dd, *J* = 9.0, 5.5 Hz, 1H, H-6), 2.44 (d, *J* = 2.1 Hz, 1H, 4-OH), 2.04 – 1.97 (m, 3H, H-5, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 159.3, 130.6, 130.3 ($C_{q\text{-}arom}$), 129.5, 129.4 (CH_{arom}), 129.2 (C-1), 125.3 (C-2), 114.0, 113.9 (CH_{arom}), 75.6 (C-4), 73.1 (CH_2 PMB), 71.5 (C-6), 70.3 (CH_2 PMB), 65.0 (C-3), 55.4 (OMe), 37.9 (C-5), 24.2 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{28}NaO_5$ 407.1829; Found 407.1824.

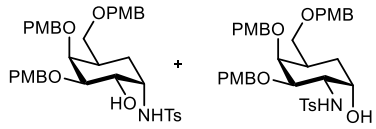
3,4,6-Tri-*O*-(4-methoxybenzyl)-carba-D-galactal (33).



Compound **32** (0.12 g, 0.31 mmol) was co-evaporated with toluene and dissolved in DMF (3.1 mL, 0.10 M). PMBCl (0.10 mL, 0.53 mmol, 1.7 eq.) and NaH (60 wt.% dispersion in mineral oil; 23 mg, 0.62 mmol, 2.0 eq.) were added on ice and the ice bath was removed after 5 min. The reaction mixture was stirred overnight at room temperature. Upon full conversion on TLC (R_f 0.45 (EtOAc:pentane, 2:8 v:v)), the reaction mixture was cooled on ice and quenched 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 (SiO_2, dry loading on Celite, 10:90 Et_2O:pentane → 30:70 Et_2O:pentane) yielded the title compound **33** (0.14 g, 0.28 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.31 – 7.18 (m, 6H, CH_{arom}), 6.91 – 6.78 (m, 6H, CH_{arom}), 5.75 (dddd, *J* = 10.1, 4.2, 2.2, 2.2 Hz, 1H, H-1), 5.69 – 5.64 (m, 1H, H-2), 4.84 (d, *J* = 11.6 Hz, 1H, C*H*H PMB), 4.61 (d, *J* = 11.7 Hz, 1H, C*H*H PMB), 4.57 (d, *J* = 11.7 Hz, 1H, CH*H* PMB), 4.51 (d, *J* = 11.6 Hz, 1H, CH*H* PMB), 4.33 – 4.27 (m, 2H, C*H*H PMB, CH*H* PMB), 4.07 (ddd, *J* = 3.3, 1.5, 1.5 Hz, 1H, H-3), 4.05 (dd, *J* = 3.7, 2.0 Hz, 1H, H-

4), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.44 (dd, *J* = 8.9, 8.8 Hz, 1H, H-6), 3.26 (dd, *J* = 8.9, 5.2 Hz, 1H, H-6), 2.05 – 1.97 (m, 1H, H-5), 1.97 – 1.87 (m, 2H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.3, 159.1, 159.0, 131.9, 131.1, 130.6 ($C_{q\text{-}arom}$), 129.5, 129.5, 129.0 (CH_{arom}), 128.2 (C-1), 126.6 (C-2), 113.9, 113.8, 113.6 (CH_{arom}), 77.1 (C-4), 73.7 (CH_2 PMB), 72.9 (C-3), 72.9 (CH_2 PMB), 70.8 (C-6), 70.6 (CH_2 PMB), 55.4, 55.4, 55.3 (OMe), 38.1 (C-5), 25.3 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{36}NaO_6$ 527.2404; Found 527.2401.

1-Deoxy-1-(*p*-toluenesulfonamido)-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (34) and 2-Deoxy-(*p*-toluenesulfonamido)-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (35).



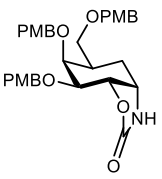
Compound **33** (2.9 g, 5.8 mmol) was dissolved in $CHCl_3$:H_2O (1:1, 58 mL, 0.10 M). Chloramine-T trihydrate (3.2 g, 12 mmol, 2.0 eq.), TEBACl (79 mg, 0.35 mmol, 0.06 eq.) and $K_2[OsO_2(OH)_4]$ (0.11 g, 0.28 mmol, 0.05 eq.) were added. The reaction mixture was stirred vigorously overnight at 60°C. Upon full conversion on TLC (R_f 0.4 and 0.2 for **34** and **35** respectively (EtOAc:pentane, 4:6 v:v)), the reaction was quenched with sat. aq. $Na_2S_2O_3$. The organic layer was separated, the aqueous layer was extracted thrice with Et_2O and the combined organic layers were washed thrice with 1.0 wt.% aq. NaOH and once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 50:50 EtOAc:pentane) yielded the title compounds **34** (1.6 g, 2.3 mmol, 40%) and **35** (2.0 g, 2.9 mmol, 50%).

Analytical data for **34**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.75 – 7.68 (m, 2H, CH_{arom}), 7.34 – 7.19 (m, 8H, CH_{arom}), 7.18 – 7.11 (m, 2H, CH_{arom}), 6.93 – 6.86 (m, 4H, CH_{arom}), 6.83 – 6.77 (m, 2H, CH_{arom}), 4.96 (s, 1H, 1-NH), 4.72 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.67 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.44 – 4.31 (m, 4H, C*H*H PMB, CH*H* PMB, CH*H* PMB, CH*H* PMB), 4.16 (d, *J* = 2.8 Hz, 1H, H-4), 3.95 (ddd, *J* = 9.9, 4.7, 1.3 Hz, 1H, H-2), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.51 – 3.36 (m, 2H, H-3, H-6), 3.32 (ddd, *J* = 3.8, 3.6, 3.6 Hz, 1H, H-1), 3.22 (dd, *J* = 8.9, 4.8 Hz, 1H, H-6), 2.47 (s, 1H, 2-OH), 2.40 (s, 3H, CH_3 Ts), 2.28 – 2.18 (m, 1H, H-5), 1.90 (ddd, *J* = 14.2, 3.4, 3.4 Hz, 1H, H-7), 1.43 (ddd, *J* = 15.2, 12.8, 2.9 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.6, 159.4, 159.2, 143.7, 135.8, 131.4, 130.5, 130.0 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.6, 129.3, 127.6, 114.2, 114.0, 113.7 (CH_{arom}), 81.2 (C-3), 74.2, 72.9 (CH_2 PMB), 72.7 (C-4), 71.5 (CH_2 PMB), 69.9 (C-6), 69.0 (C-2), 55.4, 55.4, 55.4, 52.7 (C-1), 35.4 (C-5), 25.1 (C-7), 21.7 (CH_3 Ts); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{38}H_{45}NNaO_9S$ 714.2707; Found 714.2700.

Analytical data for **35**: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.69 – 7.62 (m, 2H, CH_{arom}), 7.25 – 7.21 (m, 2H, CH_{arom}), 7.17 – 7.13 (m, 2H, CH_{arom}), 7.10 – 7.05 (m, 2H, CH_{arom}), 7.00 – 6.93 (m, 2H, CH_{arom}), 6.89 – 6.83 (m, 4H, CH_{arom}), 6.80 – 6.76 (m, 2H, CH_{arom}), 4.90 (d, *J* = 3.3 Hz, 1H, 2-NH), 4.55 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.52 (d, *J* = 10.6 Hz, 1H, C*H*H PMB), 4.41 (d, *J* = 11.6 Hz, 1H, C*H*H PMB), 4.37 (d, *J* = 11.6 Hz, 1H, CH*H* PMB), 4.28 – 4.24 (m, 2H, CH*H* PMB, H-1), 4.22 (d, *J* = 11.1 Hz, 1H, CH*H* PMB), 4.12 (dd, *J* = 2.1, 2.1 Hz, 1H, H-4), 3.82 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.56 (dd, *J* = 10.6, 2.1 Hz, 1H, H-3), 3.45 (ddd, *J* = 10.6, 3.1, 3.1 Hz, 1H, H-2), 3.41 (dd, *J* = 9.3, 9.3 Hz, 1H, H-6), 3.22 (dd, *J* = 9.0, 4.9 Hz, 1H, H-6), 2.57 (bs, 1H, 1-OH), 2.39 (s, 3H, CH_3 Ts), 2.25 – 2.11 (m, 1H, H-5), 1.51 (d, *J* = 3.0 Hz, 1H, H-7), 1.49 (dd, *J* = 3.0, 2.9 Hz, 1H, H-7); ^{13}C NMR

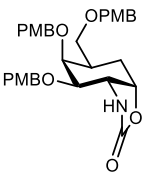
(126 MHz, $CDCl_3$, HSQC): δ 159.4, 159.3, 159.1, 143.3, 136.0, 131.3, 130.5, 129.8 ($C_{q\text{-}arom}$), 129.6, 129.5, 129.4, 129.1, 127.6, 114.0, 113.9, 113.6 (CH_{arom}), 78.1 (C-3), 73.9, 72.9 (CH_2 PMB), 72.6 (C-4), 71.0 (CH_2 PMB), 70.2 (C-6), 67.8 (C-1), 56.5 (C-2), 55.4, 55.4 (OMe), 35.2 (C-5), 28.0 (C-7), 21.7 (CH_3 Ts); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{38}H_{45}NNaO_9S$ 714.2707; Found 714.2701.

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



Compound **36** was prepared according to general procedure B using **34** (0.35 g, 0.50 mmol), pyridine (0.18 mL, 2.3 mmol, 4.5 eq.) and triphosgene (89 mg, 0.30 mmol, 0.60 eq.) in anhydrous DCM (3.1 mL, 0.10 M). Full conversion was observed on TLC (R_f 0.7 (EtOAc:pentane, 1:1 v:v)). The second step was performed using naphthalene (0.77 g, 6.0 mmol, 12 eq.) and Na (0.12 g, 5.0 mmol, 10 eq.) in anhydrous THF (6.2 mL, 0.05 M). Full conversion was observed on TLC (R_f 0.2 (EtOAc:pentane, 1:1 v:v)). Flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) yielded the title compound **36** (0.21 g, 0.37 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.35 – 7.28 (m, 2H, CH_{arom}), 7.24 – 7.18 (m, 2H, CH_{arom}), 7.17 – 7.11 (m, 2H, CH_{arom}), 6.92 – 6.84 (m, 4H, CH_{arom}), 6.85 – 6.79 (m, 2H, CH_{arom}), 5.51 – 5.30 (m, 1H, 1-NH), 4.80 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.75 – 4.69 (m, 2H, C*H*H PMB, H-2), 4.62 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.40 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.37 (d, *J* = 11.7 Hz, 1H, C*H*H PMB), 4.33 (d, *J* = 11.5 Hz, 1H, CH*H* PMB), 4.19 – 4.16 (m, 1H, H-1), 4.01 (dd, *J* = 2.0, 2.0 Hz, 1H, H-4), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.58 (dd, *J* = 7.9, 2.2 Hz, 1H, H-3), 3.38 (dd, *J* = 8.8, 8.8 Hz, 1H, H-6), 3.23 (dd, *J* = 8.9, 5.6 Hz, 1H, H-6), 2.11 – 1.99 (m, 1H, H-5), 1.71 (ddd, *J* = 14.7, 12.6, 4.7 Hz, 1H, H-7), 1.60 (ddd, *J* = 14.8, 4.7, 2.0 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.1 (C=O carbamate), 159.4, 159.3, 159.2, 131.1, 130.5, 130.2 ($C_{q\text{-}arom}$), 129.6, 129.6, 129.3, 114.0, 113.9, 113.7 (CH_{arom}), 82.0 (C-3), 81.0 (C-2), 74.2 (CH_2 PMB), 73.9 (C-4), 73.0, 72.4 (CH_2 PMB), 70.2 (C-6), 55.4, 55.4, 55.4 (OMe), 52.9 (C-1), 35.7 (C-5), 24.5 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{37}NNaO_8$ 586.2411; Found 586.2407.

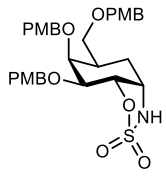
1,2-(*O*,*N*)-Carbamate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (38).



Compound **38** was prepared according to general procedure B using **35** (0.35 g, 0.50 mmol), pyridine (0.18 mL, 2.3 mmol, 4.5 eq.) and triphosgene (89 mg, 0.30 mmol, 0.60 eq.) in anhydrous DCM (1.2 mL, 0.10 M). Full conversion was observed on TLC (R_f 0.35 (EtOAc:pentane, 3:7 v:v)). The second step was performed using naphthalene (0.77 g, 6.0 mmol, 12 eq.) and Na (0.12 g, 5.0 mmol, 10 eq.) in anhydrous THF (2.4 mL, 0.05 M). Full conversion was observed on TLC (R_f 0.1 (EtOAc:pentane, 3:7 v:v)). Flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 50:50 EtOAc:pentane) yielded the title compound **38** (0.14 g, 0.24 mmol, 49%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.27 – 7.22 (m, 4H, CH_{arom}), 7.17 – 7.13 (m, 2H, CH_{arom}), 6.93 – 6.86 (m, 4H, CH_{arom}), 6.85 – 6.82 (m, 2H, CH_{arom}), 5.26 (s, 1H, 2-NH), 4.75 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.70 (d, *J* = 10.9 Hz, C*H*H PMB), 4.68 – 4.66 (m, 1H, H-1), 4.46 – 4.40 (m, 2H, C*H*H PMB, CH*H* PMB), 4.38 (d, *J* = 11.6 Hz, 1H, CH*H* PMB), 4.33 (d, *J* = 11.0 Hz, 1H, CH*H* PMB), 4.18 (dd, *J* = 1.8, 1.8 Hz, 1H, H-4), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.74 (dd, *J* = 8.7, 6.2 Hz, 1H, H-2), 3.43 (dd, *J* = 9.2, 9.2 Hz, 1H, H-6), 3.34 (dd, *J* = 8.8, 1.9 Hz, 1H, H-3), 3.30 (dd, *J* = 9.0, 5.0 Hz, 1H, H-6), 2.05 (dddd, *J* = 14.1, 9.5, 4.8, 1.5 Hz, 1H, H-5), 1.90 (dd, *J* = 14.9, 4.2 Hz,

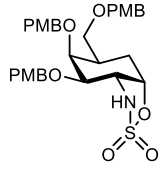
1H, H-7), 1.72 (ddd, *J* = 15.3, 13.3, 4.8 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7 (C=O carbamate), 159.7, 159.4, 159.3, 130.9, 130.2, 129.7 ($C_{q\text{-arom}}$), 129.6, 129.6, 129.5, 114.3, 114.0, 113.8 (CH_{arom}), 84.1 (C-3), 77.0 (C-1), 74.0, 72.9, 71.5 (CH_2 PMB), 71.0 (C-4), 70.0 (C-6), 55.9 (C-2), 55.4, 55.4, 55.4 (OMe), 36.3 (C-5), 24.2 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{37}NNaO_8$ 586.2411; Found 586.2406.

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



Compound **37** was prepared according to general procedure C using **34** (0.21 g, 0.31 mmol), Et_3N (0.17 mL, 1.2 mmol, 4.0 eq.) and SO_2Cl_2 (38 µL, 0.47 mmol, 1.3 eq.) in anhydrous DCM (3.1 mL, 0.10 M). Full conversion was observed on TLC (R_f 0.6 (EtOAc:pentane, 4:6 v:v)). The second step was prepared using naphthalene (0.48 g, 3.7 mmol, 12 eq.) and Na (71 mg, 3.1 mmol, 10 eq.) in anhydrous THF (6.2 mL, 0.05 M). Full conversion was observed on TLC (R_f 0.3 (EtOAc:pentane, 4:6 v:v)). Flash column chromatography (SiO_2, 20:80 EtOAc:pentane → 50:50 EtOAc:pentane) yielded the title compound **37** (64 mg, 0.11 mmol, 34%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.33 – 7.28 (m, 2H, CH_{arom}), 7.22 – 7.17 (m, 2H, CH_{arom}), 7.15 – 7.10 (m, 2H, CH_{arom}), 6.87 (m, 4H, CH_{arom}), 6.84 – 6.80 (m, 2H, CH_{arom}), 4.95 (dd, *J* = 8.8, 5.7 Hz, 1H, H-2), 4.92 (dd, *J* = 6.4, 2.8 Hz, 1H, 1-NH), 4.78 (d, *J* = 10.9 Hz, 1H, C*H*H PMB), 4.70 (d, *J* = 11.3 Hz, 1H, C*H*H PMB), 4.63 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.38 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.35 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.31 (d, *J* = 11.5 Hz, 1H, CH*H* PMB), 4.22 (dddd, *J* = 6.4, 6.4, 4.6, 1.9 Hz, 1H, H-1), 4.00 – 3.97 (m, 1H, H-4), 3.93 (dd, *J* = 8.8, 2.3 Hz, 1H, H-3), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.37 (dd, *J* = 9.0, 8.9 Hz, 1H, H-6), 3.20 (dd, *J* = 9.0, 5.9 Hz, 1H, H-6), 2.05 (dddd, *J* = 11.9, 9.6, 6.5, 3.7 Hz, 1H, H-5), 1.77 (ddd, *J* = 14.9, 12.9, 4.7 Hz, 1H, H-7), 1.62 (ddd, *J* = 15.0, 4.4, 2.1 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.4, 159.4, 159.3, 130.7, 130.2, 130.0 ($C_{q\text{-arom}}$), 129.7, 129.6, 129.5, 113.9, 113.9, 113.7 (CH_{arom}), 88.0 (C-2), 79.8 (C-3), 74.6 (C-4), 74.3, 73.0, 72.9 (CH_2 PMB), 69.9 (C-6), 55.8 (C-1), 55.4, 55.4, 55.3 (OMe), 35.5 (C-7), 24.0 (C-5); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{37}NNaO_9S$ 622.2081; Found 622.2075.

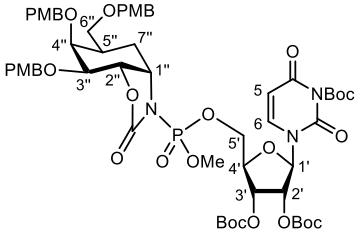
1,2-(*O*,*N*)-Sulfamidate-3,4,6-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (39).



Compound **39** was prepared according to general procedure C using **35** (0.14 g, 0.20 mmol), Et_3N (0.11 mL, 0.80 mmol, 4.0 eq.) and SO_2Cl_2 (21 µL, 0.26 mmol, 1.3 eq.) in anhydrous DCM (2.0 mL, 0.10 M). Full conversion was observed on TLC (R_f 0.6 (EtOAc:pentane, 4:6 v:v)). The second step was prepared using naphthalene (0.30 g, 2.4 mmol, 12 eq.) and sodium metal (46 mg, 2.0 mmol, 10 eq.) in anhydrous THF (4.0 mL, 0.05 M). Full conversion was observed on TLC (R_f 0.5 (EtOAc:pentane, 4:6 v:v)). Flash column chromatography (SiO_2, 20:80 EtOAc:pentane → 50:50 EtOAc:pentane) yielded the title compound **39** (67 mg, 0.11 mmol, 56%). ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.31 – 7.27 (m, 2H, CH_{arom}), 7.25 – 7.21 (m, 2H, CH_{arom}), 7.16 – 7.12 (m, 2H, CH_{arom}), 6.92 – 6.87 (m, 4H, CH_{arom}), 6.85 – 6.81 (m, 2H, CH_{arom}), 5.00 (ddd, *J* = 4.0, 4.0, 2.0 Hz, 1H, H-1), 4.79 (d, *J* = 3.3 Hz, 1H, 2-NH), 4.77 (d, *J* = 10.8 Hz, 1H, C*H*H PMB), 4.70 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.53 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.41 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.41 (d, *J* = 11.6 Hz, 1H, C*H*H PMB) 4.36 (d, *J* = 11.6 Hz,

1H, CH*H* PMB), 4.11 (dd, *J* = 1.9, 1.9 Hz, 1H, H-4), 3.90 (ddd, *J* = 9.5, 4.3, 3.2 Hz, 1H, H-2), 3.82 – 3.76 (m, 10H, H-3, OMe, OMe, OMe), 3.40 (dd, *J* = 9.0, 9.0 Hz, 1H, H-6), 3.27 (dd, *J* = 9.0, 5.4 Hz, 1H, H-6), 2.13 (dddd, *J* = 10.7, 9.2, 6.3, 6.3 Hz, 1H, H-5), 1.95 (ddd, *J* = 15.6, 4.3, 2.0 Hz, 1H, H-7), 1.79 (ddd, *J* = 15.5, 13.2, 3.8 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 159.7, 159.5), 159.4, 130.8, 130.2, 129.9 ($C_{q\text{-arom}}$), 129.7, 129.6, 129.6, 114.2, 114.0, 113.8 (CH_{arom}), 83.8 (C-1), 80.3 (C-3), 74.3, 72.9 (CH_2 PMB), 72.7 (C-4), 72.6 (CH_2 PMB), 69.7 (C-6), 60.4 (C-2), 55.4, 55.4, 55.4 (OMe), 35.8 (C-5), 24.7 (C-7); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{37}NNaO_9S$ 622.2081; Found 622.2077.

1'',2''-(*N*-(3-*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridinyl),*O*)-carbamate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (41).



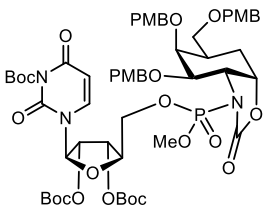
Compound **41** was prepared according to general procedure D using **36** (0.14 g, 0.24 mmol), 15-crown-5 ether (0.24 mL, 1.2 mmol, 5.0 eq.) and NaH (60 wt.% dispersion in mineral oil; 14 mg, 0.36 mmol, 1.5 eq.) in anhydrous THF (1.2 mL, 0.20 M); and **23** (0.30 g, 0.48 mmol, 2.0 eq.), DiPEA (distilled and stored over KOH; 0.17 mL, 1.0 mmol, 4.0 eq.) and $BrCCl_3$ (0.14 mL, 1.4 mmol, 6.0 eq.) in anhydrous DCM (1.6 mL, 0.30 M). Full conversion was observed on TLC (R_f 0.45 and 0.7 (EtOAc:pentane, 6:4 v:v)) and ^{31}P NMR. Flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **41** as a mixture of P(V) diastereomers (0.15 g, 0.13 mmol, 54%).

Data for first P(V) diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.64 (d, *J* = 8.3 Hz, 1H, H-6), 7.32 – 7.24 (m, 2H, CH_{arom}), 7.24 – 7.18 (m, 2H, CH_{arom}), 7.17 – 7.12 (m, 2H, CH_{arom}), 6.92 – 6.80 (m, 6H, CH_{arom}), 6.19 (d, *J* = 6.4 Hz, 1H, H-1'), 5.87 (d, *J* = 8.2 Hz, 1H, H-5), 5.32 – 5.27 (m, 1H, H-3'), 5.11 (dd, *J* = 6.4, 5.4 Hz, 1H, H-2'), 4.85 – 4.74 (m, 2H, H-2'', C*H*H PMB), 4.66 (d, *J* = 11.4 Hz, 1H, C*H*H PMB), 4.60 (d, *J* = 11.2 Hz, 1H, CH*H* PMB), 4.50 – 4.42 (m, 2H, H-1'', CH*H* PMB), 4.40 – 4.28 (m, 3H, C*H*H PMB, CH*H* PMB, H-5'), 4.27 – 4.21 (m, 2H, H-5', H4'), 4.09 – 4.05 (m, 1H, H-4''), 3.84 (s, 3H, P(O)OMe), 3.82 – 3.77 (m, 9H, OMe, OMe, OMe), 3.67 (dd, *J* = 7.3, 1.9 Hz, 1H, H-3''), 3.57 – 3.51 (m, 1H, H-6''), 3.36 – 3.29 (m, 1H, H-6''), 2.27 – 2.04 (m, 2H, H-7'', H-5''), 1.91 – 1.78 (m, 1H, H-7''), 1.61 – 1.42 (m, 9H, $C(CH_3)_3$, $C(CH_3)_3$, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.4, 159.3 ($C_{q\text{-arom}}$), 155.2 (d, *J* = 8.5 Hz, C=O cyclic carbamate), 152.2 (C=O carbamate), 152.0 (C=O uracil), 148.8, 147.6 (C=O carbonate), 139.3 (C-6), 130.9, 130.3, 130.2, 130.1 ($C_{q\text{-arom}}$), 129.6, 129.5, 129.2, 113.9, 113.9, 113.7 (CH_{arom}), 103.4 (C-5), 86.9 ($C(CH_3)_3$), 85.8 (C-1'), 83.6, 83.5 ($C(CH_3)_3$), 81.6 (C-3''), 80.9 (d, *J* = 9.5 Hz, C-2''), 80.1 (d, *J* = 8.9 Hz, C-4'), 74.6 (C-2'), 74.4 (CH_2 PMB), 74.3 (C-4''), 73.0 (CH_2 PMB), 72.3 (C-3'), 72.2 (CH_2 PMB), 70.3 (C-6''), 66.4 (d, *J* = 5.3 Hz, C-5'), 56.9 (d, *J* = 4.7 Hz, C-1''), 55.4, 55.4, 55.3 (OMe), 55.0 (d, *J* = 5.8 Hz, P(O)OMe), 35.9 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$), 24.4 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ -0.83.

Data for second P(V) diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.73 (d, *J* = 8.3 Hz, 1H, H-6), 7.32 – 7.24 (m, 2H, CH_{arom}), 7.24 – 7.18 (m, 2H, CH_{arom}), 7.17 – 7.12 (m, 2H, CH_{arom}), 6.92 – 6.80 (m, 6H, CH_{arom}), 6.15 (d, *J* = 5.8 Hz, 1H, H-1'), 5.89 (d, *J* = 8.2 Hz, 1H, H-5), 5.32 – 5.27

(m, 1H, H-3'), 5.16 (dd, *J* = 5.6 Hz, 1H, H-2'), 4.85 – 4.74 (m, 2H, H-2'', C*H*H PMB), 4.68 (d, *J* = 11.2 Hz, 1H, C*H*H PMB), 4.60 (d, *J* = 11.5 Hz, 1H, CH*H* PMB), 4.50 – 4.42 (m, 3H, H-1'', H-5', CH*H* PMB), 4.40 – 4.28 (m, 4H, H-5', C*H*H PMB, CH*H* PMB, H-4'), 4.09 – 4.05 (m, 1H, H-4''), 3.86 (s, 3H, P(O)OMe), 3.82 – 3.77 (m, 9H, OMe, OMe, OMe), 3.57 – 3.51 (m, 1H, H-3'') 3.48 (dd, J = 8.9, 8.9 Hz, 1H, H-6''), 3.36 – 3.29 (m, 1H, H-6''), 2.27 – 2.04 (m, 2H, H-7'', H-5''), 1.91 – 1.78 (m, 1H, H-7''), 1.61 – 1.42 (m, 9H, $C(CH_3)_3$, $C(CH_3)_3$, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 155.5 (d, *J* = 4.4 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), 130.8, 130.2, 129.9 ($C_{q\text{-}arom}$), 129.6, 129.6, 129.3, 114.0, 113.9, 113.8 (CH_{arom}), 103.3 (C-5), 86.9 ($C(CH_3)_3$), 86.3 (C-1'), 83.7, 83.7 ($C(CH_3)_3$), 81.0 (C-3''), 80.8 (d, *J* = 9.7 Hz, C-2''), 80.0 (d, *J* = 7.9 Hz, C-4'), 74.7 (C-2'), 74.4 (CH_2 PMB), 73.9 (C-4''), 73.1, 72.0 (CH_2 PMB), 71.8 (C-3'), 69.9 (C-6''), 66.9 (d, *J* = 6.1 Hz, C-5'), 56.8 (d, *J* = 4.4 Hz, C-1''), 55.4, 55.4, 55.3 (OMe), 54.8 (d, *J* = 5.8 Hz, P(O)OMe), 36.0 (C-5''), 27.8, 27.7, 27.7 ($C(CH_3)_3$), 24.4 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ -1.65; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{57}H_{74}N_3NaO_{22}P$ 1206.4394; Found 1206.4383.

1'',2''-(*O*,*N*-(*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridinyl))-carbamate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (43).



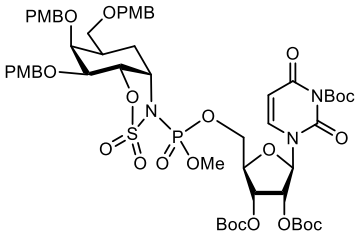
Compound **43** was prepared according to general procedure D using **37** (39 mg, 69 µmol), 15-crown-5 ether (69 µL, 0.35 mmol, 5.0 eq.) and NaH (60 wt.% dispersion in mineral oil; 8.3 mg, 0.21 mmol, 3.0 eq.) in anhydrous THF (0.35 mL, 0.20 M); and **23** (0.13 g, 0.21 mmol, 3.0 eq.) DiPEA (distilled and stored over KOH; 48 µL, 0.28 mmol, 4.0 eq.) and $BrCCl_3$ (41 µL, 0.42 mmol, 6.0 eq.) in anhydrous DCM (0.72 mL, 0.30 M). Full conversion was observed on TLC (R_f 0.6 (EtOAc:pentane, 6:4 v:v)) and ^{31}P NMR. Flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **43** as a mixture of P(V) diastereomers (42 mg, 36 µmol, 42%).

Data for first P(V) diastereomer: ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.65 (d, *J* = 8.3 Hz, 1H, H-6), 7.42 – 7.35 (m, 2H, CH_{arom}), 7.25 – 7.19 (m, 2H, CH_{arom}), 7.14 – 7.08 (m, 2H, CH_{arom}), 6.90 – 6.85 (m, 4H, CH_{arom}), 6.83 – 6.78 (m, 2H, CH_{arom}), 6.13 – 6.08 (m, 1H, H-1'), 5.82 (d, *J* = 8.3 Hz, 1H, H-5), 5.20 – 5.13 (m, 1H, H-3'), 5.11 (dd, *J* = 5.5, 5.5 Hz, 1H, H-2'), 4.83 – 4.71 (m, 3H, H-1'', C*H*H PMB, C*H*H PMB), 4.54 – 4.47 (m, 1H, CH*H* PMB), 4.43 – 4.31 (m, 4H, H-2'', C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.30 – 4.24 (m, 1H, H-5'), 4.19 – 4.16 (m, 3H, H-4'', H-4', H-5'), 3.81 – 3.69 (m, 12H, OMe, OMe, OMe, P(O)OMe), 3.50 – 3.44 (m, 1H, H-3''), 3.43 – 3.34 (m, 1H, H-6''), 3.31 – 3.24 (m, 1H, H-6''), 2.11 – 1.99 (m, 1H, H-5''), 1.97 – 1.87 (m, 1H, H-7''), 1.80 – 1.75 (m, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.3, 159.3($C_{q\text{-}arom}$), 155.7 (d, *J* = 8.6 Hz, C=O cyclic carbamate), 152.1 (C=O carbamate), 151.9 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.3 (C-6), 130.8, 130.2, 129.7 ($C_{q\text{-}arom}$), 129.6, 129.6, 129.4, 114.0, 113.9, 113.7 (CH_{arom}), 103.1 (C-5), 86.9 ($C(CH_3)_3$), 86.5 (C-1'), 83.7, 83.6 ($C(CH_3)_3$), 83.3 (C-3''), 80.1 (d, *J* = 8.4 Hz, C-4'), 78.4 (d, *J* = 7.9 Hz, C-2''), 74.8 (C-2'), 74.1, 72.9 (CH_2 PMB), 71.9 (C-3'), 71.4 (CH_2 PMB), 71.1 (C-4''), 69.8 (C-6''), 66.8 (d, *J* = 5.2 Hz, C-5'), 61.0 (d, *J*

= 2.7 Hz, C-1''), 55.4, 55.4, 55.4 (OMe), 55.2 (d, *J* = 5.5 Hz, P(O)OMe), 35.9 (C-5''), 27.7, 27.7, 27.5 (C(*C*H$_3$)$_3$), 24.1 (C-7''); ^{31}P NMR (202 MHz, CDCl$_3$): δ -0.78.

Data for second P(V) diastereomer: ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HSQC): δ 7.55 (d, *J* = 8.3 Hz, 1H, H-6), 7.42 – 7.35 (m, 2H, CH$_{arom}$), 7.25 – 7.19 (m, 2H, CH$_{arom}$), 7.14 – 7.08 (m, 2H, CH$_{arom}$), 6.90 – 6.85 (m, 4H, CH$_{arom}$), 6.83 – 6.78 (m, 2H, CH$_{arom}$), 6.13 – 6.08 (m, 1H, H-1'), 5.79 (d, *J* = 8.2 Hz, 1H, H-5), 5.23 (dd, *J* = 5.5, 4.4 Hz, 1H, H-3'), 5.20 – 5.13 (m, 1H, H-2'), 4.83 – 4.71 (m, 3H, H-1'', C*H*H PMB, C*H*H PMB), 4.54 – 4.47 (m, 1H, CH*H* PMB), 4.43 – 4.31 (m, 3H, C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.30 – 4.24 (m, 3H, H-2'', H-5'), 4.24 – 4.19 (m, 2H, H-4', H-4''), 3.81 – 3.69 (m, 12H, OMe, OMe, OMe, P(O)OMe), 3.50 – 3.44 (m, 1H, H-3''), 3.43 – 3.34 (m, 1H, H-6''), 3.31 – 3.24 (m, 1H, H-6''), 2.11 – 1.99 (m, 1H, H-5''), 1.97 – 1.87 (m, 1H, H-7''), 1.80 – 1.75 (m, 1H, H-7''), 1.58 (s, 9H, C(CH$_3$)$_3$), 1.46 (s, 9H, C(CH$_3$)$_3$), 1.44 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (126 MHz, CDCl$_3$, HSQC): δ 160.2 (C=O uracil), 159.4, 159.3, 159.3(C$_{q\text{-}arom}$), 155.8 (d, *J* = 8.6 Hz, C=O cyclic carbamate), 152.2 (C=O carbamate), 152.1 (C=O uracil), 148.6, 147.6 (C=O carbonate), 139.4 (C-6), 130.9, 130.2, 129.9 (C$_{q\text{-}arom}$), 129.5, 129.4, 129.0, 114.0, 113.9, 113.8 (CH$_{arom}$), 103.1 (C-5), 87.0 (*C*(CH$_3$)$_3$), 86.7 (C-1'), 83.8, 83.6 (*C*(CH$_3$)$_3$), 83.5 (C-3''), 80.0 (d, *J* = 7.2 Hz, C-4'), 78.3 (d, *J* = 7.9 Hz, C-2''), 74.8 (C-2'), 74.0, 72.9 (CH$_2$ PMB), 72.0 (C-3'), 71.3 (CH$_2$ PMB), 70.8 (C-4''), 69.9 (C-6''), 66.2 (d, *J* = 4.8 Hz, C-5'), 60.9 (d, *J* = 3.4 Hz, C-1''), 55.4 (d, *J* = 5.8 Hz, P(O)OMe), 55.4, 55.4, 55.3 (OMe), 35.8 (C-5''), 27.7, 27.7, 27.5 (C(*C*H$_3$)$_3$), 24.1 (C-7''); ^{31}P NMR (202 MHz, CDCl$_3$): δ -0.38; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for $C_{57}H_{74}N_3NaO_{22}P$ 1206.4394; Found 1206.4380.

1'',2''-(*N*-(*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*-(*tert*-butoxycarbonyl)uridinyl),*O*)-sulfamidate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (42).

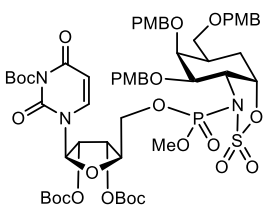


Compound **42** was prepared according to general procedure D using **38** (64 mg, 0.11 mmol), 15-crown-5 ether (0.11 mL, 0.55 mmol, 5.0 eq.) and NaH (60 wt.% dispersion in mineral oil; 6.8 mg, 0.17 mmol, 1.5 eq.) in anhydrous THF (0.55 mL, 0.20 M); and **23** (0.14 g, 0.22 mmol, 2.0 eq.) DiPEA (distilled and stored over KOH; 77 µL, 0.44 mmol, 4.0 eq.) and BrCCl$_3$ (65 µL, 0.66 mmol, 6.0 eq.) in anhydrous DCM (0.73 mL, 0.30 M). Full conversion was observed on TLC (R$_f$ 0.6 (EtOAc:pentane, 6:4 v:v)) and ^{31}P NMR. Flash column chromatography (SiO$_2$, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **42** as a mixture of P(V) diastereomers (36 mg, 30 µmol, 27%).

Data for first P(V) diastereomer: ^{1}H NMR (600 MHz, CDCl$_3$, HH-COSY, HSQC): δ 7.54 (d, *J* = 8.3 Hz, 1H, H-6), 7.32 – 7.25 (m, 2H, CH$_{arom}$), 7.21 – 7.12 (m, 4H, CH$_{arom}$), 6.92 – 6.81 (m, 6H, CH$_{arom}$), 6.22 (d, *J* = 7.4 Hz, 1H, H-1'), 5.87 (d, *J* = 8.3 Hz, 1H, H-5), 5.45 (dd, *J* = 5.1, 2.5 Hz, 1H, H-3'), 5.13 – 5.09 (m, 1H, H-2'), 5.05 – 4.99 (m, 1H, H-2''), 4.80 (d, *J* = 11.0 Hz, 1H, C*H*H PMB), 4.73 – 4.62 (m, 3H, H-1'', C*H*H PMB, CH*H* PMB), 4.46 (d, *J* = 10.9 Hz, 1H, CH*H* PMB), 4.34 – 4.29 (m, 1H, C*H*H PMB), 4.29 – 4.23 (m, 2H, H-3'', CH*H* PMB), 4.14 – 4.05 (m, 2H, H-4'', H-5'), 4.04 – 3.99 (m, 1H, H-4'), 3.98 – 3.87 (m, 1H, H-5'), 3.97 (d, *J* = 11.7 Hz, 3H, P(O)OMe), 3.83 – 3.78 (m, 9H, OMe, OMe, OMe), 3.57 (dd, *J* = 8.4, 5.6 Hz, 1H, H-6''), 3.35 (dd, *J* = 8.6, 8.6 Hz, 1H, H-6''), 2.52 (ddd, *J* = 15.7, 3.5, 3.5 Hz,

1H, H-7''), 2.30 – 2.16 (m, 1H, H-5''), 1.94 (ddd, *J* = 16.1, 12.2, 4.2 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.53 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (151 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 152.2 (C=O carbamate), 152.2 (C=O uracil), 148.9, 147.7 (C=O carbonate), 139.3 (C-6), 130.6), 130.2, 130.2 ($C_{q\text{-}arom}$), 129.8, 129.7, 129.2, 113.9, 113.9, 113.8 (CH_{arom}), 103.6 (C-5), 87.0 ($C(CH_3)_3$), 86.2 (d, *J* = 9.1 Hz, C-2''), 84.7 (C-1'), 83.5, 83.4 ($C(CH_3)_3$), 79.8 (d, *J* = 7.9 Hz, C-4'), 79.5 (C-3''), 75.4 (C-4''), 74.3 (CH_2 PMB), 74.0 (C-2'), 73.2, 73.0 (CH_2 PMB), 72.4 (C-3'), 70.9 (C-6''), 66.5 (d, *J* = 4.5 Hz, C-5'), 60.6 (d, *J* = 4.1 Hz, C-1''), 57.0 (d, *J* = 5.5 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 36.1 (C-5''), 27.9, 27.8, 27.5 ($C(CH_3)_3$), 24.1 (C-7''); ^{31}P NMR (121 MHz, $CDCl_3$): δ -1.69. Data for second P(V) diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.66 (d, *J* = 8.3 Hz, 1H, H-6), 7.32 – 7.25 (m, 2H, CH_{arom}), 7.21 – 7.12 (m, 4H, CH_{arom}), 6.92 – 6.81 (m, 6H, CH_{arom}), 6.15 (d, *J* = 6.1 Hz, 1H, H-1'), 5.87 (d, *J* = 8.3 Hz, 1H, H-5), 5.31 (dd, *J* = 5.4, 4.0 Hz, 1H, H-3'), 5.13 – 5.09 (m, 1H, H-2'), 5.05 – 4.99 (m, 1H, H-2''), 4.79 (d, *J* = 10.7 Hz, 1H, C*H*H PMB), 4.73 – 4.62 (m, 2H, C*H*H PMB, CH*H* PMB), 4.52 (ddd, *J* = 4.4, 4.1, 4.1 Hz, 1H, H-1''), 4.42 (m, 2H, CH*H* PMB, H-5'), 4.36 (d, *J* = 11.1 Hz, 1H, C*H*H PMB), 4.34 – 4.29 (m, 1H, H-5'), 4.29 – 4.23 (m, 2H, H-4', CH*H* PMB), 4.14 – 4.05 (m, 2H, H-3'', H-4''), 3.92 (d, *J* = 11.8 Hz, 3H, P(O)OMe), 3.83 – 3.78 (m, 9H, OMe, OMe, OMe), 3.44 (dd, *J* = 8.2, 8.2 Hz, 1H, H-6''), 3.30 (dd, *J* = 8.7, 6.6 Hz, 1H, H-6''), 2.30 – 2.16 (m, 2H, H-7'', H-5''), 1.85 (ddd, *J* = 15.4, 11.6, 4.2 Hz, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (151 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.4, 159.3 ($C_{q\text{-}arom}$), 152.1 (C=O carbamate), 152.0 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.3 (C-6), 130.6, 130.2, 130.0 ($C_{q\text{-}arom}$), 129.7, 129.7, 129.5, 114.0, 113.9, 113.8 (CH_{arom}), 103.4 (C-5), 86.9 ($C(CH_3)_3$), 86.0 (C-1'), 85.8 (d, *J* = 9.7 Hz, C-2''), 83.7, 83.7 ($C(CH_3)_3$), 79.8 (d, *J* = 7.9 Hz, C-4'), 79.0 (C-3''), 74.6 (C-4''), 74.6 (C-2'), 74.5, 73.1, 73.0 (CH_2 PMB), 71.7 (C-3'), 69.9 (C-6''), 67.1 (d, *J* = 5.5 Hz, C-5'), 60.1 (d, J = 2.8 Hz, C-1''), 55.9 (d, *J* = 5.7 Hz, P(O)OMe), 55.4, 55.4, 55.4 (OMe), 35.7 (C-5''), 27.8, 27.7, 27.5 ($C(CH_3)_3$), 24.0 (C-7''); ^{31}P NMR (121 MHz, $CDCl_3$): δ -2.50; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{56}H_{74}N_3NaO_{23}PS$ 1242.4064; Found 1242.4057.

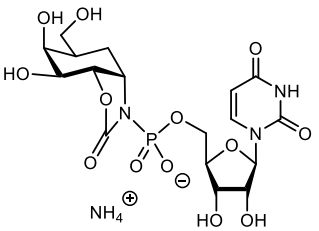
1'',2''-(*O*,*N*-(*N*-(*Tert*-butoxycarbonyl)-5'-*O*-(methylphosphinyl)-2',3'-di-*O*(*tert*-butoxycarbonyl)uridinyl))-sulfamidate-3'',4'',6''-tri-*O*-(4-methoxybenzyl)-carba-α-D-galactopyranoside (44).



Compound **44** was prepared according to general procedure D using **39** (67 mg, 0.11 mmol), 15-crown-5 ether (0.11 mL, 0.55 mmol, 5.0 eq.) and NaH (60 wt.% dispersion in mineral oil; 6.6 mg, 0.17 mmol, 1.5 eq.) in anhydrous THF (0.55 mL, 0.20 M); and **23** (0.14 g, 0.22 mmol, 2.0 eq.) DiPEA (distilled and stored over KOH; 77 µL, 0.44 mmol, 4.0 eq.) and $BrCCl_3$ (65 µL, 0.66 mmol, 6.0 eq.) in anhydrous DCM (0.73 mL, 0.30 M). Full conversion was observed on TLC (R_f 0.6 (EtOAc:pentane, 6:4 v:v)) and ^{31}P NMR. Flash column chromatography (SiO_2, 30:70 EtOAc:pentane → 70:30 EtOAc:pentane) and Sephadex™ LH-20 size exclusion chromatography yielded the title compound **44** as a mixture of P(V) diastereomers (44 mg, 36 µmol, 33%).
Data for first P(V) diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.58 (d, *J* = 8.3 Hz, 1H, H-6), 7.42 – 7.37 (m, 2H, CH_{arom}), 7.23 – 7.17 (m, 2H, CH_{arom}), 7.15 – 7.07 (m, 2H, CH_{arom}), 6.92 – 6.85 (m, 4H, CH_{arom}), 6.84 – 6.77 (m, 2H, CH_{arom}), 6.16 (d, *J* = 5.9 Hz, 1H, H-1'), 5.81 (d, *J* = 8.2 Hz, 1H, H-5), 5.31 – 5.24 (m, 2H, H-3', H-1''), 5.20 – 5.12 (m, 1H, H-2'), 4.81 – 4.71 (m, 2H, C*H*H PMB,

C*H*H PMB), 4.62 (d, *J* = 11.3 Hz, 1H, CH*H* PMB), 4.59 – 4.52 (m, 2H, H-2'', CH*H* PMB), 4.47 – 4.29 (m, 6H, H-5', H-5', H-4', C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.18 – 4.11 (m, 1H, H-4''), 3.96 – 3.85 (m, 1H, H-3''), 3.80 – 3.74 (m, 12H, OMe, OMe, OMe, P(O)OMe), 3.41 – 3.33 (m, 1H, H-6''), 3.29 – 3.23 (m, 1H, H-6''), 2.17 – 2.08 (m, 1H, H-5''), 2.01 – 1.93 (m, 1H, H-7''), 1.90 – 1.81 (m, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.3, 159.3 ($C_{q\text{-}arom}$), 152.1 (C=O carbamate), 152.1 (C=O uracil), 148.6, 147.6 (C=O carbonate), 139.3 (C-6), 130.7, 130.1, 130.0 ($C_{q\text{-}arom}$), 129.8, 129.5, 128.8, 114.0, 114.0, 113.9 (CH_{arom}), 103.2 (C-5), 86.9 ($C(CH_3)_3$), 86.1 (C-1'), 85.0 (d, *J* = 4.4 Hz, C-2''), 83.8, 83.7 ($C(CH_3)_3$), 80.5 (C-3''), 79.8 (C-4'), 74.8 (C-2'), 74.2, 72.9 (CH_2 PMB), 72.2 (C-4''), 72.1 (CH_2 PMB), 71.7 (C-3'), 69.6 (C-6''), 66.5 (d, *J* = 5.4 Hz, C-5'), 64.6 (d, *J* = 1.4 Hz, C-1''), 55.5 (d, *J* = 5.8 Hz, P(O)OMe), 55.4, 55.4 (OMe), 35.6 (C-5''), 27.7, 27.7, 27.5 ($C(CH_3)_3$, 24.8 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ -1.25. Data for second P(V) diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC): δ 7.61 (d, *J* = 8.3 Hz, 1H, H-6), 7.37 – 7.31 (m, 2H, CH_{arom}), 7.23 – 7.17 (m, 2H, CH_{arom}), 7.15 – 7.07 (m, 2H, CH_{arom}), 6.92 – 6.85 (m, 4H, CH_{arom}), 6.84 – 6.77 (m, 2H, CH_{arom}), 6.14 (d, *J* = 5.9 Hz, 1H, H-1'), 5.85 (d, *J* = 8.2 Hz, 1H, H-5), 5.20 – 5.12 (m, 2H, H-3', H-1''), 5.06 (dd, *J* = 5.7, 5.7 Hz, 1H, H-2'), 4.81 – 4.71 (m, 2H, C*H*H PMB, C*H*H PMB), 4.47 – 4.29 (m, 4H, H-2'', C*H*H PMB, CH*H* PMB, CH*H* PMB), 4.27 – 4.20 (m, 1H, H-5'), 4.18 – 4.11 (m, 3H, H-4'', H-4', H-5'), 3.96 – 3.85 (m, 1H, H-3''), 3.80 – 3.74 (m, 12H, OMe, OMe, OMe, P(O)OMe), 3.41 – 3.33 (m, 1H, H-6''), 3.29 – 3.23 (m, 1H, H-6''), 2.17 – 2.08 (m, 1H, H-5''), 2.01 – 1.93 (m, 1H, H-7''), 1.90 – 1.81 (m, 1H, H-7''), 1.59 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, HSQC): δ 160.3 (C=O uracil), 159.4, 159.4, 159.3 ($C_{q\text{-}arom}$), 152.1 (C=O carbamate), 151.9 (C=O uracil), 148.7, 147.7 (C=O carbonate), 139.3 (C-6), 130.6, 130.1, 129.7 ($C_{q\text{-}arom}$), 129.6, 129.5, 129.0, 114.0, 113.8, 113.7 (CH_{arom}), 103.4 (C-5), 86.9 ($C(CH_3)_3$), 85.9 (C-1'), 84.3 (d, *J* = 4.8 Hz, C-1''), 83.7, 83.6 ($C(CH_3)_3$), 80.4 (C-3''), 79.7 (d, *J* = 1.7 Hz, C-4'), 74.7 (C-2'), 74.3, 72.9 (CH_2 PMB), 72.2 (C-4''), 71.8 (C-3'), 71.8 (CH_2 PMB), 69.5 (C-6''), 66.5 (d, *J* = 6.0 Hz, C-5'), 64.5 (d, *J* = 2.4 Hz, C-2''), 55.78 (d, *J* = 5.8 Hz, P(O)OMe), 55.4, 55.3 (OMe), 35.6 (C-5''), 27.7, 27.5, 27.5 C($CH_3)_3$), 24.8 (C-7''); ^{31}P NMR (202 MHz, $CDCl_3$): δ -1.88; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{56}H_{74}N_3NaO_{23}PS$ 1242.4064; Found 1242.4051.

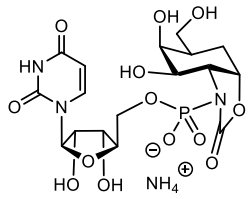
1'',2''-(*N*-(5'-*O*-Phosphoryluridinyl),*O*)-carbamate-carba-α-D-galactopyranoside (6).



Compound **6** was prepared according to general procedure E using **41** (77 mg, 65 µmol), TES (0.10 mL, 0.65 mmol, 10 eq.) and TFA (0.56 mL, 7.2 mmol, 30% v:v) in DCM (1.3 mL, 0.05 M). The reaction mixture was stirred overnight at 0°C, before full conversion was observed on TLC and pyridine (12 mL, 0.15 mol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at 35°C, before full conversion was observed on TLC (R_f 0.5 (H_2O:ACN, 2:8 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 15:85 H_2O:ACN), NH_4^+-Dowex® 50WX4 ion exchange and lyophilization yielded the title compound **6** (10 mg, 19 µmol, 30%). ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC): δ 7.94 (d, *J* = 8.1 Hz, 1H, H-6), 5.92 (d, *J* = 4.7 Hz, 1H, H-1'), 5.89 (d, *J* = 8.1 Hz, 1H, H-5), 4.59 – 4.56 (m, 1H, H-2''), 4.41 (ddd, *J* = 7.7, 4.1, 4.1 Hz, 1H, H-1''), 4.32 (dd, *J* = 5.0, 5.0 Hz, 1H, H-2'), 4.28 (dd, *J* = 5.0, 5.0 Hz, 1H, H-3'), 4.25 – 4.21 (m, 1H, H-4'), 4.19 – 4.11 (m, 2H, H-5'), 4.07 (dd, *J* = 2.6, 2.6 Hz, 1H, H-4''), 3.73 (dd, *J* = 8.0, 2.8 Hz, 1H, H-3''), 3.59 (dd, *J* = 11.1, 8.2 Hz, 1H, H-

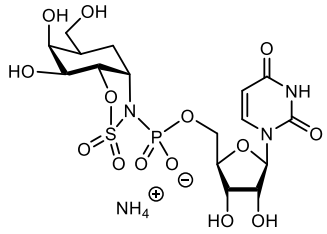
6''), 3.50 (dd, *J* = 11.1, 6.1 Hz, 1H, H-6''), 2.37 (ddd, *J* = 15.4, 4.2, 4.2 Hz, 1H, H-7''), 1.94 (dddd, *J* = 14.9, 10.8, 5.5, 2.3 Hz, 1H, H-5''), 1.67 (ddd, *J* = 15.9, 11.6, 4.8 Hz, 1H, H-7''); ^{13}C NMR (151 MHz, D_2O, HSQC): δ 167.2 (C=O uracil), 160.1 (d, *J* = 8.2 Hz, C=O carbamate), 152.7 (C=O uracil), 142.8 (C-6), 103.3 (C-5), 89.7 (C-1'), 83.8 (d, *J* = 9.0 Hz, C-4'), 80.2 (d, *J* = 8.3 Hz, C-2''), 74.7 (C-2'), 73.8 (C-3''), 70.4 (C-3'), 69.6 (C-4''), 65.6 (d, *J* = 3.1 Hz, C-5'), 62.8 (C-6''), 58.0 (d, *J* = 9.7 Hz, C-1''), 37.5 (C-5''), 23.1 (C-7''); ^{31}P NMR (121 MHz, D_2O): δ -5.07; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}N_3NaO_{13}P$ 527.1385; Found 527.1381.

1'',2''-(*O*,*N*-(5'-*O*-Phosphoryluridinyl))-carbamate-carba-α-D-galactopyranoside (8).



Compound **8** was prepared according to general procedure E using **43** (35 mg, 30 µmol), TES (48 µL, 0.30 mmol, 10 eq.) and TFA (0.26 mL, 3.3 mmol, 30% v:v) in DCM (0.60 mL, 0.05 M). The reaction mixture was stirred overnight at 0°C, before full conversion was observed on TLC and pyridine (5.4 mL, 67 mmol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at 35°C, before full conversion was observed on TLC (R_f 0.5 (H_2O:ACN, 2:8 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 15:85 H_2O:ACN), NH_4^+-Dowex® 50WX4 ion exchange and lyophilization yielded the title compound **8** (8.5 mg, 16 µmol, 54%). ^{1}H NMR (500 MHz, D_2O,HH-COSY, HSQC): δ 7.96 (d, *J* = 8.1 Hz, 1H, H-6), 5.98 (d, *J* = 4.9 Hz, 1H, H-1'), 5.96 (d, *J* = 8.1 Hz, 1H, H-5), 4.92 (ddd, *J* = 6.2, 4.3, 1.8 Hz, 1H, H-1''), 4.39 (dd, *J* = 5.1, 5.1 Hz, 1H, H-2'), 4.34 (dd, *J* = 5.0, 5.0 Hz, 1H, H-3'), 4.30 – 4.27 (m, 1H, H-4'), 4.27 – 4.20 (m, 2H, H-5'), 4.09 (ddd, *J* = 8.2, 6.4, 1.6 Hz, 1H, H-2''), 4.07 – 4.06 (m, 2H, H-4''), 3.77 (dd, *J* = 8.4, 2.7 Hz, 1H, H-3''), 3.68 (dd, *J* = 11.1, 7.6 Hz, 1H, H-6''), 3.59 (dd, *J* = 11.1, 6.4 Hz, 1H, H-6''), 2.06 (dd, *J* = 15.5, 4.2 Hz, 1H, H-7''), 2.00 – 1.92 (m, 1H, H-5''), 1.77 (ddd, *J* = 15.5, 13.2, 4.4 Hz, 1H, H-7''); ^{13}C NMR (126 MHz, D_2O, HSQC): δ 166.3 (C=O uracil), 158.5 (d, *J* = 8.2 Hz, C=O carbamate), 151.8 (C=O uracil), 141.9 (C-6), 102.6 (C-5), 88.9 (C-1'), 83.0 (d, *J* = 9.1 Hz, C-4'), 77.6 (d, *J* = 6.8 Hz, C-1''), 75.2 (C-3''), 73.7 (C-2'), 69.7 (C-3'), 68.1 (C-4''), 65.1 (d, *J* = 5.6 Hz, C-5') 62.4 (C-6''), 61.4 (d, *J* = 3.3 Hz, C-2''), 36.3 (C-5''), 22.6 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ -4.51; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}N_3NaO_{13}P$ 527.1385; Found 527.1382.

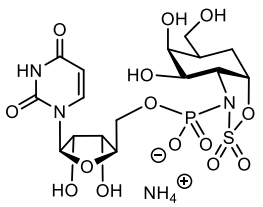
1'',2''-(*N*-(5'-*O*-Phosphoryluridinyl),*O*)-sulfamidate-carba-α-D-galactopyranoside (5).



Compound **5** was prepared according to general procedure E using **42** (36 mg, 30 µmol), TES (48 µL, 0.30 mmol, 10 eq.) and TFA (0.26 mL, 3.3 mmol, 30% v:v) in DCM (0.60 mL, 0.05 M). The reaction mixture was stirred for 3 h at 0°C, before full conversion was observed on TLC (R_f 0.1 (MeOH:DCM, 2:8 v:v)) and pyridine (5.4 mL, 67 mmol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at room temperature, before full conversion was observed on TLC (R_f 0.7 (H_2O:ACN, 2:8 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 15:85 H_2O:ACN), NH_4^+-Dowex® 50WX4 ion exchange and lyophilization yielded the title compound **5** (9.2 mg, 16 µmol, 55%). ^{1}H NMR (600 MHz, D_2O, HH-COSY, HSQC): δ 7.88 (d, *J* = 8.1 Hz, 1H, H-6), 5.93 (d, *J* = 4.5 Hz, 1H, H-1'), 5.91 (d, *J* = 8.1 Hz, 1H, H-5), 4.84 (dd, *J* = 8.1, 5.4 Hz, 1H, H-2''), 4.50 (ddd,

J = 6.0, 2.6, 2.6 Hz, 1H, H-1''), 4.33 (dd, *J* = 4.9, 4.9 Hz, 1H, H-2'), 4.29 (dd, *J* = 5.0, 5.0 Hz, 1H, H-3'), 4.26 – 4.21 (m, 3H, H-4', H-5'), 4.16 – 4.11 (m, 1H, H-4''), 4.12 (d, *J* = 2.9 Hz, 1H, H-3''), 3.54 (dd, *J* = 11.1, 8.7 Hz, 1H, H-6''), 3.44 (dd, *J* = 11.1, 5.5 Hz, 1H, H-6''), 2.19 (ddd, *J* = 15.6, 3.2, 3.2 Hz, 1H, H-7''), 1.99 (ddddd, *J* = 10.1, 7.5, 4.3, 4.3, 4.1 Hz, 1H, H-5''), 1.72 (ddd, *J* = 16.5, 13.0, 4.2 Hz, 1H, H-7''); ^{13}C NMR (151 MHz, D_2O, HSQC): δ 167.1, 152.6 (C=O uracil), 142.6 (C-6), 103.4 (C-5), 89.9 (C-1'), 85.8 (d, *J* = 8.5 Hz, C-2''), 83.5 (d, *J* = 8.6 Hz, C-4'), 74.5 (C-2'), 71.6 (C-3''), 70.2 (C-3'), 69.9 (C-4''), 65.9 (d, *J* = 5.6 Hz, C-5'), 62.4 (C-6''), 59.9 (d, *J* = 1.4 Hz, C-1''), 37.4 (C-5''), 23.3 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ -6.88; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{24}N_3NaO_{14}PS$ 563.1055; Found 563.1049.

1'',2''-(*O*,*N*-(5'-*O*-Phosphoryluridinyl))-sulfamidate-carba-α-D-galactopyranoside (7).



Compound **7** was prepared according to general procedure E using **44** (44 mg, 36 µmol), TES (58 µL, 0.36 mmol, 10 eq.) and TFA (0.31 mL, 4.0 mmol, 30% v:v) in DCM (0.72 mL, 0.05 M). The reaction mixture was stirred for 3 h at 0°C, before full conversion was observed on TLC and pyridine (6.4 mL, 80 mmol, 20:1 pyridine:TFA) was added. The reaction mixture was stirred overnight at room temperature, before full conversion was observed on TLC (R_f 0.6 (H_2O:ACN, 2:8 v:v)) and ^{31}P NMR. Flash column chromatography (neutralized SiO_2, dry loading on Celite, 0:100 H_2O:ACN → 15:85 H_2O:ACN), NH_4^+-Dowex® 50WX4 ion exchange and lyophilization yielded the title compound **7** (4.5 mg, 8.0 µmol, 22%). ^{1}H NMR (850 MHz, D_2O, HH-COSY, HSQC): δ 7.86 (d, *J* = 8.1 Hz, 1H, H-6), 5.94 (m, 2H, H-5, H-1'), 5.24 (ddd, *J* = 3.9, 3.9, 2.1 Hz, 1H, H-1''), 4.36 (dd, *J* = 5.4, 4.6 Hz, 1H, H-2'), 4.34 (dd, *J* = 5.1, 5.1 Hz, 1H, H-3'), 4.32 – 4.29 (m, H-5'), 4.26 – 4.24 (m, 1H, H-4'), 4.24 – 4.20 (m, 1H, H-5'), 4.07 (d, *J* = 2.4 Hz, 1H, H-4''), 4.06 – 4.03 (m, 1H, H-2''), 3.97 (dd, *J* = 9.0, 2.7 Hz, 1H, H-3''), 3.64 (dd, *J* = 11.1, 7.6 Hz, 1H, H-6''), 3.54 (dd, *J* = 11.1, 6.5 Hz, 1H, H-6''), 2.10 (ddd, *J* = 16.0, 3.2, 3.2 Hz, 1H, H-7''), 2.04 – 1.98 (m, 1H, H-5''), 1.80 (ddd, *J* = 15.9, 13.3, 3.6 Hz, 1H, H-7''); ^{13}C NMR (214 MHz, D_2O, HSQC): δ 166.8, 152.3 (C=O uracil), 142.2 (C-6), 103.3 (C-5), 89.5 (C-1'), 83.5 (d, *J* = 5.3 Hz, C-1''), 83.2 (d, *J* = 9.1 Hz, C-4'), 74.1 (C-2'), 73.7 (C-3''), 70.0 (C-3'), 68.8 (C-4''), 65.6 (d, *J* = 5.7 Hz, C-5'), 64.8 (C-2''), 62.7 (C-6''), 36.6 (C-5''), 23.7 (C-7''); ^{31}P NMR (202 MHz, D_2O): δ -6.51; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{24}N_3NaO_{14}PS$ 563.1055; Found 563.1050.

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