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Expedient Synthesis of L-Heptose Derived Septacidin Building Blocks from L-Glucose

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Highlights

- We present a successful synthesis of *L/D-glycero-L-glucoheptoside* building blocks derived from L-glucose.
- Key reaction steps involve carbon homologation, encompassing the oxidation of C6-OH, followed by methylenation wherein the C4-moiety exhibits notable influence.
- Three distinct groups (N₃, OPMB, and OBn) were investigated. The observed order of methylenation yields was OBn > OPMB > N₃.

Abstract

Bacterial natural products containing heptosides such as septacidin represent interesting scaffolds for the development of drugs to combat antimicrobial resistance. However, very few synthetic strategies have been reported to grant access to these derivatives. Here, we have devised a synthetic pathway to *L-glycero-L-glucoheptoside*, a key building block *en route* to septacidin, directly from L-glucose. Importantly, we show that carbon homologation at C6, encompassing oxidation of the C6-OH followed by methylenation, is significantly influenced by the nature of the C4-moiety. In order to observe the effect of various patterns, namely azide (N₃), *p*-methoxybenzyloxy (OPMB), and benzyloxy (OBn), a thorough analysis was conducted on the corresponding L-glucosides. The results unveiled a distinct trend where the efficiency of methylenation followed the trend OBn > OPMB > N₃. Finally, the C6-alkene was dihydroxylated in the presence of osmium tetroxide to yield the expected *L/D-glycero-L-glucoheptosides*. The

lead building block, which features a C-4 azide, was delivered as a phenyl thioglycoside. Added to the suitable masking of the 6,7-diol, this combination enables further functionalization to achieve versatile compounds of biological interest. The study insights into the interplay between substitution at C-4 and carbon homologation at C-6 provide valuable guidance for future endeavors in the synthesis of these carbohydrate molecules.

Introduction

Carbohydrates represent an important class of biomolecules. They assume diverse and important roles in many biological processes whether as energy storage (glucose), storage of genetic information (deoxyribose), infection facilitation, immune recognition, signal transduction, and fertilization.[1, 2] In addition to monosaccharides, oligosaccharides adopt a variety of physiological and pathological functions especially when conjugated to proteins,[3] lipids,[4] or nucleic acids.[5]

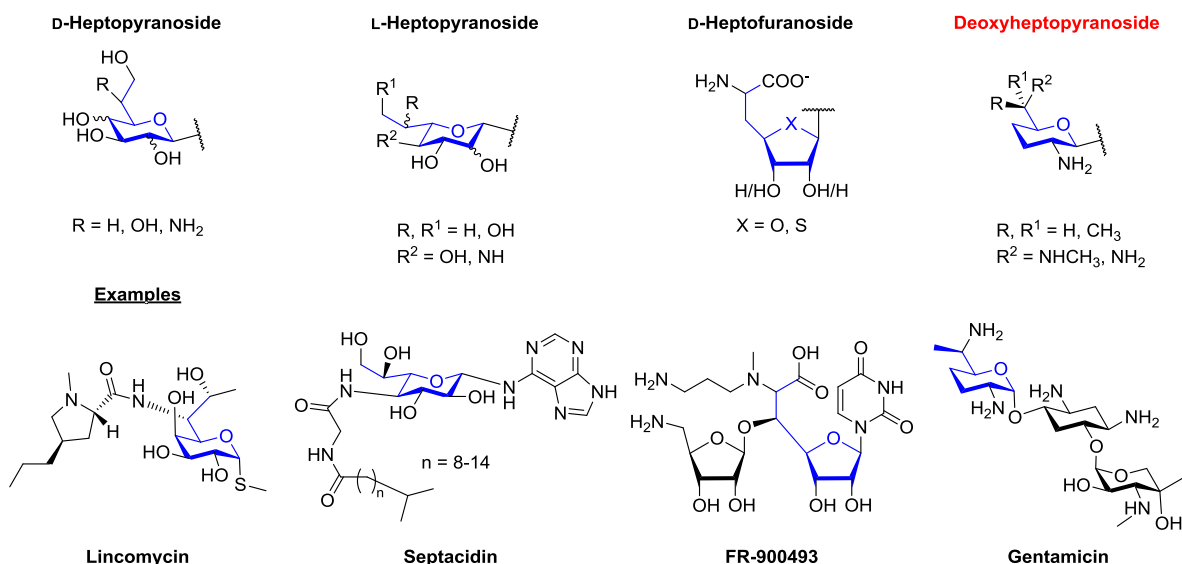
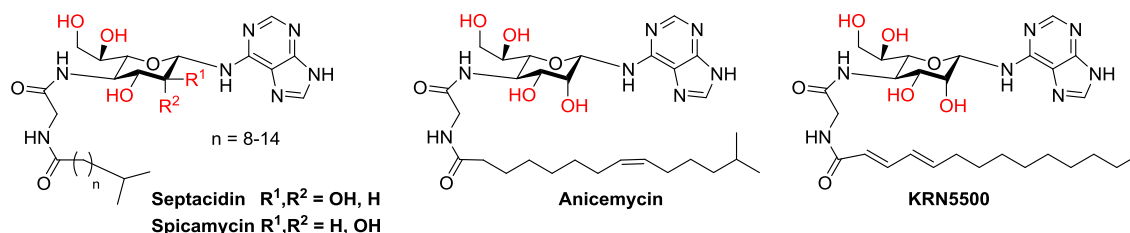


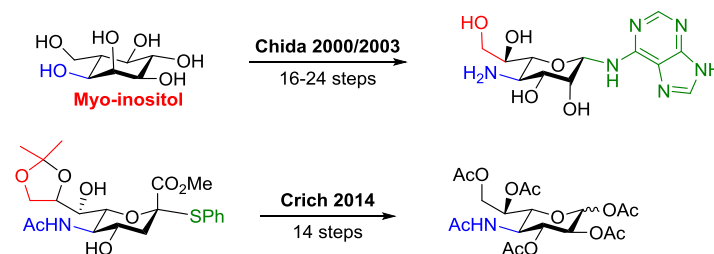
Figure 1. Chemical structures of representative types of heptoses and heptose-containing natural products.

Of special interest, heptoses are seven-carbon-chain-containing monosaccharides that are essential constituents of bacterial lipopolysaccharides and otherwise of capsular polysaccharides and various metabolites, but are not produced in humans.[6-9] These monosaccharides primarily fall into four major structural classes, namely D-heptopyranose, L-heptopyranose, heptofuranose, and highly reduced heptopyranose (Figure 1).[10] Glycosylated natural products such as avermectin, doxorubicin, erythromycin, or vancomycin are potent drugs. However, alternative scaffolds need to be discovered to combat increased antimicrobial resistance, including against the above.[11] Another possible strategy to identify next generation antibiotics is by chemically altering existing scaffolds in order to improve their lifetime and potentially elude resistance mechanisms.[11-14] Small alterations of existing antibiotics can be achieved for instance by integrating metal ions [15-17] or by changing the nature of the carbohydrate residue in the case

of glycan-containing drugs.[18, 19] In this context, bacterial natural products that incorporate heptosides showcase a wide range of biological properties, including antibacterial, antifungal, antiparasitic, and antitumor effects. There has been an increasing interest in the preparation of heptosides by chemoenzymatic and chemical synthesis approaches to understand their structural properties and biological activities [20-23]. More generally, this class of carbohydrates is also of interest for the design of innovative small molecule drugs [24], their incorporation into nucleic acids [25], or for the preparation of self-assembled structures [26].



Previous work



This work

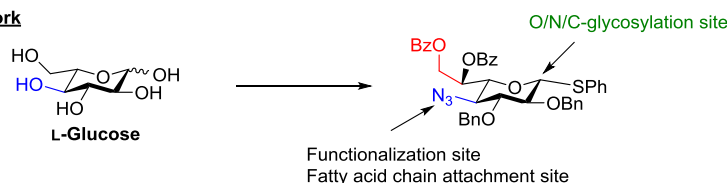


Figure 2. Top: Structure of L-heptosides and septacidin analogues. Middle and bottom: synthetic approaches to heptosides and precursors thereof [27-29].

Of all L-heptopyranose-containing bacterial natural products, septacidin is a structurally unique nucleolipid type of molecule produced by members of the *actinomyces* species.[30] Septacidin together with the related spicamycin and anicemycin are nucleoside antibiotics that combine constituents of all four classes of biomolecules, namely a fatty acid, a heptose moiety, an amino acid-like moiety (glycine), and a nucleobase-type (adenine) heterocycle (Figure 2). Particularly, the four common key structural motifs found in these natural compounds are (1) a rare 4-amino-4-deoxy-L-heptopyranose, (2) an unusual 6-N-linked adenine aglycon [31, 32], (3) an amide-

linked glycine at C-4, and (4) a variety of *N*-glycyl-linked acyl groups. Besides configuration divergence at C-2 of the 4-amino heptoside residue [33], the three compounds have different fatty acid side-chains. Novel septacidin congeners differing in their fatty acid modifications were recently disclosed [24]. It is worth noticing that structure–activity relationship (SAR) studies on these nucleolipids could reveal the contribution of the fatty acid chain length and composition to biological activity. For example, introduction of altered lipid chains on the core tunicamycin scaffold led to the identification of potent antibiotics for tuberculosis [34]. The potential of these natural compounds in medicinal chemistry is showcased by modified spicamycin (KRN5500, Figure 2) which was used in clinical trials for the treatment of neuropathic pain suppression of patients resistant to opioid drug treatment [35].

Surprisingly, only few synthetic campaigns towards these aminoheptosyl-based nucleoside antibiotics or model compounds have been launched so far [27-29, 31, 36]. The dearth of synthetic access might be partially ascribed to the fact that while D-heptosides can easily be obtained from commonly occurring sugars [37-39], the synthesis of L-heptosides and L-heptoside-derived analogues has been overlooked. The first synthesis of spicamycin congeners was reported in 2000 by Chida's group. The authors described a successful, albeit lengthy, synthetic route starting from myo-inositol [40]. More than a decade later, Crich et al used the readily available, albeit costly, nine carbon-containing *N*-acetylneuraminic acid, to synthesize a 4-acetamido peracetylated analogue of the septacidin heptose core by a shorter although uncommon route. Indeed, the selected route involved the removal of carbons C-1 and C-9, inversion at C-7 and functionalization at C-3 of the starting 9-carbon sugar [29].

Given their essential roles in biology, heptosides and their derivatives, particularly 4-azido-containing heptosides, represent important targets in chemical synthesis. Here, we propose an alternative synthetic pathway to a septacidin precursor and related building blocks. We have synthesized protected *L*-*gluco*-heptosides by implementing an expedient and high yielding approach starting from commercially available L-glucose. To do so, we have devised a synthetic approach that involves a carbon homologation followed by a double inversion step. A key step of the synthetic route is the methylenation at C-6 of a suitable intermediate. A thorough analysis revealed that this reaction is highly influenced by the nature of the C-4 moiety (Figure 2). The precursor to septacidin features a C-4 azide substitution and a thiophenyl aglycon (Figure 2). Besides conversion to septacidin, this building block also grants a facile access to synthetic analogs as the C-4 azide moiety permits a large range of modifications including the introduction of fatty acid side chains either via the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction or following conversion into an amine and subsequent reductive amination or amide bond formation.

Results:

A retrosynthetic analysis suggests that septacidin-related molecules can be achieved from commercially available L-glucose. Assuming that the introduction of the different lipid side-chains is straightforward, three synthetic challenges can be outlined 1) *N*-glycosylation for the introduction of the nucleobase, 2) amine group installation at C-4 and 3) carbon homologation at C-6 to reach the 6,7-*L*-glycero diol. These three tasks can be performed in different sequences.

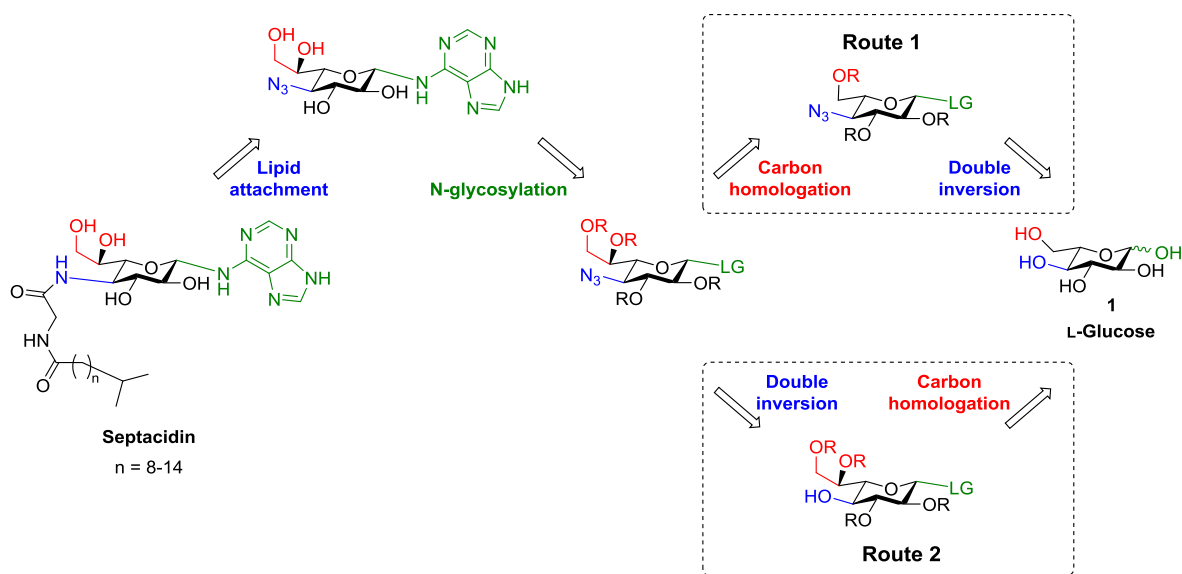
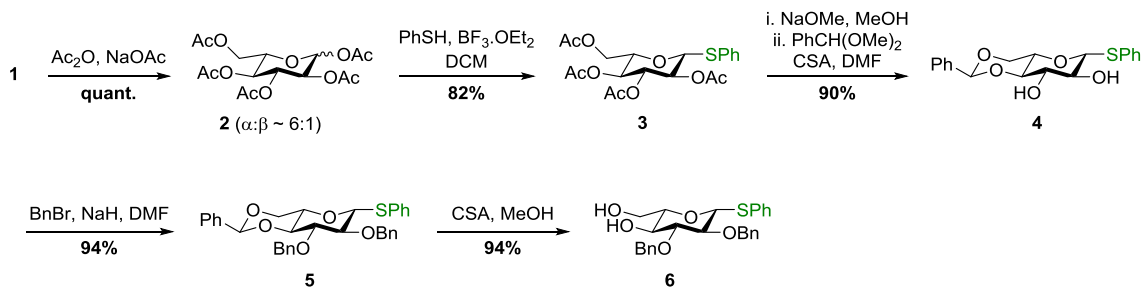


Figure 3. Retrosynthetic strategy of septacidin from L-glucose. LG: leaving group. R: protecting group.

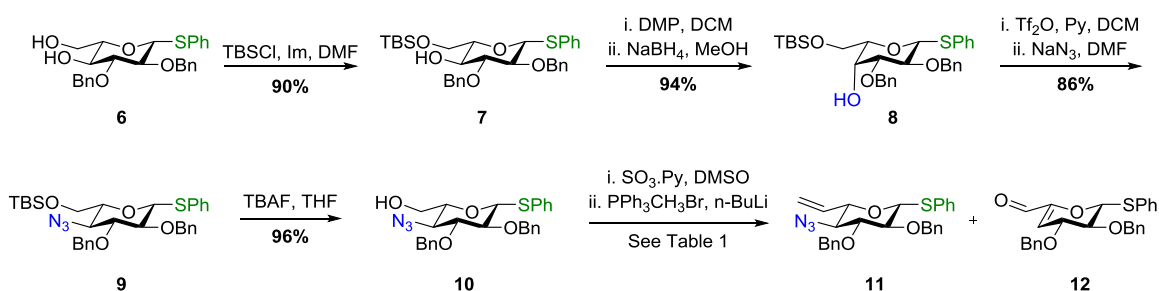
Herein, we investigated two synthetic routes to achieve a protected heptose building block compatible with *N*-glycosylation, either by first carrying out substitution at C-4 followed by carbon homologation (Route 1 in Figure 3) or conversely by carbon homologation followed by double inversion at C-4 (Route 2 in Figure 3).



Scheme 1. Synthesis of diol **6**, a key intermediate common to routes 1 and 2.

Thus, we prepared the key diol **6**, pre-identified as an intermediate common to routes 1 and 2 (Scheme 1). To do so, L-glucose **1** was first peracetylated with acetic anhydride in the presence of sodium acetate to give **2** as a ~1:6 α : β mixture (Scheme 1). Next, pentaacetate **2** was glycosylated with thiophenol in presence of boron trifluoride diethyletherate ($\text{BF}_3 \cdot \text{OEt}_2$) to afford thioglycoside **3** in 82% yield over two steps. As expected, the α -isomer did not react under these conditions and was completely recovered after purification. The thiophenyl aglycon was introduced as a temporary protecting group compatible with a late stage *N*-glycosylation step [41]. Deacetylation followed by protection of the 4,6-diol with a benzylidene acetal gave diol **4** in 90% yield over two steps. Benzylation afforded the fully protected **5** (94%). Cleavage of the benzylidene acetal was performed with CSA in MeOH to give the corresponding 4,6-diol **6** (94%). Taken together, by starting with 10 g of L-glucose, 16.8 g of the key diol **6** were recovered over six steps in a very satisfactory 65% yield (Scheme 1).

Route 1 – Double inversion at C-4 and carbon homologation at C-6.



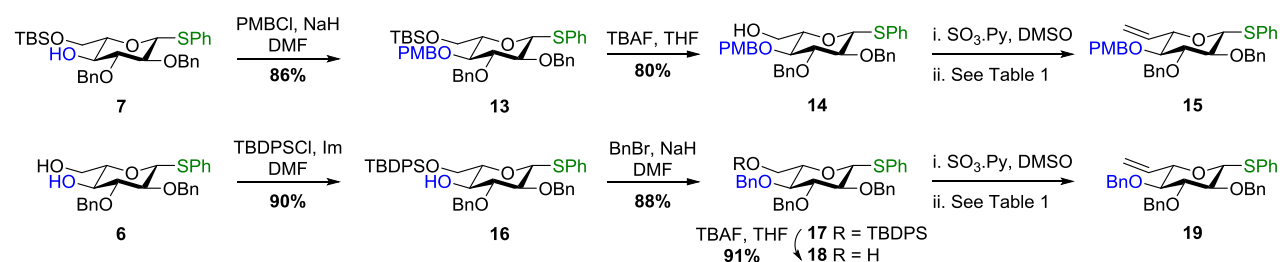
Scheme 2. Synthesis of the 4-azido-4-deoxy-L-gluco-heptoside **11** by means of the 4-azido-4-deoxy-L-thiogalactoside derivative **9**. TBS: *tert*-butyldimethyl silyl, Im: imidazole, DMP: Dess-Martin periodinane, Py: pyridine, TBAF: tetrabutylammonium fluoride, n-BuLi: n-butyllithium.

Selective protection of the primary alcohol of **6** with the *tert*-butyldimethylsilyl ether group gave alcohol **7** in good yield (Scheme 1). Introduction of an azido group at the C4-position of **7** while retaining the *L*-gluco configuration required two successive inversion steps. Generally, epimerisation processes are carried out in two steps. On the one hand, protocols are based on an activation/displacement such as the Mitsunobu reaction and the Lattreux-Dax method of nitrite-mediated substitution of a triflate intermediate. On the other hand, epimerization on carbohydrates involves oxidation of the secondary alcohol to a keto group followed by reduction with hydride reducing agents (such as NaBH_4 or LiBH_4). We evaluated both strategies on derivative **7**. Initial attempts by means of C4-epimerisation of **7** through triflation followed by treatment with NaNO_2 gave moderate to good yields of the expected product (not described). It is noteworthy mentioning that $\text{S}_{\text{N}}2$ displacement reactions on carbohydrate sulfonates depend on several factors such as the nature of the carbohydrate backbone, steric hindrance surrounding the leaving group, stereoelectronic environment of the latter, nucleophile, and reaction

conditions.[42] Otherwise, the oxidation of **7** with Dess-Martin periodinane followed by reduction of the intermediate ketone with NaBH₄ gave the inversion product **8** in an excellent yield of 94% over two steps. Hence, the latter pathway was preferred over the Lattreux-Dax protocol. Triflation of the hydroxyl group of **8** using triflic anhydride in presence of pyridine followed by substitution with sodium azide of the intermediate triflate gave the azide **9** in a very good 86% yield over two steps. Subsequently, silyl ether removal of **9** with TBAF gave the expected derivative **10** (96%).

Alcohol **10** was subjected to oxidation under Parikh-Doering conditions [43] using sulfur trioxide complex to yield the intermediate crude aldehyde which was directly reacted under Wittig olefination conditions with methyltriphenylphosphonium bromine in presence of *n*-butyllithium (*n*BuLi). However, the desired product **11** was only isolated in trace amounts and the major product (49%) was identified as the product of β-elimination **12** (Scheme 1, Table 1 Entry 1). The influence of the C4-substitution on C6-methylenation under standard Wittig olefination condition is not well-described. However, it is well known that glucuronic esters are highly sensitive to basic conditions, which usually result in a 4,5-elimination [44, 45]. We reasoned that the azide could act as a leaving group under harsh Wittig reaction conditions, which eventually would lead to **12**. Changing the base to the milder sodium hexamethyldisilazide (NaHMDS) led to no improvement (Entry 2). When even milder conditions were used, by changing methyltriphenylphosphonium bromine for the Tebbe reagent, the desired product **11** was obtained in 30% yield. However, even under these mild conditions the formation of the elimination product **12** could not be avoided (Entry 3). Changing the oxidation conditions to the milder Dess-Martin Periodinane reagent did not improve the outcome of the two-step conversion of **10** into **11** (Entry 3). Hence, the original Parikh-Doering conditions were adopted. We thus considered a different strategy whereby carbon homologation would precede azide introduction.

Route 2 – Carbon homologation at C-6

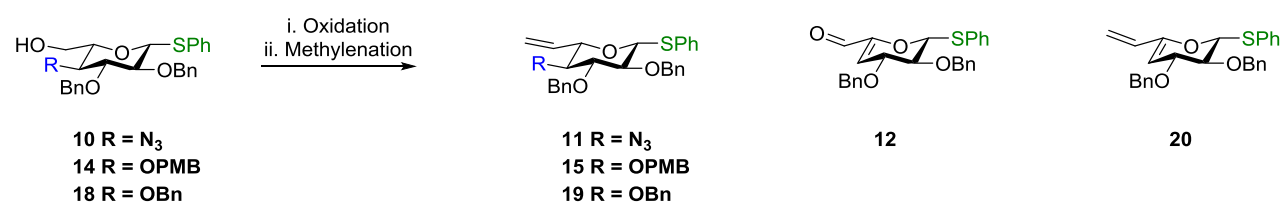


Scheme 3. Synthesis of the *L*-gluco-thioheptosides **15** (top) and **19** (bottom).

To this end, we designed alcohol **14** featuring a *para*-methoxybenzyl ether to mask OH-4 temporarily (Scheme 3). Hence, the silyl ether **7** was treated with 4-methoxybenzyl chloride in

presence of NaH to give **13** (86%). The subsequent removal of the silyl ether using tetrabutylammonium fluoride (TBAF) gave alcohol **14** (80%). In order to evaluate the impact of the OH-4 protecting group on the methylenation reaction, we synthesized the corresponding benzyl ether **18** (Scheme 3). Thus, the C6-OH of diol **6** was selectively silylated with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) in presence of imidazole to give alcohol **16** (90%). Benzylation with BnBr and NaH followed by TBDPS removal with TBAF gave alcohol **18** in 80% yield over two steps. The C6-alcohols **14** and **18** were oxidized into the corresponding aldehydes, then subjected to methylenation under different conditions (Table 1).

Table 1: Optimization of the oxidation/methylenation steps^a



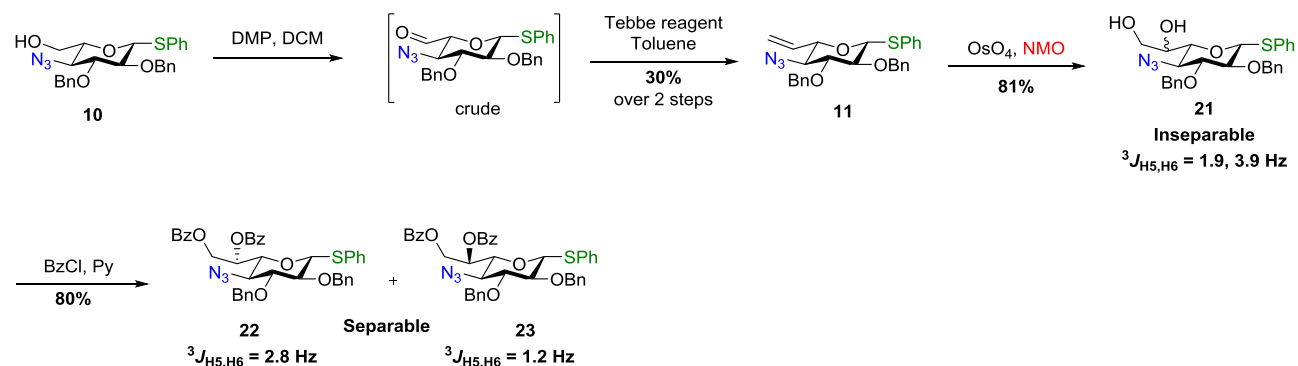
Entry	Precursor	Methylenation conditions	Yield (%)		
			(Target)	12	20
1	10	CH ₃ P(C ₆ H ₅) ₃ Br, n-BuLi, THF -80 °C-rt, 24 h	11 (11)	49	--
2		CH ₃ P(C ₆ H ₅) ₃ Br, NaHMDS, THF 0 °C-rt, 24 h	Nd (11)	23	Nd
3		Tebbe reagent, Toluene, rt, 24 h	30 (11)	<5	--
4	14	CH ₃ P(C ₆ H ₅) ₃ Br, n-BuLi, THF -80 °C-rt, 24 h	8 (15)	41	17
5		CH ₃ P(C ₆ H ₅) ₃ Br, n-BuLi, THF -40 °C-rt, 24 h	21 (15)	8	13
6		CH ₃ P(C ₆ H ₅) ₃ Br, NaHMDS, THF 0 °C-rt, 24 h	22 (15)	10	8
7		Tebbe reagent, Toluene, rt, 24 h	58 (15)	Nd	Nd
8	18	CH ₃ P(C ₆ H ₅) ₃ Br, n-BuLi, THF -40 °C-rt, 24 h	63 (19)	--	--
9		CH ₃ P(C ₆ H ₅) ₃ Br, NaHMDS, THF 0 °C-rt, 24 h	65 (19)	--	--

^a Reactions were performed on the 100-200 mg scale using the crude aldehyde obtained upon oxidation of alcohols **10**, **14** and **18**, respectively. Oxidation was performed either using the SO₃Py complex (Parikh-Doering oxidation) for entries 1-2, 4-7 and 8-9 or the Dess-Martin periodinane reagent (Entry 3). Yields were determined based on the

isolated products after flash chromatography purification. Nd: Not determined (the pure product was not isolated in significant amount). NaHMDS: Sodium bis(trimethylsilyl)amide. n-BuLi: n-Butyllithium.

Oxidation of compound **14** followed by methylenation under standard Wittig reaction conditions led to compound **15** in a poor yield (8%, Entry 4) resembling to that of the conversion of **10** to **11**. However, increasing the temperature from -80 °C to -40 °C generated the desired product **15** in a slightly improved yield (Entry 5). Changing n-BuLi to NaHMDS had no impact (Entry 6). In contrast, use of the Tebbe reagent was much more efficient leading to the target **15** in a good 58% yield *without* the formation of *any* of the side-products (Entry 7). Interestingly, the oxidation/methylenation of compound **18** resulted in **19** in a good yield when initiating the Wittig reaction in presence of n-BuLi at -40 °C (Entry 8). The difference of reactivity between **14** and **18** is somewhat surprising and might be ascribed to the slight difference in pK_a values of the corresponding benzyloxy anions or the lower oxidation potential of PMB compared to that of Bn [46, 47]. Lastly, the use of the milder NaHMDS did not result in any meaningful improvement and yields remained in the 60-70% range.

Overall, data in Table 1 clearly indicate that carbon homologation at C-6 of L-glucopyranoside derivatives is highly influenced by the group present at C-4. In particular, electron donating groups such as a benzyloxy group are suitable for the two step carbon homologation under Wittig conditions, which is not the case for the *para*-methoxybenzyloxy group and N₃, as formation of the 4,5-elimination product is observed in significant amounts. To our satisfaction, the use of the Tebbe reagent was shown to be compatible with these more sensitive moieties, paving the way forward to future developments.



Scheme 4. Synthesis of the 4-azido-4-deoxy-D/L-gluco-heptosides building blocks **22** and **23**. NMO: 4-methylmorpholine *N*-oxide.

Finally, alcohol **10** was oxidized with Dess-Martin periodinane followed by Tebbe olefination to deliver alkene **11** in a 30% yield (Scheme 4). Dihydroxylation of **11** with osmium tetroxide in presence of 4-methylmorpholine *N*-oxide gave the heptoside **21** as an inseparable mixture of both *D/L-glycero* isomers.[48] In order to facilitate separation of the diastereoisomers, we considered several protecting group strategies. Gratifyingly, benzoylation of diol **21** gave a mixture of the corresponding isomers **22** and **23** that could be separated by flash chromatography

(Scheme 4). The two individual diastereoisomers were characterized by use of 1D ^1H , ^{13}C , DEPT-135 NMR and 2D COSY, HSQC, HMBC, and 2D NOESY NMR. In particular, in the absence of X-ray analytical data, distinction between the *L-glycero* and *D-glycero* isomers **22** and **23**, respectively, was based on a tentative analysis of the $^3J_{5,6}$ coupling constants.

Available literature data reveal that the $^3J_{5,6}$ coupling constants for H-5 in two related septacidin precursors are of 1.5 Hz for the α - and 1.8 Hz for the β -isomer [29]. Similar values were recorded for spicamycin derivatives, since the reported $^3J_{\text{H5,H6}}$ values are 1.7 Hz for both H-5 and H-6 [31]. In an interesting study, methyl *L-glycero*- α -*D-manno*-heptopyranoside was synthesized and characterized by NMR and X-ray crystal structure analysis [49]. Close inspection of the crystal structure reveals that H-5 and H-6 are *gauche* to each other. Expectedly, the coupling constants ($^3J_{\text{H5,H6}}$) in most identified synthetic intermediates are in the 1.2-2.0 Hz range. Hence, based on this tentative analysis, we expect the desired *L-glycero*- β -*L-gluco*-heptopyranoside diastereoisomer to display $^3J_{\text{H5,H6}}$ coupling constants < 2.0 Hz since both hydrogen atoms are *gauche* to each other and undesired *D-glycero*- β -*L-gluco*-heptopyranoside diastereoisomer to present higher (> 2.0 Hz) coupling constants due to a *trans* or *gauche-trans* relationship [50]. We therefore tentatively assign **22** as the *D-glycero*- β -*L-gluco*-heptopyranoside diastereoisomer ($^3J_{\text{H5,H6}} = 2.8$ Hz) and **23** as the *L-glycero*- β -*L-gluco*-heptopyranoside diastereoisomer ($^3J_{\text{H5,H6}} = 1.2$ Hz). Similar observations can be drawn from NMR data in a recent report on a series of *L-glycero*- and *D-glycero*-*D-manno*-heptose scaffolds [21] and 6-*O*-methyl-*D-glycero*-*L-gluco*-heptopyranose derivatives (Table S1, Supporting Information) [51, 52]. Otherwise, in their study on *D-manno*- and *D-galacto*-heptosides, the authors reported a nice correlation based on the chemical shifts for H-6 of the two *L-glycero*- and *D-glycero*-diastereoisomers, respectively (Table S2) [53]. Accordingly and in agreement with our above tentative assignment, we can assume that **22** (δ_{H6} : 5.75 ppm) and **23** (δ_{H6} : 5.90-5.87 ppm) are the undesired *D-glycero*- and desired *L-glycero*- β -*L-gluco*-heptopyranoside diastereoisomers, respectively. Lastly, the NOESY spectrum (400 MHz) of analogue **23** reveals a direct correlation between H-6 and H-4 but regrettably, the NOESY spectrum of compound **22** failed to provide valuable information due to signal overlap between H-4 and H-5, both appearing in the same chemical shift range (δ 3.55-3.51 ppm). Data obtained from NOESY spectra does not entirely coincide with this analysis but in the absence of data on the second diastereoisomer the usefulness of this data remains debatable. Additional experiments towards further clarifying diastereoisomer assignment including NMR experiments at higher field (800 MHz) and switching solvents (from CDCl_3 to pyridine-*d*₅) remained unsuccessful (data not shown).

Discussion and conclusions

We have synthesized 4-azido-*D/L-glycero-L-gluco*-heptoside derivatives (**22**, **23**) starting from the commercially available *L*-glucose in an expedient and promising approach (16 steps; 4.4%

total yield) whereby carbon homologation at C-6 followed azide introduction. In the course of this synthesis, we have observed that the former modification was the limiting factor. We showed that carbon homologation at C-6 of phenyl 1-thio- β -L-glucoside precursors was highly influenced by the nature of the C-4 moiety. As exemplified for compounds **10** and **14**, the presence at C-4 of leaving groups such as the azide and the 4-methoxybenzyloxy group, respectively, is not compatible with standard Wittig reaction conditions. In contrast, poor leaving groups such as the benzyloxy moiety are suitable for this transformation. Indeed, our data suggest the OBn > OPMB > N₃ order for the preferred modification at C-4 of the L-thioglucofuranoside intermediate. We expect that these findings can be applied to the preparation of other related L-heptoside derivatives. Herein, we have described a route to the key L-glucoheptoside precursors to septacidin by use of route 1, whereby carbon homologation at C-6 follows azide introduction at C-4 (Figure 3). In addition to fine-tuning the proposed path (Scheme 2), one could also consider route 2 (Figure 3) whereby carbon homologation precedes azidation at C-4. To this end, the L-glucoheptoside **15**, featuring an orthogonal protecting group at O-4, appears well-suited. Ultimately, the C-6-alkene **11** was dihydroxylated using osmium tetroxide, resulting in the formation of a mix of L/D-*glycero*- β -L-thioglucoheptosides **21**, which could be separated in the form of the 6,7-di-*O*-benzoyl analogues **22** and **23**. While the two diastereoisomers could be tentatively assigned based on the H-6 chemical shifts and the ³J_{5,6} coupling constants due to the differential relationships of protons H-5 and H-6 in **22** and **23**, additional experimentation (e.g. X-ray structure) will be required for a conclusive assignment on these or subsequent analogues. Nonetheless, these valuable building blocks carry a thiophenyl aglycon and an azide group at C-4, allowing for further functionalization to achieve a range of chemical probes and/or biologically significant compounds. In particular, the ability to chemically produce L-glucoheptosides holds significant importance not only because they are part of important nucleolipids but also as major components of bacterial polysaccharides [54]. More generally, L-heptoses are involved in various biological processes, particularly within metabolic pathways and molecular recognition phenomena involving the bacterial cell wall [6, 7]. Thus, while not as developed as their D-counterparts, the synthesis of L-heptosides, L-heptoside-containing nucleosides and their derivatives opens up avenues for exploring their therapeutic potential and expanding our understanding of their complex biological functions. Overall, building blocks **22** and **23** prepared herein grant direct access to the natural product septacidin. The presence of the azide moiety represents a synthetic handle for the inclusion of side-chains different from that present in the natural products by the CuAAC reaction and hence will provide an easy access for the preparation of synthetic analogs of septacidin. Finally, selective removal of the benzoyl groups will unmask a diol that can be converted into phosphoramidite building blocks for the synthesis of novel carbohydrate-RNA/DNA conjugates and alternative synthetic nucleic acids [32, 55-60].

Experimental Section

General Procedures

Anhydrous (Anhyd.) solvents and solvents for purification including dichloromethane (DCM), 1,2-dichloroethane (DCE), cyclohexane (cHex), tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), methanol (MeOH), acetonitrile (MeCN), pyridine (Py), and toluene (Tol) were delivered from commercial suppliers and used as received. Reactions requiring anhyd. conditions were run under an argon (Ar) atmosphere. Freshly activated 4Å MS were prepared before use by heating with a hot air gun (20-30 min.) under high vacuum. Analytical TLC was performed using silica gel 60 F254, 0.25 mm pre-coated TLC aluminium foil plates. Compounds were visualized using UV ($\lambda = 254$ nm) and/or orcinol (1 mg·mL⁻¹) in 10% aqueous (aq.) H₂SO₄ with charring. Automated flash column chromatography was carried out using prepacked columns of silica gel (40 µm particle size). Manual flash column chromatography was carried out using silica gel (40-63 µm particle size). NMR spectra were recorded at 303 K on a Bruker Avance spectrometer equipped with a BBO probe at 400 MHz (¹H) and 101 MHz (¹³C). Spectra were recorded in CDCl₃, MeOH-*d*₄, or MeCN-*d*₃. Chemical shifts are reported in ppm (δ) relative to residual solvent peak, CHCl₃ in the case of CDCl₃ at 7.28/77.0 ppm for the ¹H and ¹³C spectra, respectively. Coupling constants are reported in hertz (Hz). Elucidation of chemical structures is based on ¹H, COSY, DEPT-135, HSQC, decoupled HSQC, and HMBC. Signals are reported as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), q (quartet), dq (doublet of quartet), ddd (doublet of doublet of doublet), m (multiplet). Signals can also be described as broad (prefix brd), overlapped (suffix o). Of the two magnetically non-equivalent geminal protons, such as C6 and C7, the one resonating at lower field is denoted H-Xa (X = 6 or 7), and the one at higher field is denoted H-Xb. HRMS spectra were recorded in the positive-ion electrospray ionisation (ESI⁺) mode on a Q exactive mass spectrometer (Thermo Fisher Scientific) equipped with a H-ESI II Probe source. Solutions were prepared using 1:1 MeCN/H₂O containing 0.1% formic acid. In the case of sensitive compounds, solutions were prepared using 1:1 MeOH/H₂O to which was added 10 mM ammonium acetate.

General procedure for carbon homologation or methylenation:

Step 1: To a solution of the alcohol (200 mg, 1.0 equiv.) in anhyd. DCM (6 mL) were added DMSO (5.0 equiv.) and DIPEA (3.0 equiv.). The reaction mixture was cooled to 0 °C. The SO₃Py complex (3.0 equiv.) was added and the mixture was left to stir for 2 h at 0 °C. Upon completion, DCM (10 mL) was added and washed successively with 0.5 M aq. NH₄Cl (15 mL) and brine (15 mL). The organic phase was dried over Na₂SO₄, concentrated, and dried under high vacuum for 2 h to yield the crude aldehyde.

Step 2: Ph₃PMeBr (2.0 equiv. with respect to the starting alcohol) was dissolved in anhyd. THF (5 mL). The solution was cooled to -40 °C and *n*-BuLi (1.0 M in hexane, 1.8 equiv.) was added. The reaction mixture was stirred under Ar for 2 h while allowing the mixture to attain rt. The obtained red-yellow solution was again cooled to -40 °C. A solution of the crude aldehyde in

anhyd. THF (55 mL) was transferred to the phosphonium ylide solution by used of a cannula. The reaction mixture was stirred overnight while the cooling bath slowly returned to rt. At completion, 0.5 M aq. NH₄Cl was added. The aqueous layer was washed with EtOAc (2 × 10 mL). The combined organic parts were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude was purified by flash chromatography (cHex:EtOAc) to give the desired product.

1,2,3,4,6-Penta-O-acetyl- α/β -L-glucopyranose (2): A suspension of L-glucose (10.0 g, 55.5 mmol, 1.0 equiv.) in acetic anhydride (68 mL, 666 mmol, 12 equiv.) was placed in a heating bath. Anhyd. sodium acetate (5.3 g, 66.6 mmol, 1.2 equiv.) was added. The reaction mixture was heated to 100 °C for 30 min. and the suspension turned into a clear solution. The mixture was cooled to rt and diluted with DCM (400 mL), and washed with water (500 mL), 5% aq. NaHCO₃ (500 mL) and brine (500 mL). The organic part was dried over Na₂SO₄ and concentrated under reduced pressure, then dried extensively under high vacuum. The product was obtained as a white solid (21.7 g, 55.5 mmol, quantitative) in the form of a 1:6 α/β mixture. Pentaacetate **2** had R_f 0.4 (Tol/EtOAc 4:1). ¹H NMR (CDCl₃) δ 6.26 (d, 0.15H, *J*_{1,2} = 3.4 Hz, H-1 α), 5.64 (d, 1H, *J*_{1,2} = 8.0 Hz, H-1 β), 5.40 (t, 0.15H, *J*_{2,3} = 10.2 Hz, H-3 α), 5.18 (t, 1H, *J*_{2,3} = 10.3 Hz, H-3 β), 5.09-5.01 (m, 2.3H, H-2 β , H-4 β , H-2 α , H-4 α), 4.24-4.17 (1.15H, H-6a β , H-6a α), 4.06-4.01 (m, 1.3H, H-6b β , H-6b α , H-5 α), 3.79-3.75 (m, 1H, H-5 β), 2.11-1.94 (m, 16.3H, CH₃Ac β , CH₃Ac α). ¹³C NMR (CDCl₃) δ 170.54, 170.04, 169.34, 169.19, 168.90 (CO_{Ac} β), 170.54, 170.17, 169.60, 168.69 (CO_{Ac} α), 91.71 (C-1 β , ¹*J*_{C,H} = 166 Hz), 89.07 (C-1 α , ¹*J*_{C,H} = 180 Hz), 72.80 (C-5 β), 72.74 (C-3 β), 70.26 (C-2 β), 69.84 (C-5 α , C-3 α), 69.20 (C-2 α), 67.92 (C-4 α), 67.79 (C-4 β), 61.46 (C-6 β , C-6 α), 20.83, 20.77, 20.66, 20.62, 20.52, 20.51, 20.40 (10C, C_{Ac} β , C_{Ac} α). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₁₆H₂₆NO₁₁ 408.1500; found 408.1493.

Phenyl 2,3,4,6-tetra-O-acetyl-1-thio- β -L-glucopyranoside (3): Thiophenol (11.4 mL, 111 mmol, 2.0 equiv.) was added to a solution of pentaacetate **2** (21.6 g, 55.5 mmol, 1.0 equiv.) in DCM (370 mL). The mixture was stirred with freshly activated MS 4Å (11 g) under an argon atmosphere for 1 h at rt, then cooled to 0 °C. Boron trifluoride diethyl etherate (BF₃·OEt₂, 20.5 mL, 166 mmol, 3.0 equiv.) was added dropwise over 30 min. The reaction mixture was slowly allowed to attain rt and left to stir overnight at this temperature. The suspension was filtered and washed with DCM (2×50 mL). The filtrate was washed with water (500 mL), 5% aq. NaHCO₃ (500 mL) and brine (500 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica-gel column chromatography (85:15, Tol/EtOAc) to give the desired product **3** as a white solid (20.2 g, 45.8 mmol, 82%). The unreacted 1,2,3,4,6-penta-O-acetyl- α -L-glucopyranose was recovered as a white solid (3.6 g, 9.22 mmol, 16%). The thioglycoside **3** had R_f 0.45 (Tol/EtOAc 4:1). ¹H NMR (CDCl₃) δ 7.53-7.50 (m, 2H, H_{Ar}), 7.35-7.32 (m, 3H, H_{Ar}), 5.24 (t, 1H, *J*_{2,3} = 9.3 Hz, H-3), 5.06 (t, 1H, *J*_{4,5} = *J*_{3,4} = 9.7 Hz, H-4), 4.99 (t, 1H, H-2), 4.73 (d, 1H, *J*_{1,2} = 10.0 Hz, H-1), 4.27-4.18 (m, 2H, H-6a, H-6b), 3.77-3.72 (m, 1H, H-5), 2.10, 2.10, 2.03, 2.01 (4s, 12H, CH₃Ac). ¹³C NMR (CDCl₃) δ 170.5, 170.1, 169.3, 169.2 (4C, CO_{Ac}), 133.1 (C_{q,Ar}), 131.6, 128.9, 128.4 (C_{Ar}), 85.7 (C-1), 75.8 (C-5),

73.9 (C-3), 69.9 (C-2), 68.2 (C-4), 62.1 (C-6), 20.7, 20.5 (4C, C_{Ac}). HRMS (ESI⁺): *m/z* [M+Na]⁺ calc. for C₂₀H₂₄O₉SNa 463.1033; found 463.1032.

1,2,3,4,6-Penta-*O*-acetyl- α -L-glucopyranose had *R_f* 0.4 (Tol/EtOAc 4:1). ¹H NMR (CDCl₃) δ 6.34 (d, 1H, *J*_{1,2} = 3.6 Hz, H-1), 5.48 (t, 1H, *J*_{2,3} = 10.0 Hz, H-3), 5.17-5.09 (m, 2H, H-2, H-4), 4.27 (dd, 1H, *J*_{5,6a} = 4.2 Hz, *J*_{6a,6b} = 12.4 Hz, H-6a), 4.14-4.08 (m, 2H, H-5, H-6b), 2.18, 2.10, 2.05, 2.03, 2.02 (m, 15 H, CH_{3Ac}). ¹³C NMR (CDCl₃) δ 170.58, 170.17, 169.61, 169.35, 168.70 (CO_{Ac}), 89.07 (C-1), 69.84 (C-3), 69.83 (C-5), 69.20 (C-2), 67.92 (C-4), 61.47 (C-6), 20.83, 20.65, 20.62, 20.52, 20.40 (C, C_{Ac}). HRMS (ESI⁺): *m/z* [M+Na]⁺ calc. for C₁₆H₂₂O₁₁Na 413.1054; found 413.1048.

Phenyl 4,6-*O*-benzylidene-1-thio- β -L-glucopyranoside (4): *Step 1:* Tetraacetate **3** (20.2 g, 45.8 mmol, 1.0 equiv.) was dissolved in MeOH (200 mL). DCM (20 mL) was added to reach a homogeneous solution. Solid NaOMe (990 mg, 18.3 mmol, 0.4 equiv.) was added and the reaction was stirred at rt for 4 h. At completion, H⁺ resin was added to reach pH ~7. The suspension was filtered, washed with methanol (2 \times 50 mL). The filtrate was concentrated and dried over high vacuum to get the crude tetraol as a white solid (12.5 g, 45.8 mmol). The intermediate tetraol had *R_f* 0.2 (EtOAc). ¹H NMR (CD₃OD) δ 7.48-7.45 (m, 2H, H_{Ar}), 7.23-7.14 (m, 3H, H_{Ar}), 4.50 (d, 1H, *J*_{1,2} = 9.8 Hz, H-1), 3.77 (dd, 1H, *J*_{5,6a} = 2.0 Hz, *J*_{6a,6b} = 12.0 Hz, H-6a), 3.57 (dd, 1H, *J*_{5,6b} = 5.2 Hz, H-6b), 3.29 (t, 1H, *J*_{2,3} = *J*_{3,4} = 8.4 Hz, H-3), 3.23-3.20 (m, 2H, H-4, H-5), 3.12 (dd, 1H, H-2). ¹³C NMR (CD₃OD) δ 133.86 (C_{q,Ar}), 131.33, 128.45, 126.90 (C_{Ar}), 88.01 (C-1), 80.64 (C-4), 78.30 (C-3), 72.38 (C-2), 69.98 (C-5), 61.49 (C-6). HRMS (ESI⁺): *m/z* [M+Na]⁺ calc. for C₂₀H₂₄O₉SNa 463.1033; found 463.1032.

Step 2: The crude tetraol (12.5 g, 45.8 mmol) was dissolved in anhyd. DMF (220 mL). Benzaldehyde dimethyl acetal (9.6 mL, 64.2 mmol, 1.4 equiv.) was added followed by the addition of camphorsulfonic acid (CSA, 2.13 g, 9.17 mmol, 0.2 equiv.). The reaction mixture was stirred overnight at rt under an Ar atmosphere. At completion, trimethylamine was added and the mixture was concentrated under reduce pressure. The residue was purified by silica gel chromatography (80:20 \rightarrow 60:40, Tol/EtOAc) to give the desired **4** as a white solid (15.0 g, 41.6 mmol, 91%). Diol **4** had *R_f* 0.35 (Tol/EtOAc, 6:4). ¹H NMR (CDCl₃) δ 7.58-7.35 (m, 10H, H_{Ar}), 5.55 (s, 1H, PhCH), 4.65 (d, 1H, *J*_{1,2} = 9.6 Hz, H-1), 4.42-4.38 (m, 1H, H-6a), 3.88-3.77 (m, 2H, H-3, H-6b), 3.55-3.46 (m, 3H, H-2, H-4, H-5), 2.86 (brs, 1H, OH), 2.72 (brs, 1H, OH). ¹³C NMR (CDCl₃) δ 136.89, 131.31 (C_{q,Ar}), 133.09, 129.33, 129.14, 128.49, 128.36, 126.29 (C_{Ar}), 101.95 (PhCH), 88.63 (C-1), 80.23 (C-4), 74.62 (C-3), 72.63 (C-2), 70.58 (C-5), 68.59 (C-6). HRMS (ESI⁺): *m/z* [2M+NH₄]⁺ calc. for C₃₈H₄₄O₁₀S₂N 738.2401; found 738.2396.

Phenyl 3,4-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio- β -L-glucopyranoside (5): Diol **4** (15.0 g, 41.6 mmol, 1.0 equiv.) was dissolved in DMF and cooled to 0 °C. NaH (50% in mineral oil, 6.0 g, 124 mmol, 3.0 equiv.) and BnBr (12.6 mL, 104 mmol, 2.5 equiv.) were added. The reaction was stirred for 1 h at 0 °C. At completion, 0.5 M aq. NH₄Cl was added. The aq. phase was extracted with DCM (2 \times 200 mL). The DCM parts were combined and washed with 10% brine (500 mL), dried over anhyd. Na₂SO₄, and concentrated under reduced pressure. The crude was

purified by silica-gel column chromatography (95:5→90:10, Tol/EtOAc) to give the desired **5** as a white solid (21.2 g, 33.7 mmol, 94%). The fully protected **5** had R_f 0.65 (cHex/EtOAc, 10:1). ^1H NMR (CDCl_3) δ 7.60-7.31 (m, 20H, H_{Ar}), 5.64 (s, 1H, PhCH), 5.00 (d, 1H, $J = 11.2$ Hz, $\text{CH}_{2\text{Bn}}$), 4.94-4.80 (m, 4H, $\text{CH}_{2\text{Bn}}$, H-1), 4.43 (dd, 1H, $J_{5,6a} = 5.0$ Hz, $J_{6a,6b} = 10.4$ Hz, H-6a), 3.91-3.83 (m, 2H, H-4, H-6b), 3.76 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 3.59-3.49 (m, 2H, H-2, H-5). ^{13}C NMR (CDCl_3) δ 138.36, 138.09, 137.32, 133.19 ($\text{C}_{\text{q,Ar}}$), 132.39, 129.05, 129.04, 128.43, 128.29, 128.25, 128.14, 127.90, 127.79, 126.05 (C_{Ar}), 101.20 (PhCH), 88.34 (C-1), 83.06 (C-4), 81.52 (C-3), 80.55 (C-2), 75.92 ($\text{CH}_{2\text{Bn}}$), 75.33 ($\text{CH}_{2\text{Bn}}$), 70.30 (C-5), 68.76 (C-6). HRMS (ESI^+): m/z $[\text{M}+\text{Na}]^+$ calc. for $\text{C}_{33}\text{H}_{32}\text{O}_5\text{SNa}$ 563.1863; found 563.1857.

Phenyl 2,3-di-*O*-benzyl-1-thio- β -L-glucopyranoside (6): CSA (4.84 g, 20.8 mmol, 0.4 equiv.) was added to a solution of compound **5** (21.2 g, 39.2 mmol, 1.0 equiv.) in DCM/MeOH (300 mL, 1:1 v/v). The solution was left to stir at rt. After 1 h, more MeOH (100 mL) was added. After another 8 h, the mixture was diluted with DCM (600 mL), washed with 10% aq. NaHCO_3 (600 mL) and brine (600 mL). The organic phase was collected, dried over anhyd. Na_2SO_4 and concentrated. The crude was purified by flash chromatography (60:40→50:50, Tol/EtOAc) to give the desired **6** as a white solid (16.8 g, 37.1 mmol, 94%). Diol **6** had R_f 0.4 (Tol/EtOAc 1:1). ^1H NMR (CDCl_3) δ 7.44-7.16 (m, 15H, H_{Ar}), 4.88-4.85 (m, 2H, $\text{CH}_{2\text{Bn}}$), 4.68-4.62 (m, 3H, H-1, $\text{CH}_{2\text{Bn}}$), 3.79 (dd, 1H, $J_{5,6a} = 3.4$ Hz, $J_{6a,6b} = 11.8$ Hz, H-6a), 3.66 (dd, 1H, $J_{5,6b} = 5.2$ Hz, H-6b), 3.52-3.37 (m, 3H, H-2, H-3, H-4), 3.28-3.24 (m, 1H, H-5), 2.27-2.02 (brd, 2H, OH). ^{13}C NMR (CDCl_3) δ 138.3, 137.8, 133.5 ($\text{C}_{\text{q,Ar}}$), 131.7, 129.0, 128.7, 128.4, 128.2, 128.0, 127.9, 127.9, 127.7 (C_{Ar}), 87.7 (C-1), 86.1 (C-3), 80.9 (C-2), 79.1 (C-5), 75.4 ($\text{CH}_{2\text{Bn}}$), 75.4 ($\text{CH}_{2\text{Bn}}$), 70.4 (C-4), 62.7 (C-6). HRMS (ESI^+): m/z $[\text{M}+\text{NH}_4]^+$ calc. for $\text{C}_{26}\text{H}_{32}\text{NO}_5\text{S}$ 470.1996; found 470.1993.

Phenyl 2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio- β -L-glucopyranoside (7): Diol **6** (3.1 g, 6.85 mmol, 1.0 equiv.) was dissolved in anhyd. DMF (25 mL). Imidazole (1.03 g, 15.0 mmol, 2.2 equiv.) and *tert*-butyldimethylsilyl chloride (1.14 g, 7.54 mmol, 1.1 equiv.) were added to the solution stirred at 0 °C. After overnight stirring while slowly allowing the reaction mixture to attain rt, methanol (2 mL) was added. After another 5 min, the mixture was concentrated under reduced pressure. The crude was purified by flash chromatography (95:5→80:20, cHex/EtOAc) to give the desired **7** as a colorless oil (3.5 g, 5.57 mmol, 90%). The silyl ether **7** had R_f 0.65 (Tol/EtOAc 9:1). ^1H NMR (CDCl_3) δ 7.47-7.16 (m, 15H, H_{Ar}), 4.81-4.72 (m, 3H, $\text{CH}_{2\text{Bn}}$), 4.64 (d, 1H, $J = 10.4$ Hz, $\text{CH}_{2\text{Bn}}$), 4.59 (d, 1H, $J_{1,2} = 9.7$ Hz, H-1), 3.84-3.75 (m, 2H, H-6a, H-6b), 3.59 (dt, 1H, $J_{4,5} = 8.8$ Hz, H-4), 3.46 (t, 1H, $J_{2,3} = J_{3,4} = 8.8$ Hz, H-3), 3.36 (t, 1H, H-2), 3.29-3.24 (m, 1H, H-5), 2.74 (d, 1H, $J_{4,\text{OH}} = 1.6$ Hz, OH), 0.82 (s, 9H, $\text{C}(\text{CH}_3)_{\text{TBS}}$), 0.01 (s, 3H, CH_3_{TBS}), 0.00 (s, 3H, CH_3_{TBS}). ^{13}C NMR (CDCl_3) δ 138.57, 138.11, 133.94 ($\text{C}_{\text{q,Ar}}$), 128.91, 128.56, 128.41, 128.23, 127.99, 127.85, 127.42 (C_{Ar}), 87.66 (C-1), 86.25 (C-3), 80.26 (C-2), 78.55 (C-5), 75.52 ($\text{CH}_{2\text{Bn}}$), 75.36 ($\text{CH}_{2\text{Bn}}$), 72.47 (C-4), 64.29 (C-6), 25.9 (CH_3_{TBS}), 18.30 ($\text{C}_{\text{q,TBS}}$), -5.42 (2C, CH_3_{TBS}). HRMS (ESI^+): m/z $[\text{M}+\text{NH}_4]^+$ calc. for $\text{C}_{32}\text{H}_{46}\text{O}_5\text{SSiN}$ 584.2860; found 584.2852.

Phenyl 2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio- β -L-galactopyranoside (8): *Step 1:* Dess-Martin periodinane (786 mg, 1.85 mmol, 1.4 equiv.) was added to a solution of alcohol **7** (750 mg, 1.32 mmol, 1.0 equiv.) in DCM (10 mL) at 0 °C. The reaction mixture was left to stir for 2 h at this temperature. At completion, DCM (15 mL) was added and the mixture was washed with 10% aq. Na₂S₂O₃, 0.5 M aq. NaHCO₃ and brine. The DCM part was dried over Na₂SO₄, concentrated under reduced pressure and dried extensively under high vacuum.

Step 2: Sodium borohydride (NaBH₄, 760 mg, 2.64 mmol, 2.0 equiv.) was added to a solution of the crude in anhyd. MeOH (10 mL). After stirring for 4 h at rt, NH₄Cl was added. The aq. part was washed with DCM (3 × 15 mL). The combined DCM part was washed with brine, dried over anhyd. Na₂SO₄, and concentrated under vacuum. The residue was purified by flash chromatography (95:5→90:10, cHex/EtOAc) to give the desired galactoside **8** (710 mg, 1.13 mmol, 94%) as a colorless oil. The silyl ether **8** had R_f 0.65 (Tol/EtOAc 9:1). ¹H NMR (CDCl₃) δ 7.50-7.47 (m, 2H, H_{Ar}), 7.34-7.13 (m, 13H, H_{Ar}), 4.75 (d, 1H, *J* = 10.4 Hz, CH_{2Bn}), 4.67 (d, 1H, CH_{2Bn}), 4.64 (brs, 2H, CH_{2Bn}), 4.54 (d, 1H, *J*_{1,2} = 9.8 Hz, H-1), 4.01 (d, 1H, *J*_{3,4} = 2.8 Hz, H-4), 3.85 (dd, 1H, *J*_{5,6a} = 6.0 Hz, *J*_{6a,6b} = 10.0 Hz, H-6a), 3.85 (dd, 1H, *J*_{5,6b} = 5.2 Hz, H-6b), 3.69 (t, 1H, *J*_{2,3} = 9.8 Hz, H-2), 3.47 (dd, 1H, H-3), 3.36-3.33 (m, 1H, H-5), 2.62 (brs, 1H, OH), 0.82 (s, 9H, C(CH₃)_{TBS}), 0.01 (s, 3H, CH_{3,TBS}), 0.00 (s, 3H, CH_{3,TBS}). ¹³C NMR (CDCl₃) δ 138.32, 137.88, 134.17 (C_{q,Ar}), 133.16, 128.85, 128.52, 128.35, 128.27, 127.95, 127.87, 127.77, 127.23 (C_{Ar}), 87.89 (C-1), 82.78 (C-3), 78.08 (C-5), 77.06 (C-2), 75.73 (CH_{2Bn}), 72.15 (CH_{2Bn}), 66.81 (C-4), 62.77 (C-6), 25.85 (CH_{3,TBS}), 18.29 (C_{q,TBS}), -5.37, -5.45 (2C, CH_{3,TBS}). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₃₂H₄₆O₅SSiN 584.2860; found 584.2854.

Phenyl 4-azido-2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-4-deoxy-1-thio- β -L-glucopyranoside (9): *Step 1:* Alcohol **8** (710 mg, 1.25 mmol, 1.0 equiv.) was dissolved in anhyd. DCM (12.5 mL) under an Ar atmosphere. The solution was cooled to -10 °C. Anhyd. pyridine (302 μ L, 3.76 mmol, 3.0 equiv.) was added followed by addition of triflic anhydride (316 μ L, 1.88 mmol, 1.5 equiv.). The solution was stirred for 1 h at -10 °C and diluted with DCM (10 mL). The organic layer was washed with 1 N aq. HCl (20 mL) and 0.5 M aq. NaHCO₃ (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The crude was dried under high vacuum for 2 h.

Step 2: The residue was dissolved in anhyd. DMF (12.5 mL) and sodium azide (820 mg, 12.5 mmol, 10 equiv.) was added. After stirring at rt overnight, the reaction mixture was diluted with DCM (20 mL) and washed with H₂O (30 mL) and brine (30 mL). The organic phase was dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (95:5→90:10, cHex/EtOAc) to give the 4-azido glucopyranoside **9** (640 mg, 10.8 mmol, 86%) as a white solid. The azido derivative **9** had R_f 0.3 (cHex/EtOAc 19:1). ¹H NMR (CDCl₃) δ 7.48-7.13 (m, 15H, H_{Ar}), 4.77-4.70 (m, 3H, CH_{2Bn}), 4.57 (d, 1H, *J* = 10.4 Hz, CH_{2Bn}), 4.48 (d, 1H, *J*_{1,2} = 9.6 Hz, H-1), 3.82-3.73 (m, 2H, H-6a, H-6b), 3.55 (t, 1H, *J*_{2,3} = *J*_{3,4} = 9.8 Hz, H-4), 3.44 (t, 1H, *J*_{4,5} = 8.5 Hz, H-3), 3.36 (t, 1H, H-2), 3.08-3.05 (m, 1H, H-5), 0.84 (s, 9H, C(CH₃)_{TBS}), 0.02 (s, 3H, CH_{3,TBS}), 0.00 (s, 3H, CH_{3,TBS}). ¹³C NMR (CDCl₃) δ 138.06, 137.72, 133.41 (C_{q,Ar}), 132.33, 128.98, 128.57, 128.52, 128.36, 128.14, 128.07, 127.96,

127.69 (C_{Ar}), 87.36 (C-1), 85.04 (C-3), 80.33 (C-2), 79.20 (C-5), 75.97 (CH_{2Bn}), 75.35 (CH_{2Bn}), 62.62 (C-6), 61.62 (C-2), 25.98 (CH_{3,TBS}), 18.39 (C_{q,TBS}), -5.17, -5.39 (2C, CH_{3,TBS}). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₃₂H₄₅N₄O₄SSi 609.2925; found 609.2906.

Phenyl 4-azido-2,3-di-O-benzyl-4-deoxy-1-thio-β-L-glucopyranoside (10): 1M TBAF in THF (1.62 mL, 1.62 mmol, 1.2 equiv.) was added to a solution of azide **9** (800 mg, 1.35 mmol, 1.0 equiv.) in THF (15 mL). The reaction mixture was left to stir for 6 h at rt. At completion, volatiles were evaporated. The residue was purified by flash chromatography (90:10→80:20, Tol/EtOAc) to give the desired **10** as a white solid (620 mg, 1.29 mmol, 96%). Alcohol **10** had R_f 0.55 (Tol/EtOAc 4:1). ¹H NMR (CDCl₃) δ 7.42-7.17 (m, 15H, H_{Ar}), 4.85-4.73 (m, 3H, CH_{2Bn}), 4.64 (d, 1H, *J* = 10.4 Hz, CH_{2Bn}), 4.58 (d, 1H, *J*_{1,2} = 9.6 Hz, H-1), 3.79 (dd, 1H, *J*_{5,6a} = 2.8 Hz, *J*_{6a,6b} = 12.0 Hz, H-6a), 3.63 (d, 1H, *J*_{5,6b} = 6.0 Hz, H-6b), 3.53-3.38 (m, 3H, H-3, H-4, H-2), 3.14-3.10 (m, 1H, H-5), 1.94 (brs, 1H, OH). ¹³C NMR (CDCl₃) δ 137.75, 137.60, 133.28 (C_{q,Ar}), 131.99, 129.14, 128.52, 128.34, 128.19, 128.17, 128.03, 127.90 (C_{Ar}), 87.77 (C-1), 84.87 (C-3), 80.82 (C-2), 78.49 (C-5), 75.82 (CH_{2Bn}), 75.54 (CH_{2Bn}), 62.39 (C-6), 61.63 (C-4). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₂₆H₃₁N₄O₄S 495.2061; found 495.2048.

Phenyl 4-azido-2,3-di-O-benzyl-1-thio-4,6,7-tri-deoxy-β-L-gluco-hept-6-enopyranoside (11) and (2S, 3R, 4S)-3,4-bis(benzyloxy)-2-(phenylthio)-3,4-dihydro-2H-pyran-6-carbaldehyde (12): *Protocol 1:* The alcohol **10** (310 mg, 650 μmol, 1.0 equiv.) was subjected to methylenation following the general procedure to give the desired **11** as a colorless oil (35 mg, 74 μmol, 11%) and the elimination product **12** obtained as a colorless oil (140 mg, 323 μmol, 49%). The alkene **11** had R_f 0.75 (cHex:EtOAc 9:1). ¹H NMR (CDCl₃) δ 7.49-7.44 (m, 2H, H_{Ar}), 7.34-7.18 (m, 13H, H_{Ar}), 5.89-5.81 (m, 1H, C-6), 5.70 (dt, *J*_{6,7a} = 17.2 Hz, *J*_{7a,7b} = 1.2 Hz, H-7a), 5.70 (dt, *J*_{6,7b} = 10.6 Hz, H-7b), 4.85 (d, 1H, *J* = 10.2 Hz, CH_{2Bn}), 4.81-4.75 (m, 2H, CH_{2Bn}), 4.66 (d, 1H, CH_{2Bn}), 4.58 (d, 1H, *J*_{1,2} = 9.6 Hz, H-1), 3.58-3.53 (m, 1H, H-5), 3.47 (t, 1H, *J*_{3,4} = *J*_{2,3} = 8.8 Hz, H-3), 3.42 (t, 1H, H-2), 3.21 (dd, 1H, H-4). ¹³C NMR (CDCl₃) δ 137.84, 137.66, 133.28 (C_{q,Ar}), 133.79 (C-6), 132.35, 128.97, 128.49, 128.47, 128.18, 128.14, 127.98, 127.96, 127.82 (C_{Ar}), 119.29 (C-7), 87.67 (C-1), 84.68 (C-3), 80.71 (C-2), 78.93 (C-5), 75.86 (CH_{2Bn}), 75.48 (CH_{2Bn}), 66.23 (C-4). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₂₇H₃₁N₄O₃S 491.2111; found 491.2106.

The aldehyde **12** had R_f 0.65 (Tol:EtOAc 9:1). ¹H NMR (CDCl₃) δ 9.22 (s, 1H, CHO), 7.48-7.44 (m, 2H, H_{Ar}), 7.30-7.20 (m, 13H, H_{Ar}), 6.00 (dd, 1H, *J* = 1.4 Hz, *J* = 4.6 Hz, H-4), 5.67 (dd, 1H, *J* = 2.6 Hz, H-1), 4.61-4.45 (m, 4H, CH_{2Bn}), 4.02-4.01 (m, 1H, H-2), 3.99-3.97 (m, 1H, H-3). ¹³C NMR (CDCl₃) δ 186.59 (CHO), 149.02 (C-5), 137.32, 137.02, 134.57 (C_{q,Ar}), 132.29, 129.16, 128.63, 128.61, 128.22, 128.13, 128.01, 127.95 (C_{Ar}), 117.05 (C-4), 84.03 (C-1), 74.73 (C-2), 72.01 (CH_{2Bn}), 71.31 (CH_{2Bn}), 70.01 (C-3). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₂₆H₂₈NO₄S 450.1739; found 450.1727.

Protocol 2: Step 1: To a solution of the alcohol **10** (100 mg, 210 μmol, 1.0 equiv.) in DCM (5.0 mL) was added Dess-Martin Periodinane (116 mg, 272 μmol, 1.3 equiv.). The reaction was left to stirred for 2 h at 0 °C. At completion, the suspension was filtered over a pad of Celite and

washed with DCM (2×5 mL). The filtrate was concentrated and co-evaporated with toluene. The crude was left under high vacuum for 2 h. *Step 2*: The crude aldehyde (~100 mg, 210 μ mol, 1.0 equiv.) was dissolved in anhyd. toluene (4 mL). The solution was transferred to another flask using a syringe. The Tebbe reagent (1M in toluene, 251 μ L, 251 μ mol, 1.2 equiv.) was added. The reaction was left to stir overnight at rt. At completion, the reaction mixture was diluted with potassium tartrate (10 mL) and EtOAc (10 mL). The EtOAc part was collected, dried over Na_2SO_4 and concentrated. The crude was purified by silica gel column chromatography (96:4 \rightarrow 94:6 cHex:EtOAc) to give the desired **11** as a white solid (30 mg, 63 μ mol, 30%). The elimination product **12** was obtained as a yellowish solid (3 mg, 3%). Analytical data for compounds **11** and **12** were as above.

Phenyl 2,3-di-O-benzyl-6-O-tert-butyltrimethylsilyl-4-O-(4-methoxybenzyl)-1-thio- β -L-glucopyranoside (13): Alcohol **7** (2.0 g, 3.53 mmol, 1.0 equiv.) was dissolved in DMF (12 mL) and the solution was cooled to 0 $^\circ\text{C}$. 4-Methoxybenzyl chloride (PMB-Cl, 719 μ L, 4.59 mmol, 1.3 equiv.) was added, followed by the portionwise addition of sodium hydride (60% in mineral oil, 310 mg, 7.77 mmol, 2.2 equiv.). After stirring for 1 h at 0 $^\circ\text{C}$, 5% aq. NH_4Cl was added. The aq. layer was washed with DCM (3×20 mL). The combined DCM part was washed with 10% brine (50 mL), dried over anhyd. Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (95:5 \rightarrow 90:10 cHex:EtOAc) to give the desired **13** as a colorless oil (2.1 g, 3.05 mmol, 86%). The fully protected **13** had R_f 0.5 (Tol:EtOAc, 19:1). ^1H NMR (CDCl_3) δ 7.47-7.45 (m, 2H, H_{Ar}), 7.27-7.07 (m, 15H, H_{Ar}), 6.74-6.71 (m, 2H, H_{Ar}), 4.75-4.71 (m, 3H, $\text{CH}_{2\text{Bn}}$), 4.65 (d, 1H, $J = 10.4$ Hz, $\text{CH}_{2\text{Bn}}$), 4.58 (d, 1H, $\text{CH}_{2\text{Bn}}$), 4.51 (d, 2H, $J = 9.8$ Hz, $\text{CH}_{2\text{Bn}}$, H-1), 3.78-3.67 (m, 5H, H-6a, H-6b, OCH_3), 3.59-3.49 (m, 2H, H-3, H-4), 3.34 (dd, 1H, $J = 8.4$ Hz, $J = 9.6$ Hz, H-2), 3.20-3.16 (m, 1H, H-5), 0.81 (s, 9H, $\text{C}(\text{CH}_3)_{\text{TBS}}$), 0.00 (s, 3H, CH_3_{TBS}), -0.03 (s, 3H, CH_3_{TBS}). ^{13}C NMR (CDCl_3) δ 159.36, 138.51, 128.20, 134.00 ($\text{C}_{\text{q,Ar}}$), 131.95, 130.52, 129.62, 128.84, 128.46, 128.39, 128.16, 127.79, 127.70, 127.33, 113.92 (C_{Ar}), 87.40 (C-1), 86.82 (C-3), 80.81 (C-2), 80.16 (C-5), 77.19 (C-4), 75.89 ($\text{CH}_{2\text{Bn}}$), 75.35 ($\text{CH}_{2\text{Bn}}$), 74.69 ($\text{CH}_{2\text{Bn}}$), 62.19 (C-6), 55.28 (OCH_3), 25.96 (CH_3_{TBS}), 18.34 ($\text{C}_{\text{q,TBS}}$), -5.07, -5.34 (2C, CH_3_{TBS}). HRMS (ESI $^+$): m/z [$\text{M}+\text{NH}_4$] $^+$ calc. for $\text{C}_{40}\text{H}_{54}\text{NO}_6\text{SSi}$ 704.3436; found 704.3421.

Phenyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-1-thio- β -L-glucopyranoside (14): The silyl ether **13** (2.0 g, 2.91 mmol, 1.0 equiv.) was dissolved in anhyd. THF (20 mL). TBAF (1.0 M in THF, 3.49 mL, 3.49 mmol, 1.2 equiv.) was added at rt. The reaction mixture was left to stir overnight at rt. At completion, AcOH (200 μ L, 3.49 mmol, 1.2 equiv.) was added and volatiles were evaporated under reduced pressure. The crude was purified by flash chromatography (65:35 \rightarrow 50:50 cHex:EtOAc) to give alcohol **14** as a white solid (1.35 g, 2.35 mmol, 81%). Alcohol **14** had R_f 0.25 (Tol:EtOAc, 90:10). ^1H NMR (CDCl_3) δ 7.55-7.52 (m, 2H, H_{Ar}), 7.42-7.28 (m, 15H, H_{Ar}), 6.90-6.86 (m, 2H, H_{Ar}), 4.96-4.92 (m, 3H, $\text{CH}_{2\text{Bn}}$), 4.82-4.78 (m, 2H, $\text{CH}_{2\text{Bn}}$), 4.74 (d, 1H, $J_{1,2} = 9.8$ Hz, H-1), 4.61 (d, 1H, $J = 10.6$ Hz, $\text{CH}_{2\text{Bn}}$), 3.90-3.86 (m, 1H, H-6a), 3.82 (s, 3H, OCH_3), 3.77-3.68 (m, 2H, H-3, H-6b), 3.58 (t, 1H, $J_{3,4} = J_{4,5} = 9.2$ Hz, H-4), 3.51 (dd, 1H,

$J_{2,3} = 8.8$ Hz, H-2), 3.42-3.38 (m, 1H, H-5), 1.92 (brs, 1H, OH). ^{13}C NMR (CDCl_3) δ 159.48, 138.42, 137.95, 133.53, 130.03 ($\text{C}_{\text{q,Ar}}$), 131.88, 129.76, 129.05, 128.48, 128.43, 128.22, 127.90, 127.74, 127.68, 113.96 (C_{Ar}), 87.56 (C-1), 86.62 (C-3), 81.18 (C-2), 79.37 (C-5), 77.41 (C-4), 75.79 (CH_2Bn), 75.55 (CH_2Bn), 74.79 (CH_2Bn), 62.24 (C-6), 55.29 (OCH_3). HRMS (ESI^+): m/z $[\text{M}+\text{NH}_4]^+$ calc. for $\text{C}_{34}\text{H}_{40}\text{NO}_6\text{S}$ 590.2571; found 590.2552.

Phenyl 2,3-di-O-benzyl-4-O-(4-methoxybenzyl)-1-thio-6,7-dideoxy- β -L-gluco-hept-6-enopyranoside (15) and (2S, 3R, 4S)-3,4-bis(benzyloxy)-2-(phenylthio)-6-vinyl-3,4-dihydro-2H-pyran (20):

Protocol 1: The alcohol **14** (200 mg, 350 μmol , 1.0 equiv.) was subjected to methylenation following the general procedure to give the desired **15** as a white solid (42 mg, 73 μmol , 21%) and the undesired **20** as a white solid (20 mg, 46 μmol , 13%). The elimination product **12** was obtained as a colorless oil (12 mg, 27 μmol , 8%). The desired alkene **15** had R_f 0.7 (90:10 Tol:EtOAc). ^1H NMR (CDCl_3) δ 7.48-7.46 (m, 2H, H_{Ar}), 7.32-7.17 (m, 13H, H_{Ar}), 7.11-7.09 (m, 2H, H_{Ar}), 6.76-6.74 (m, 2H, H_{Ar}), 5.92-5.84 (m, 1H, H-6), 5.38 (dt, $J_{6,7a} = 17.2$ Hz, $J_{7a,7b} = 1.4$ Hz, H-7a), 5.22 (dt, $J_{6,7b} = 10.5$ Hz, H-7b), 4.82-4.79 (m, 3H, CH_2Bn), 4.66 (d, 1H, $J = 10.4$ Hz, CH_2Bn), 4.60 (d, 2H, H-1, CH_2Bn), 3.72-3.68 (m, 4H, H-5, OCH_3), 3.60 (t, 1H, $J_{2,3} = 8.8$ Hz, H-3), 3.41 (dd, 1H, $J_{1,2} = 9.6$ Hz, H-3), 3.25 (t, 1H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4). ^{13}C NMR (CDCl_3) δ 159.40, 138.52, 138.09, 133.71, 130.13 ($\text{C}_{\text{q,Ar}}$), 134.61 (C-6), 132.17, 129.71, 128.90, 128.45, 128.41, 128.22, 127.85, 127.79, 127.69, 127.57, 113.86 (C_{Ar}), 118.20 (C-7), 87.50 (C-1), 86.42 (C-3), 81.76 (C-4), 80.98 (C-2), 79.89 (C-5), 75.87 (CH_2Bn), 75.48 (CH_2Bn), 74.84 (CH_2Bn), 55.29 (OCH_3). HRMS (ESI^+): m/z $[\text{M}+\text{NH}_4]^+$ calc. for $\text{C}_{35}\text{H}_{40}\text{NO}_5\text{S}$ 586.2622; found 586.2599.

The diene **20** had R_f 0.45 (9:1 cHex:EtOAc). ^1H NMR (CDCl_3) δ 7.49-7.46 (m, 2H, H_{Ar}), 7.29-7.18 (m, 13H, H_{Ar}), 6.06 (dd, $J_{6,7a} = 17.0$ Hz, $J_{6,7b} = 10.6$ Hz, H-6), 5.58 (dd, $J = 1.2$ Hz, $J = 3.0$ Hz, H-1), 5.53 (dd, $J_{7a,7b} = 1.2$ Hz, H-7a), 5.12-5.07 (m, H-7b, H-4), 4.61 (d, 1H, $J = 12.0$ Hz, CH_2Bn), 4.54-4.46 (m, 3H, CH_2Bn), 3.93-3.90 (m, 2H, H-2, H-3). ^{13}C NMR (CDCl_3) δ 149.25 (C-5), 138.09, 137.57, 135.46 ($\text{C}_{\text{q,Ar}}$), 131.77 (C-6), 132.21, 128.90, 128.55, 128.44, 128.02, 127.95, 127.86, 127.74, 127.55 (C_{Ar}), 116.05 (C-7), 101.23 (C-4), 83.81 (C-1), 75.04 (C-2), 72.11 (CH_2Bn), 70.96 (C-3), 70.43 (CH_2Bn). HRMS (ESI^+): m/z $[\text{2M}+\text{NH}_4]^+$ calc. for $\text{C}_{54}\text{H}_{56}\text{NO}_6\text{S}_2$ 878.3544; found 878.3522.

Protocol 2: Step 1: The alcohol **14** (200 mg, 350 μmol , 1.0 equiv.) was dissolved in anhyd. DCM (8 mL). DMSO (124 μL , 1.74 mmol, 5.0 equiv.) and DIPEA (183 μL , 1.04 mmol, 3.0 equiv.) were added. The reaction mixture was placed in an ice-bath. Sulfur trioxide pyridine complex (SO_3Py , 167 mg, 1.04 mmol, 3.0 equiv.) was added and the mixture was left to stir for 2 h at 0 $^\circ\text{C}$. At completion, DCM (10 mL) was added and the organic layer was washed successively with NH_4Cl (15 mL) and brine (15 mL). The organic phase was collected, dried over Na_2SO_4 , and concentrated. The crude aldehyde was left to dry under high vacuum for 2 h. *Step 2:* The crude aldehyde was dissolved in anhyd. toluene and transferred to a flamed-dried flask using a cannula. Tebbe reagent (1M in Toluene, 350 μL , 350 μmol , 1.0 equiv.) was added. The reaction mixture was left to stir overnight at rt. At completion, the mixture was diluted with aq. potassium tartrate and EtOAc. The EtOAc part was collected, dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography (90:10 \rightarrow 80:20 cHex:EtOAc) to

give the desired **15** as a white solid (115 mg, 202 μmol , 58%). Analytical data for compound **15** were as above.

Phenyl 2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio- β -L-glucopyranoside (16**):** To a solution of diol **6** (800 mg, 1.76 mmol, 1.0 equiv.) was added imidazole (265 mg, 3.89 mmol, 2.2 equiv.). The reaction mixture was cooled to 0 $^{\circ}\text{C}$. TBDPS-Cl (535 mg, 1.94 mmol, 1.1 equiv.) was added. The reaction mixture was slowly allowed to attain rt and stirred overnight. At completion, methanol (\sim 1 mL) was added. The mixture was concentrated. The crude was purified by flash chromatography (90:10 \rightarrow 85:15 cHex:EtOAc) to give the desired **16** as a colorless oil (1.1 g, 1.59 mmol, 90%). The alcohol **16** had R_f 0.35 (cHex/EtOAc 6:1). ^1H NMR (CDCl_3) δ 7.76-7.74 (m, 4H, H_{Ar}), 7.61-7.57 (m, 2H, H_{Ar}), 7.48-7.31 (m, 16H, H_{Ar}), 7.26-7.25 (m, 3H, H_{Ar}), 4.95-4.92 (m, 2H, $\text{CH}_{2\text{Bn}}$), 4.82 (d, 1H, $J = 11.2$ Hz, $\text{CH}_{2\text{Bn}}$), 4.76 (d, 1H, $J = 10.4$ Hz, $\text{CH}_{2\text{Bn}}$), 4.72 (d, 1H, $J_{1,2} = 9.4$ Hz, H-1), 4.01-3.93 (m, 2H, H-6a, H-6b), 3.77 (td, 1H, H-4), 3.58 (t, 1H, $J_{2,3} = J_{3,4} = 8.8$ Hz, H-3), 3.52 (t, 1H, H-2), 3.43 (dt, 1H, $J_{4,5} = 9.6$ Hz, H-5), 2.48 (d, 1H, $J_{4,\text{OH}} = 2.4$ Hz, OH), 1.16 (s, 9H, CH_3 , TBDPS). ^{13}C NMR (CDCl_3) δ 138.50, 138.12, 134.01, 133.14, 133.01 ($\text{C}_{\text{q,Ar}}$), 135.71, 135.66, 134.81, 131.70, 129.79, 129.77, 129.66, 128.92, 128.61, 128.43, 128.22, 128.02, 127.94, 127.87, 127.77, 127.74, 127.34 (C_{Ar}), 87.76 (C-1), 86.36 (C-3), 80.33 (C-2), 79.19 (C-5), 75.54 ($\text{CH}_{2\text{Bn}}$), 75.30 ($\text{CH}_{2\text{Bn}}$), 71.25 (C-4), 64.19 (C-6), 26.87 (CH_3 , TBDPS), 19.27 ($\text{C}(\text{CH}_3)_3$, TBDPS). HRMS (ESI^+): m/z $[\text{M}+\text{NH}_4]^+$ calc. for $\text{C}_{42}\text{H}_{50}\text{NO}_5\text{SSi}$ 708.3173; found 708.3160.

Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio- β -L-glucopyranoside (17**):** The alcohol **16** (1.1 g, 1.59 mmol, 1.0 equiv.) was dissolved in DMF (10 mL). The mixture was cooled to 0 $^{\circ}\text{C}$. BnBr (227 μL , 1.91 mmol, 1.2 equiv.) and NaH (60% in mineral oil, 139 mg, 3.50 mmol, 2.2 equiv.) were added. The reaction mixture was left to stir vigorously for 1 h at 0 $^{\circ}\text{C}$. At completion, 5% aq. NH_4Cl was added. The aq. phase was extracted with DCM (3 \times 15 mL). The combined DCM layer washed with 10% brine (50 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography (96:4 \rightarrow 98:2 cHex:EtOAc) to give the desired **17** as a colorless oil (1.1 g, 1.41 mmol, 88%). Compound **17** had R_f 0.6 (Tol:EtOAc 9:1). ^1H NMR (CDCl_3) δ 7.85-7.84 (m, 2H, H_{Ar}), 7.79-7.76 (m, 2H, H_{Ar}), 7.69-7.65 (m, 2H, H_{Ar}), 7.45-7.20 (m, 24H, H_{Ar}), 4.98-4.91 (m, 3H, $\text{CH}_{2\text{Bn}}$), 4.81 (d, 1H, $J = 10.4$ Hz, $\text{CH}_{2\text{Bn}}$), 4.77-4.74 (m, 2H, H-1, $\text{CH}_{2\text{Bn}}$), 4.08-3.98 (m, 2H, H-6a, H-6b), 3.86 (t, 1H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 3.79 (t, 1H, $J_{2,3} = 9.4$ Hz, H-3), 3.62 (dd, 1H, $J_{1,2} = 8.8$ Hz, H-2), 3.49-3.45 (m, 1H, H-5), 1.16 (s, 9H, CH_3 , TBDPS). ^{13}C NMR (CDCl_3) δ 138.43, 138.24, 138.15, 134.26, 133.55, 132.98 ($\text{C}_{\text{q,Ar}}$), 135.92, 135.68, 131.69, 129.69, 129.65, 128.94, 128.52, 128.45, 128.19, 128.00, 127.89, 127.85, 127.78, 127.71, 127.28 (C_{Ar}), 87.59 (C-1), 86.93 (C-3), 80.90 (C-2), 80.04 (C-5), 77.51 (C-4), 76.01 ($\text{CH}_{2\text{Bn}}$), 75.43 ($\text{CH}_{2\text{Bn}}$), 75.16 ($\text{CH}_{2\text{Bn}}$), 62.77 (C-6), 26.92 (CH_3 , TBDPS), 19.34 ($\text{C}(\text{CH}_3)_3$, TBDPS). HRMS (ESI^+): m/z $[\text{M}+\text{NH}_4]^+$ calc. for $\text{C}_{43}\text{H}_{56}\text{NO}_5\text{SSi}$ 798.3643; found 798.3632.

Phenyl 2,3,4-tri-*O*-benzyl-1-thio- β -L-glucopyranoside (18**):** TBAF (1.0 M in THF, 1.55 mL, 1.55 mmol, 1.1 equiv.) was added to a solution of starting material **17** (1.1 g, 1.41 mmol, 1.0

equiv.) in THF (10 mL). The reaction mixture was stirred overnight at rt. At completion, acetic acid (~100 μ L) was added. The mixture was concentrated and the crude was purified by flash chromatography (85:15 \rightarrow 75:25 Tol:EtOAc) to give the alcohol **18** as a white solid (700 mg, 1.29 mmol, 91%). Compound **18** had R_f 0.45 (Tol:EtOAc 4:1). ^1H NMR (CDCl_3) δ 7.55-7.53 (m, 2H, H_{Ar}), 7.43-7.28 (m, 18H, H_{Ar}), 4.96-4.87 (m, 4H, $\text{CH}_{2\text{Bn}}$), 4.80 (d, 1H, $J = 10.4$ Hz, $\text{CH}_{2\text{Bn}}$), 4.75 (d, 1H, $J_{1,2} = 9.6$ Hz, H-1), 4.68 (d, 1H, $J = 11.0$ Hz, $\text{CH}_{2\text{Bn}}$), 3.92-3.89 (m, 1H, H-6a), 3.78-3.71 (m, 2H, H-3, H-6b), 3.61 (t, 1H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 3.52 (dd, 1H, $J_{2,3} = 9.0$ Hz, H-2), 3.44-3.40 (m, 1H, H-5), 1.90 (brs, 1H, OH). ^{13}C NMR (CDCl_3) δ 138.34, 137.94, 137.88 ($\text{C}_{\text{q,Ar}}$), 135.51, 131.89, 129.05, 128.52, 128.47, 128.44, 128.21, 128.03, 127.97, 127.91, 127.79, 127.75, 127.70 (C_{Ar}), 87.57 (C-1), 86.59 (C-3), 81.17 (C-2), 79.35 (C-5), 77.65 (C-4), 75.82 ($\text{CH}_{2\text{Bn}}$), 75.55 ($\text{CH}_{2\text{Bn}}$), 75.12 ($\text{CH}_{2\text{Bn}}$), 62.19 (C-6). HRMS (ESI^+): m/z [$\text{M}+\text{NH}_4$] $^+$ calc. for $\text{C}_{33}\text{H}_{38}\text{NO}_5\text{S}$ 560.2465; found 560.2453.

Phenyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-1-thio- β -L-gluco-hept-6-enopyranoside (19): *Step 1:* DMSO (65 μ L, 922 μ mol, 5.0 equiv.) and DIPEA (96 μ L, 553 μ mol, 3.0 equiv.) were added to a solution of the alcohol **18** (100 mg, 1.0 equiv.) in anhyd. DCM (5 mL). The reaction mixture was cooled to 0 $^\circ\text{C}$ and sulfur trioxide pyridine complex (SO_3Py , 88 mg, 553 μ mol, 3.0 equiv.) was added. The mixture was left to stir for 2 h at 0 $^\circ\text{C}$. Upon completion, DCM (10 mL) was added and the organic part was washed successively with 5% aq. NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4 , concentrated, and further dried under high vacuum for 2 h. The crude aldehyde was used in the next step without further purification. *Step 2:* Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M in THF, 350 μ L, 350 μ mol, 1.9 equiv.) was added to triphenylphosphonium methyl bromide (131 mg, 369 μ mol, 2.0 equiv.) in anhyd. THF/DMF (3:1, 4 mL) at 0 $^\circ\text{C}$. The solution was stirred for 2 h at 0 $^\circ\text{C}$ under argon. The crude aldehyde in anhyd. THF (2 mL) was added at 0 $^\circ\text{C}$. The system was slowly allowed to attain rt and stir for 24 h at this temperature. At completion, the reaction was quenched by 5% aq NH_4Cl was added. The aqueous layer was washed with EtOAc (2 \times 10 mL). The combined EtOAc part was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography (95:5 \rightarrow 90:10 cHex:EtOAc) to give the desired alkene **19** as a white solid (65 mg, 120 μ mol, 65%). The target **19** had R_f 0.55 (cHex:EtOAc 9:1). ^1H NMR (CDCl_3) δ 7.43-7.40 (m, 2H, H_{Ar}), 7.27-7.11 (m, 18H, H_{Ar}), 5.87-5.79 (m, 1H, H-6), 5.33 (dt, $J_{6,7a} = 17.2$ Hz, $J_{7a,7b} = 1.4$ Hz, H-7a), 5.16 (dt, $J_{6,7b} = 10.6$ Hz, H-7b), 4.78-4.73 (m, 3H, $\text{CH}_{2\text{Bn}}$), 4.64-4.60 (m, 2H, $\text{CH}_{2\text{Bn}}$), 4.56 (d, 1H, $J_{1,2} = 9.6$ Hz, H-1), 4.51 (d, 1H, $J = 10.8$ Hz, $\text{CH}_{2\text{Bn}}$), 3.69-3.65 (m, 1H, H-5), 3.57 (t, 1H, $J_{2,3} = J_{3,4} = 8.8$ Hz, H-3), 3.36 (dd, 1H, H-2), 3.20 (dd, 1H, $J_{4,5} = 9.4$ Hz, H-4). ^{13}C NMR (CDCl_3) δ 138.44, 138.09, 137.96, 133.69 ($\text{C}_{\text{q,Ar}}$), 134.55 (C-6), 132.18, 128.91, 128.45, 128.42, 128.42, 128.21, 128.01, 127.85, 127.72, 127.59 (C_{Ar}), 118.25 (C-7), 87.51 (C-1), 86.41 (C-3), 82.06 (C-4), 80.98 (C-2), 79.84 (C-5), 75.90 ($\text{CH}_{2\text{Bn}}$), 75.48 ($\text{CH}_{2\text{Bn}}$), 75.16 ($\text{CH}_{2\text{Bn}}$). HRMS (ESI^+): m/z [$\text{M}+\text{Na}$] $^+$ calc. for $\text{C}_{34}\text{H}_{34}\text{O}_4\text{SNa}$ 561.2070; found 561.2062.

Phenyl 4-azido-2,3-di-*O*-benzyl-4-deoxy-1-thio-D/L-glycero- β -L-gluco-heptopyranoside (21): The alkene **11** (30 mg, 63 μ mol, 1.0 equiv.) was dissolved in a mixture of acetone-water (10:1,

v/v, 5 mL). The mixture was placed in an ice-bath of 0 °C. Osmium tetroxide (4 mg, 32 μmol, 0.25 equiv.) was added followed by the addition of *N*-methylmorpholine *N*-oxide (14 mg, 127 μmol, 2.0 equiv.). The reaction was left to stir for 2 h at 0 °C. At completion, satd aq. Na₂S₂O₃ was added. The resulting mixture was concentrated to remove volatiles. The aqueous phase was washed with DCM (2 × 10 mL). The DCM part was collected, washed with brine (20 mL), dried over Na₂S₂O₄, and concentrated under reduced pressure. The crude was purified by flash chromatography (40:60→50:50 cHex:EtOAc) to give the desired product as a mixture of *D*-glycero and *L*-glycero isomer **21**, isolated as a white solid (26 mg, 51 μmol, 81%). The mixture of diols **21** had R_f 0.6 (Tol:EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.17 (m, 31H), 4.88-4.81 (m, 4.1H), 4.79-4.74 (m, 2.1H), 4.69-4.66 (m, 2.1H), 4.60 (d, 1H, *J* = 9.6 Hz), 4.56 (d, 1H, *J* = 9.6 Hz), 3.84 (brd, 1.1H), 3.77 (brd, 1H), 3.76 – 3.67 (m, 2H), 3.74-3.60 (m, 4.3H), 3.56-3.39 (m, 6.4H), 3.23 (dd, *J* = 10.0, 3.9 Hz, 1.1H), 3.10 (dd, *J* = 10.2, 1.9 Hz, 1H), 2.72 (s, 1H), 2.43-2.41 (m, 1H), 2.02 (s, 1H), 1.89 (s, 1H). ¹³C NMR (CDCl₃) δ 137.61, 137.58, 137.39, 132.81, 132.63, 132.42, 132.20, 129.28, 129.21, 128.52, 128.22, 128.18, 128.16, 128.08, 128.01, 87.94, 84.98, 84.72, 81.00, 80.77, 79.42, 79.06, 75.87, 75.81, 75.60, 75.52, 71.96, 69.11, 64.38, 62.67, 62.56, 61.56. HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₂₇H₃₃N₄O₅S 525.2166; found 525.2145.

Phenyl 4-azido-6,7-di-*O*-benzoyl-2,3-di-*O*-benzyl-4-deoxy-1-thio-*D*-glycero-β-*L*-gluco-heptopyranoside (22) and Phenyl 4-azido-6,7-di-*O*-benzoyl-2,3-di-*O*-benzyl-4-deoxy-1-thio-*L*-glycero-β-*L*-gluco-heptopyranoside (23): The mixture of diols **21** (20 mg, 39 μmol, 1.0 equiv.) was dissolved in anhyd. pyridine (3 mL) and placed in an ice-bath at 0 °C. Benzoyl chloride (11 μL, 99 μmol, 2.5 equiv.) was added. The reaction mixture was left to stir for 3 h at 0 °C under argon. At completion, MeOH (~20 μL) was added. The mixture was concentrated under reduced pressure. The crude was dissolved in DCM (15 mL) and washed with 1N aq. HCl (5 mL), 10 % aq. NaHCO₃ (5 mL) and brine (5 mL). The DCM part was collected, dried over Na₂SO₄ and concentrated. The crude was purified by flash chromatography to give as hypothesized, by order of elution, the undesired dibenzoylated *D*-glycero-*L*-gluco-heptopyranoside **22** (9 mg, 13 μmol, 32%), a mixture of **22** and **23** (8 mg, 11 μmol, 28%), and the desired dibenzoylated *L*-glycero-*L*-gluco-heptopyranoside **23** (6 mg, 8 μmol, 21%). Diastereomer **22** had R_f 0.45 (cHex:EtOAc 10:1). ¹H NMR (CDCl₃) δ 7.98-7.91 (m, 4H, H_{Ar}), 7.55-7.03 (m, 21H, H_{Ar}), 5.75 (ddd, 1H, *J* = 6.8, 3.8, 2.8 Hz, H-6), 4.88 (d, 1H, *J* = 10.4 Hz, CH₂Bn), 4.83 (d, 1H, *J* = 10.8 Hz, CH₂Bn), 4.77 (d, 1H, CH₂Bn), 4.75 (m, 3H), 4.71 (dd, 1H, *J* = 12.2, 3.9 Hz, H-7a), 4.66 (d, 1H, *J* = 10.4 Hz, CH₂Bn), 4.59-4.54 (m, 2H, H-7b, H-1), 3.65-3.56 (m, 2H, H-4, H-3), 3.52 (dd, 1H, *J* = 10.2, 2.8 Hz, H-5), 3.44 (dd, 1H, *J* = 9.7, 8.4 Hz, H-2). ¹³C NMR (CDCl₃) δ 166.19, 165.51 (CO_{Bz}), 137.64, 137.33, 133.05, 132.30 (C_{q,Ar}), 133.40, 133.18, 129.90, 129.75, 129.62, 129.56, 128.95, 128.50, 128.42, 128.24, 128.13, 128.06, 128.03, 127.84, 88.08 (C-1), 85.02 (C-3), 80.75 (C-2), 77.21 (C-5) 75.96 (CH₂Bn), 75.51 (CH₂Bn), 71.52 (C-6), 62.62 (C-7), 62.48 (C-4). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₄₁H₄₁N₄O₇S 733.2690; found 733.2654.

Diastereoisomer **23** had R_f 0.4 (cHex:EtOAc 10:1). ¹H NMR (CDCl₃) δ 8.15-8.13 (m, 2H, H_{Ar}), 7.99-7.96 (m, 2H, H_{Ar}), 7.63-7.25 (m, 21H, H_{Ar}), 5.90-5.87 (m, 1H, H-6), 4.96 (d, 1H, *J* = 10.3

Hz, CH_{2Bn}), 4.90 (d, 1H, *J* = 10.4 Hz, CH_{2Bn}), 4.84 (d, 1H, *J* = 10.4 Hz, CH_{2Bn}), 4.75-4.68 (m, 2H, H-7a, CH_{2Bn}), 4.65 (d, 1H, *J* = 9.6 Hz, H-1), 4.58 (dd, 1H, *J* = 11.2, 5.6 Hz, H-7b), 3.68-3.63 (ddd, *J* = 8.9, 7.2, 2.1 Hz, 1H, H-3), 3.55-3.51 (m, 3H, H-4, H-5, H-2). ¹³C NMR (101 MHz, CDCl₃) δ 165.94, 165.49 (CO_{Bz}), 137.74, 137.26 (C_{q,Ar}), 133.57, 133.16, 133.08, 132.30, 130.02, 129.69, 129.57, 129.21, 129.02, 128.57, 128.54, 128.52, 128.40, 128.33, 128.17, 128.12, 128.09, 128.03 (25C, C_{Ar}), 87.70 (C-1), 84.95 (C-3), 80.31 (C-2), 76.62 (C-5), 76.09 (CH_{2Bn}), 75.40 (CH_{2Bn}), 68.95 (C-6), 63.03 (C-7), 61.66 (C-4). HRMS (ESI⁺): *m/z* [M+NH₄]⁺ calc. for C₄₁H₄₁N₄O₇S 733.2690; found 733.2682.

Supporting information

¹H and ¹³C NMR spectra of all synthesized novel compounds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] A. Varki, Biological roles of glycans, *Glycobiology*, 27 (2017) 3-49. 10.1093/glycob/cww086.
- [2] M. Panza, S.G. Pistorio, K.J. Stine, A.V. Demchenko, Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges, *Chemical Reviews*, 118 (2018) 8105-8150. 10.1021/acs.chemrev.8b00051.
- [3] Rationally Designed Anti-CRISPR Nucleic Acid Inhibitors of CRISPR-Cas9, *Nucleic Acid Therapeutics*, 29 (2019) 136-147. 10.1089/nat.2018.0758.
- [4] C. Kirschbaum, K. Greis, E. Mucha, L. Kain, S. Deng, A. Zappe, S. Gewinner, W. Schöllkopf, G. von Helden, G. Meijer, P.B. Savage, M. Marianski, L. Teyton, K. Pagel, Unravelling the structural complexity of glycolipids with cryogenic infrared spectroscopy, *Nat. Commun.*, 12 (2021) 1201. 10.1038/s41467-021-21480-1.
- [5] R.A. Flynn, K. Pedram, S.A. Malaker, P.J. Batista, B.A.H. Smith, A.G. Johnson, B.M. George, K. Majzoub, P.W. Villalta, J.E. Carette, C.R. Bertozzi, Small RNAs are modified with N-glycans and displayed on the surface of living cells, *Cell*, 184 (2021) 3109-3124.e3122. <https://doi.org/10.1016/j.cell.2021.04.023>.
- [6] Z. Guo, Y. Tang, W. Tang, Y. Chen, Heptose-containing bacterial natural products: structures, bioactivities, and biosyntheses, *Nat. Prod. Rep.*, 38 (2021) 1887-1909. 10.1039/D0NP00075B.
- [7] D. Williams, M.P. Jamshidi, J. Sauvageau, Pathogen-Associated Molecular Patterns: The Synthesis of Heptose Phosphates and Derivatives, *Synthesis*, 54 (2022) 79-91. 10.1055/s-0040-1720179.
- [8] R.G. Gaudet, S.D. Gray-Owen, Heptose Sounds the Alarm: Innate Sensing of a Bacterial Sugar Stimulates Immunity, *PLoS Pathog.*, 12 (2016) e1005807. 10.1371/journal.ppat.1005807.
- [9] K.V. Potapov, R.A. Novikov, P.N. Solyev, S.N. Kochetkov, A.A. Makarov, V.A. Mitkevich, Synthetic Optimizations for Gram-Scale Preparation of 1-O-Methyl d-Glycero- α -d-glucosyl heptoside 7-Phosphate from d-Glucose, *Molecules*, 27 (2022) 7534.
- [10] W. Tang, Z. Guo, Z. Cao, M. Wang, P. Li, X. Meng, X. Zhao, Z. Xie, W. Wang, A. Zhou, C. Lou, Y. Chen, d-Sedoheptulose-7-phosphate is a common precursor for the heptoses of septacidin and hygromycin B, *Proc Natl Acad Sci U S A*, 115 (2018) 2818-2823. 10.1073/pnas.1711665115.
- [11] C. Hobson, A.N. Chan, G.D. Wright, The Antibiotic Resistome: A Guide for the Discovery of Natural Products as Antimicrobial Agents, *Chem. Rev.*, 121 (2021) 3464-3494. 10.1021/acs.chemrev.0c01214.
- [12] C. Figazzolo, F. Bonhomme, S. Saidjalolov, M. Ethève-Quellejeu, M. Hollenstein, Enzymatic Synthesis of Vancomycin-Modified DNA, *Molecules*, 27 (2022) 8927. 10.3390/molecules27248927.
- [13] S.M. Silverman, J.E. Moses, K.B. Sharpless, Reengineering Antibiotics to Combat Bacterial Resistance: Click Chemistry [1,2,3]-Triazole Vancomycin Dimers with Potent Activity against MRSA and VRE, *Chem. Eur. J.*, 23 (2017) 79-83. <https://doi.org/10.1002/chem.201604765>.
- [14] D. Guan, F. Chen, W. Shi, L. Lan, W. Huang, Single Modification at the N-Terminus of Norvancomycin to Combat Drug-Resistant Gram-Positive Bacteria, *ChemMedChem*, 18 (2023) e202200708. <https://doi.org/10.1002/cmdc.202200708>.

- [15] T.D. Epstein, B. Wu, K.D. Moulton, M. Yan, D.H. Dube, Sugar-Modified Analogs of Auranofin Are Potent Inhibitors of the Gastric Pathogen *Helicobacter pylori*, *ACS Infect. Dis.*, 5 (2019) 1682-1687. 10.1021/acsinfecdis.9b00251.
- [16] I. Amarsy, S. Papot, G. Gasser, Stimuli-Responsive Metal Complexes for Biomedical Applications, *Angew. Chem. Int. Ed.*, 61 (2022) e202205900. <https://doi.org/10.1002/anie.202205900>.
- [17] A. Frei, A.D. Verderosa, A.G. Elliott, J. Zuegg, M.A.T. Blaskovich, Metals to combat antimicrobial resistance, *Nat. Rev. Chem.*, 7 (2023) 202-224. 10.1038/s41570-023-00463-4.
- [18] C.-H. Liang, S. Yao, Y.-H. Chiu, P.Y. Leung, N. Robert, J. Seddon, P. Sears, C.-K. Hwang, Y. Ichikawa, A. Romero, Synthesis and biological activity of new 5-O-sugar modified ketolide and 2-fluoro-ketolide antibiotics, *Bioorg. Med. Chem. Lett.*, 15 (2005) 1307-1310. <https://doi.org/10.1016/j.bmcl.2005.01.027>.
- [19] S.I. Elshahawi, K.A. Shaaban, M.K. Kharel, J.S. Thorson, A comprehensive review of glycosylated bacterial natural products, *Chem. Soc. Rev.*, 44 (2015) 7591-7697. 10.1039/C4CS00426D.
- [20] R.M. Giuliano, Synthesis of 4-Amino-4-Deoxy Sugar Components of Antibiotics and Bacterial Glycans, in: *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*, Elsevier, 2018.
- [21] C. Suster, I.R. Baxendale, M.D. Mihovilovic, C. Stanetty, Straight Forward and Versatile Differentiation of the l-glycero and d-glycero-d-manno Heptose Scaffold, *Front. Chem.*, 8 (2020) 625. 10.3389/fchem.2020.00625.
- [22] M. Chen, Z. Guo, J. Sun, W. Tang, M. Wang, Y. Tang, P. Li, B. Wu, Y. Chen, Insights into the biosynthesis of septacidin l-heptosamine moiety unveils a VOC family sugar epimerase, *Acta Pharm. Sin. B.*, 13 (2023) 765-774. <https://doi.org/10.1016/j.apsb.2022.05.031>.
- [23] W. Tang, P. Li, M. Chen, Z. Guo, Y. Chen, Characterization of SepE and SepF for the N6-Glycosylated Adenine Structure Formation in Septacidin Biosynthesis, *Org. Lett.*, 22 (2020) 5251-5254. 10.1021/acs.orglett.0c01918.
- [24] M. Chen, Z. Cao, W. Tang, M. Wang, Y. Chen, Z. Guo, Discovery of novel septacidin congeners from a high yield heterologous expression strain *Streptomyces albus* 1597, *J. Antibiot.*, 75 (2022) 172-175. 10.1038/s41429-022-00499-6.
- [25] M. Yadav, R. Kumar, R. Krishnamurthy, Chemistry of Abiotic Nucleotide Synthesis, *Chem. Rev.*, 120 (2020) 4766-4805. 10.1021/acs.chemrev.9b00546.
- [26] V. Allain, C. Bourgaux, P. Couvreur, Self-assembled nucleolipids: from supramolecular structure to soft nucleic acid and drug delivery devices, *Nucleic Acids Res.*, 40 (2011) 1891-1903. 10.1093/nar/gkr681.
- [27] T. Suzuki, S. Tanaka, I. Yamada, Y. Koashi, K. Yamada, N. Chida, Total Synthesis of Spicamycin Amino Nucleoside, *Org. Lett.*, 2 (2000) 1137-1140. 10.1021/ol005715l.
- [28] S. Tamotsu, C. Noritaka, The New and Efficient Synthesis of a Heptose Moiety of Spicamycin, *Chem. Lett.*, 32 (2003) 190-191. 10.1246/cl.2003.190.
- [29] N.P.J. Price, T. Furukawa, F. Cheng, J. Qi, W. Chen, D. Crich, Biosynthesis of 4-aminoheptose 2-epimers, core structural components of the septacidins and spicamycins, *J. Antibiot.*, 67 (2014) 405-414. 10.1038/ja.2014.15.
- [30] Y. Hayakawa, M. Nakagawa, H. Kawai, K. Tanabe, H. Nakayama, A. Shimazu, H. Seto, N. Otake, Studies on the differentiation inducers of myeloid leukemic cells. III. Spicamycin, a new inducer of differentiation of HL-60 human promyelocytic leukemia cells, *J Antibiot (Tokyo)*, 36 (1983) 934-937. 10.7164/antibiotics.36.934.

- [31] T. Suzuki, S.T. Suzuki, I. Yamada, Y. Koashi, K. Yamada, N. Chida, Total Synthesis of Spicamycin, *J. Org. Chem.*, 67 (2002) 2874-2880. 10.1021/jo010925c.
- [32] L.K. McKenzie, R. El-Khoury, J.D. Thorpe, M.J. Damha, M. Hollenstein, Recent progress in non-native nucleic acid modifications, *Chem. Soc. Rev.*, 50 (2021) 5126-5164. 10.1039/d0cs01430c.
- [33] W. Tang, P. Li, M. Chen, Z. Guo, Y. Chen, Characterization of SepE and SepF for the N6-Glycosylated Adenine Structure Formation in Septacidin Biosynthesis, *Organic Letters*, 22 (2020) 5251-5254. 10.1021/acs.orglett.0c01918.
- [34] Y.Y. Dong, H. Wang, A.C.W. Pike, S.A. Cochrane, S. Hamedzadeh, F.J. Wyszynski, S.R. Bushell, S.F. Royer, D.A. Widdick, A. Sajid, H.I. Boshoff, Y. Park, R. Lucas, W.-M. Liu, S.S. Lee, T. Machida, L. Minall, S. Mehmood, K. Belaya, W.-W. Liu, A. Chu, L. Shrestha, S.M.M. Mukhopadhyay, C. Strain-Damerell, R. Chalk, N.A. Burgess-Brown, M.J. Bibb, C.E. Barry Iii, C.V. Robinson, D. Beeson, B.G. Davis, E.P. Carpenter, Structures of DPAGT1 Explain Glycosylation Disease Mechanisms and Advance TB Antibiotic Design, *Cell*, 175 (2018) 1045-1058.e1016. <https://doi.org/10.1016/j.cell.2018.10.037>.
- [35] S.M. Weinstein, A.P. Abernethy, S.E. Spruill, I.M. Pike, A. True Kelly, L.G. Jett, A Spicamycin Derivative (KRN5500) Provides Neuropathic Pain Relief in Patients With Advanced Cancer: A Placebo-Controlled, Proof-of-Concept Trial, *Journal of Pain and Symptom Management*, 43 (2012) 679-693. <https://doi.org/10.1016/j.jpainsymman.2011.05.003>.
- [36] E.M. Acton, K.J. Ryan, A.E. Luetzow, Antitumor septacidin analogs, *J. Med. Chem.*, 20 (1977) 1362-1371. 10.1021/jm00221a002.
- [37] S.K. Mulani, K.-C. Cheng, K.-K.T. Mong, General Homologation Strategy for Synthesis of l-glycero- and d-glycero-Heptopyranoses, *Organic Letters*, 17 (2015) 5536-5539. 10.1021/acs.orglett.5b02620.
- [38] T. Li, A. Tikad, M. Durka, W. Pan, S.P. Vincent, Multigram-scale synthesis of l,d-heptoside using a Fleming-Tamao oxidation promoted by mercuric trifluoroacetate, *Carbohydrate Research*, 432 (2016) 71-75. <https://doi.org/10.1016/j.carres.2016.07.010>.
- [39] D. Crich, A. Banerjee, Stereocontrolled Synthesis of the d- and l-glycero- β -d-manno-Heptopyranosides and Their 6-Deoxy Analogues. Synthesis of Methyl α -l-Rhamno-pyranosyl-(1 \rightarrow 3)-d-glycero- β -d-manno-heptopyranosyl- (1 \rightarrow 3)-6-deoxy-glycero- β -d-manno-heptopyranosyl-(1 \rightarrow 4)- α -l- rhamno-pyranoside, a Tetrasaccharide Subunit of the Lipopolysaccharide from *Plesimonas shigelloides*, *Journal of the American Chemical Society*, 128 (2006) 8078-8086. 10.1021/ja061594u.
- [40] T. Suzuki, S.T. Suzuki, I. Yamada, Y. Koashi, K. Yamada, N. Chida, Total Synthesis of Spicamycin, *The Journal of Organic Chemistry*, 67 (2002) 2874-2880. 10.1021/jo010925c.
- [41] S.M. Canham, D.J. France, L.E. Overman, Total Synthesis of (+)-Sieboldine A: Evolution of a Pinacol-Terminated Cyclization Strategy, *J. Org. Chem.*, 78 (2013) 9-34. 10.1021/jo300872y.
- [42] K.J. Hale, L. Hough, S. Manaviazar, A. Calabrese, An Update of the Rules for Pyranoside Sulfonate Displacement, *Organic Letters*, 16 (2014) 4838-4841. 10.1021/o1502193j.
- [43] J.R. Parikh, W.v.E. Doering, Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide, *Journal of the American Chemical Society*, 89 (1967) 5505-5507. 10.1021/ja00997a067.
- [44] D. Dhara, A. Dhara, P.V. Murphy, L.A. Mulard, Protecting group principles suited to late stage functionalization and global deprotection in oligosaccharide synthesis, *Carbohydrate Research*, 521 (2022) 108644. <https://doi.org/10.1016/j.carres.2022.108644>.

- [45] D. Dhara, L.A. Mulard, Exploratory N-Protecting Group Manipulation for the Total Synthesis of Zwitterionic *Shigella sonnei* Oligosaccharides, *Chemistry – A European Journal*, 27 (2021) 5694-5711. <https://doi.org/10.1002/chem.202003480>.
- [46] L.L. Miller, J.F. Wolf, E.A. Mayeda, Electrooxidative cleavage of benzylic ethers and esters, *J. Am. Chem. Soc.*, 93 (1971) 3306-3307. 10.1021/ja00742a047.
- [47] D.K. Ahn, Y.W. Kang, S.K. Woo, Oxidative Deprotection of p-Methoxybenzyl Ethers via Metal-Free Photoredox Catalysis, *J. Org. Chem.*, 84 (2019) 3612-3623. 10.1021/acs.joc.8b02951.
- [48] V. VanRheenen, R.C. Kelly, D.Y. Cha, An improved catalytic OsO₄ oxidation of olefins to cis-1,2-glycols using tertiary amine oxides as the oxidant, *Tetrahedron Letters*, 17 (1976) 1973-1976. [https://doi.org/10.1016/S0040-4039\(00\)78093-2](https://doi.org/10.1016/S0040-4039(00)78093-2).
- [49] D. Artner, C. Stanetty, K. Mereiter, A. Zamyatina, P. Kosma, Crystal and molecular structure of methyl l-glycero- α -d-manno-heptopyranoside, and synthesis of 1 \rightarrow 7 linked l-glycero-d-manno-heptobiose and its methyl α -glycoside, *Carbohydrate Res.*, 346 (2011) 1739-1746. <https://doi.org/10.1016/j.carres.2011.05.033>.
- [50] I. Alkorta, P.L.A. Popelier, Linking the Interatomic Exchange-Correlation Energy to Experimental J-Coupling Constants, *J. Phys. Chem. A*, 127 (2023) 468-476. 10.1021/acs.jpca.2c07693.
- [51] R.A. Ashmus, A.B. Jayasuriya, Y.-J. Lim, G.A. O'Doherty, T.L. Lowary, De Novo Asymmetric Synthesis of a 6-O-Methyl-d-glycero-l-gluco-heptopyranose-Derived Thioglycoside for the Preparation of *Campylobacter jejuni* NCTC11168 Capsular Polysaccharide Fragments, *J. Org. Chem.*, 81 (2016) 3058-3063. 10.1021/acs.joc.6b00296.
- [52] W. Peng, A.B. Jayasuriya, A. Imamura, T.L. Lowary, Synthesis of the 6-O-Methyl-d-glycero- α -l-gluco-heptopyranose Moiety Present in the Capsular Polysaccharide from *Campylobacter jejuni* NCTC 11168, *Org. Lett.*, 13 (2011) 5290-5293. 10.1021/ol202152r.
- [53] S.K. Mulani, K.-C. Cheng, K.-K.T. Mong, General Homologation Strategy for Synthesis of l-glycero- and d-glycero-Heptopyranoses, *Org. Lett.*, 17 (2015) 5536-5539. 10.1021/acs.orglett.5b02620.
- [54] H. Rosemeyer, Nucleolipids: Natural Occurrence, Synthesis, Molecular Recognition, and Supramolecular Assemblies as Potential Precursors of Life and Bioorganic Materials, *Chem. Biodivers.*, 2 (2005) 977-1063. <https://doi.org/10.1002/cbdv.200590082>.
- [55] R. Lucas, I. Gómez-Pinto, A. Aviñó, J.J. Reina, R. Eritja, C. González, J.C. Morales, Highly Polar Carbohydrates Stack onto DNA Duplexes via CH/ π Interactions, *J. Am. Chem. Soc.*, 133 (2011) 1909-1916. 10.1021/ja108962j.
- [56] E. Vengut-Climent, P. Peñalver, R. Lucas, I. Gómez-Pinto, A. Aviñó, A.M. Muro-Pastor, E. Galbis, M.V. de Paz, C. Fonseca Guerra, F.M. Bickelhaupt, R. Eritja, C. González, J.C. Morales, Glucose-nucleobase pairs within DNA: impact of hydrophobicity, alternative linking unit and DNA polymerase nucleotide insertion studies, *Chem. Sci.*, 9 (2018) 3544-3554. 10.1039/C7SC04850E.
- [57] M. Dubber, J.M.J. Fréchet, Solid-Phase Synthesis of Multivalent Glycoconjugates on a DNA Synthesizer, *Bioconjugate Chem.*, 14 (2003) 239-246. 10.1021/bc0256244.
- [58] D. Sabatino, M.J. Damha, Oxepane Nucleic Acids: Synthesis, Characterization, and Properties of Oligonucleotides Bearing a Seven-Membered Carbohydrate Ring, *J. Am. Chem. Soc.*, 129 (2007) 8259-8270. 10.1021/ja071336c.
- [59] J.C. Chaput, Redesigning the Genetic Polymers of Life, *Acc. Chem. Res.*, 54 (2021) 1056-1065. 10.1021/acs.accounts.0c00886.

[60] A. Ramaswamy, M. Froeyen, P. Herdewijn, A. Ceulemans, Helical Structure of Xylose-DNA, *J. Am. Chem. Soc.*, 132 (2010) 587-595. 10.1021/ja9065877.