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Synthesis of Deoxygenated Disaccharide Precursors for Modified Lipid II Synthesis

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The synthesis of novel deoxygenated disaccharide precursors for modified lipid II synthesis is described. The 3- and 4-deoxy-GlcNAc donors were obtained, respectively, by radical reduction of the iodo derivative by TBTH/AIBN and hydrogen reduction of the triflate using a borohydride reagent (nBu$_4$NBH$_4$). *O*-Glycosylation of the acceptor, promoted by NIS/TMSOTf, led to the 3- and 4-deoxygenated disaccharides.

Introduction

As antibiotic resistance is becoming an increasing medical problem, there is an urgent need for new anti-infectious agents with new modes of action.[1] Because of its uniqueness, the bacterial cell wall remains an attractive target for new antibiotics. The major component of the bacterial cell wall is the peptidoglycan, which is a carbohydrate polymer that forms a network through peptide cross-links. Although the cell walls of different bacterial strains have different constitutions, the compositions of the peptidoglycan polymer are strikingly similar as are their biosynthesis. Theoretically, any inhibitor of the peptidoglycan synthesis may have the same impact on bacterial survival as known inhibitors of the cross-linking reaction (β-lactam antibiotics).

The biosynthesis of peptidoglycan occurs in three stages (Figure 1). Based on the current understanding at the molecular level, several intermediates of natural origin, such as lipid I[2] and lipid II,[3] have been synthesized to study the properties of the enzymes involved in peptidoglycan synthesis. The transglycosylases, the enzymes involved in the polymerization of lipid II to give the glycan chain in the final stage of the biosynthesis (stage III), have been difficult to study due to the unavailability of appropriate substrates. The transglycosylase reaction, though, is considered as an interesting target for developing new antibiotics for several reasons. First, these enzymes are located on the outer surface of the bacterial membrane, which means that potential antibiotics do not need to penetrate the whole bacterial membrane. Secondly, several homologous transglycosylases are found in each bacterial strain and inhibitors targeting one of these enzymes could hit several others. Finally, compounds that inhibit transglycosylases kill bacteria rapidly (i.e., they are bactericidal) by a process that surpasses cessation of glycan synthesis.[4] These three arguments, likewise, could be used as arguments in the prediction that transglycosylase inhibitors might have a lower frequency of resistance formation than existing antibiotics. Therefore, information on substrate specificity for the bacterial transglycosylase reaction could be very helpful in the design of new antibiotics.

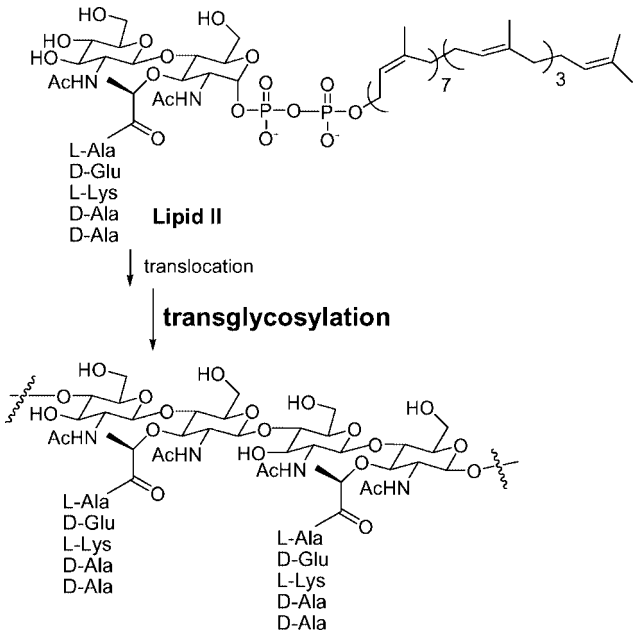

Figure 1. Transglycosylation reaction for peptidoglycan synthesis.

We have envisioned a synthetic strategy for the synthesis of new types of lipid II precursors. The 3- and 4-hydroxy groups of the GlcNAc (*N*-acetyl-D-glucosamine) moiety of lipid II are considered the nucleophilic sites of the transglycosylase reaction. Therefore, we have synthesized the 3- and

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4-deoxy analogs of the GlcNAc-MurNAc disaccharide (*N*-acetyl-D-muramic acid) (i.e., **1a** and **1b**), which can be used in the synthesis of new lipid II derivatives that could be potential inhibitors of transglycosylases.

Results and Discussion

The lipid II precursor is a disaccharide composed of GlcNAc and MurNAc, with GlcNAc normally named the donor and MurNAc the acceptor in the glycosylation reaction (Scheme 1). The overall synthetic challenge for synthesizing modified lipid II is the careful selection of protecting groups so that selective deprotection and activation reactions of functional groups in several stages of the synthetic process are possible giving the highest yield. The selection of the protecting groups should allow easy global deprotection in the final steps of the total synthesis and suitable protecting groups could also activate the glycosylation reaction, as reported by Wong and co-workers.[5] We prefer to use the benzyl group (Bn) to protect the 6-hydroxy group of both the donor and acceptor. This is especially necessary for the acceptor. When the 6-position was protected by other electron-withdrawing groups (acetyl), the coupling reaction with thioglycosides (**2a**, **2b**, **2c**) was seriously hampered. Trichloroethoxycarbonyl (Troc) and phthalimido (Phth) groups were used to protect the 2-amino group of the donor and acceptor.

Herein we describe the synthetic route for obtaining the 3- and 4-deoxy donors **2a**, **2b** and **2c** and the successful synthesis of the protected disaccharides. The acceptor **3** can be prepared by a somewhat improved procedure in five steps from commercially available *N*-acetyl-D-glucosamine.[6]

Many methods for the deoxygenation of the hydroxy groups of sugars have been described over the years.[7] The 3- and 4-hydroxy groups, respectively, of compounds **4** and **6**, which can be prepared from D-glucosamine,[8] were converted into a series of thiocarbonyl derivatives, **7a**–**7c** and **8a**–**8c**. However, the Barton deoxygenation reaction[9] under radical conditions [tri-*n*-butyltin hydride (TBTH) with AIBN as initiator] did not lead to the desired donor molecules **2b** and **2c** (Scheme 2), whatever conditions we tried (the thiocarbonyl derivatives **7a**–**c** and **8a**–**c** decomposed during the reaction). This may be due to the presence of the Troc protecting group and/or to competing reactions of the SEt activating group in the anomeric position.

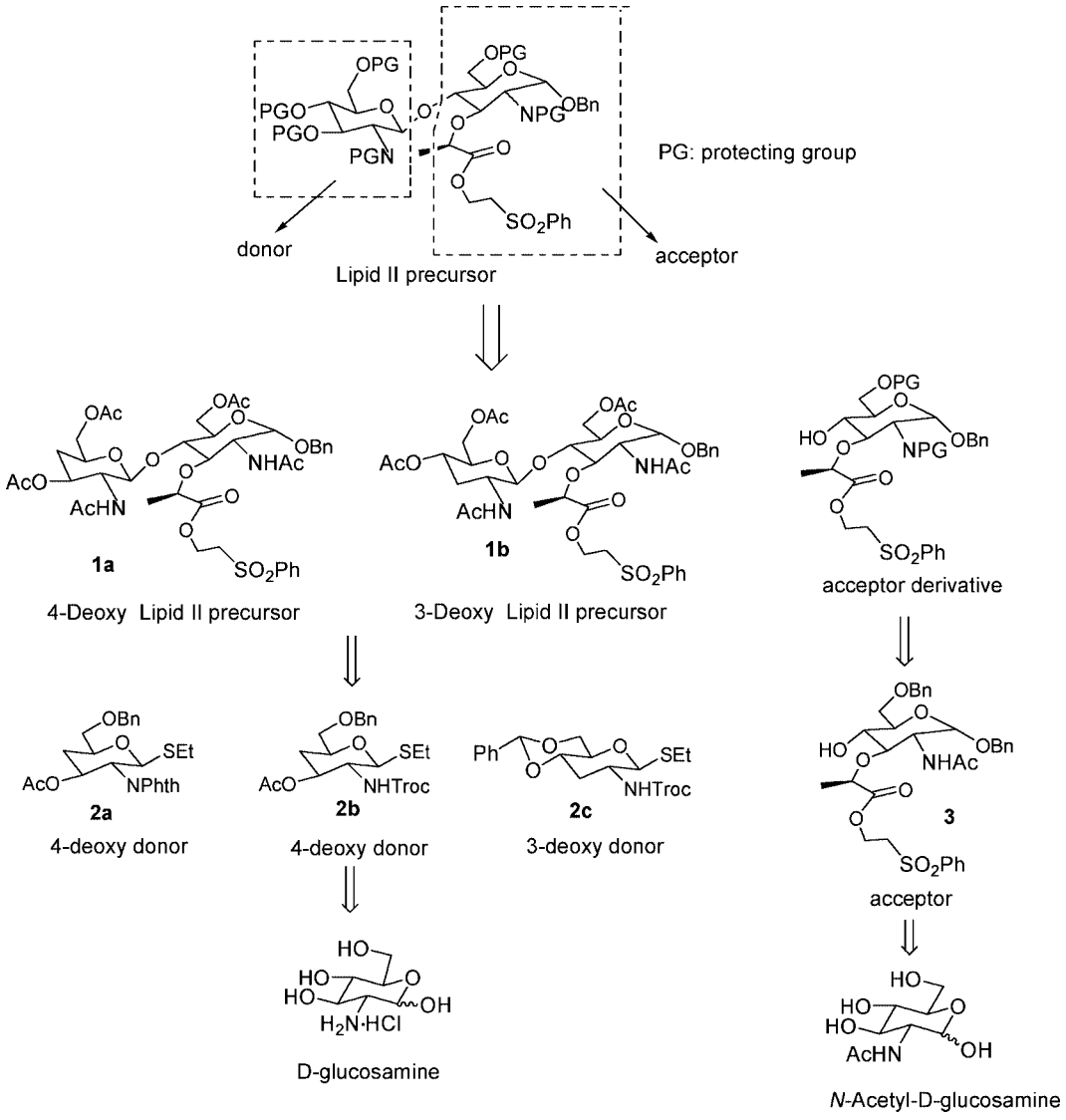
Hashimoto and co-workers[10] reported that the reduction of an iodosugar, such as the 4-iodo derivative of **2d**, using TBTH/AIBN in toluene can afford the 4-deoxy donor **2d** in 87% yield (Scheme 3). Considering the harsher reaction conditions required to deprotect a pivaloyl (Piv) group in comparison to an acetyl (Ac) group, we selected **2a** as one of the desired donor molecules with a benzyl (Bn) at the 6-O position and an acetyl group at the 3-O position. Starting from **9**[11] a mixture of the α and β anomers **10** and **11** was obtained in the first stage of the substitution reaction of the 1-acetoxy group by an SEt group catalyzed by $BF_3{\cdot}OEt_2$.[12]

Without isolation of **10** and **11**, this mixture was then submitted to a TMSOTf-promoted[13] reaction with ethanethiol to give the β-anomeric **11** in a total yield of 74%. Deprotection of **11** with sodium methoxide as catalyst in MeOH followed by protection of the 4- and 6-OH functions with a benzylidene group afforded compound **13** in 84% yield. After quantitative acetylation, the 4-hydroxy group of **14** was unmasked by a selective 4,6-benzylidene acetal ring-opening reaction.[14] Excellent yield and selectivity was obtained using trifluorosulfonic (TfOH) acid and triethylsilane (TES) as reducing agent at a very low temperature. Small experimental changes to the originally described procedures for synthesizing **12**–**15** are mentioned in the Exp. Sect. Compound **15** was then converted into the iodosugar **17**. However, radical reduction of the iodo derivative **17** using TBTH/AIBN as described for the synthesis of **2d**[10] did not work in our hands. As an alternative, we used the method of Yang and co-workers[15] reported for the reduction of a sugar triflate with tetrabutylammonium borohydride in refluxing benzene. We carried out this reaction in strictly anhydrous THF, and we successfully obtained the desired compound **2a** by reduction of **16** with Bu_4NBH_4 at room temperature in an acceptable yield (52% for two steps).

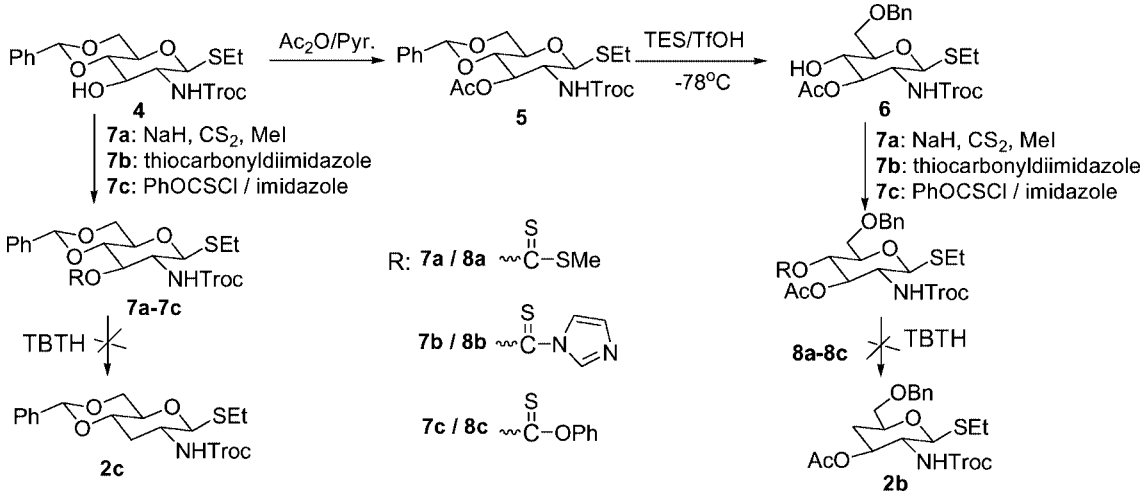
Wong and co-workers[5] reported that a donor bearing a Troc protecting group at the 2-amino function experiences a 40-fold enhancement of the glycosidation reaction as compared with a building block having a Phth-protected 2-amino function. Therefore, we synthesized the 4-deoxy donor **2b** (Scheme 4). Reduction of the 4-iodo derivative **19** using TBTH/AIBN was again unsuccessful and **2b** was obtained by the Bu_4NBH_4-mediated reduction of triflate **18**.

The method involving reduction of an iodo precursor[10] was investigated for the preparation of the 3-deoxy donor compound **2c** (Scheme 5). Compound **21** was obtained in good yield by iodination of **20**. Reduction of the iodine group of **21** by TBTH/AIBN was successful. However, a mixture of **2c** and **2f** was obtained due to partial reductive elimination of the chlorine in the protecting group (Troc).[16] The ratio of **2c/2f** could be turned in favor of the desired compound **2c** (over 5:1) by strictly controlling the reaction time and the amount of TBTH used. After recrystallization from ethyl acetate and *n*-hexane, **2c** was obtained as a pure compound in a yield of 89%. The successful reduction of the iodo precursor at the 3-position (compound **21**) and not at the 4-position might be due to a difference in the stabilization of the radical intermediate.

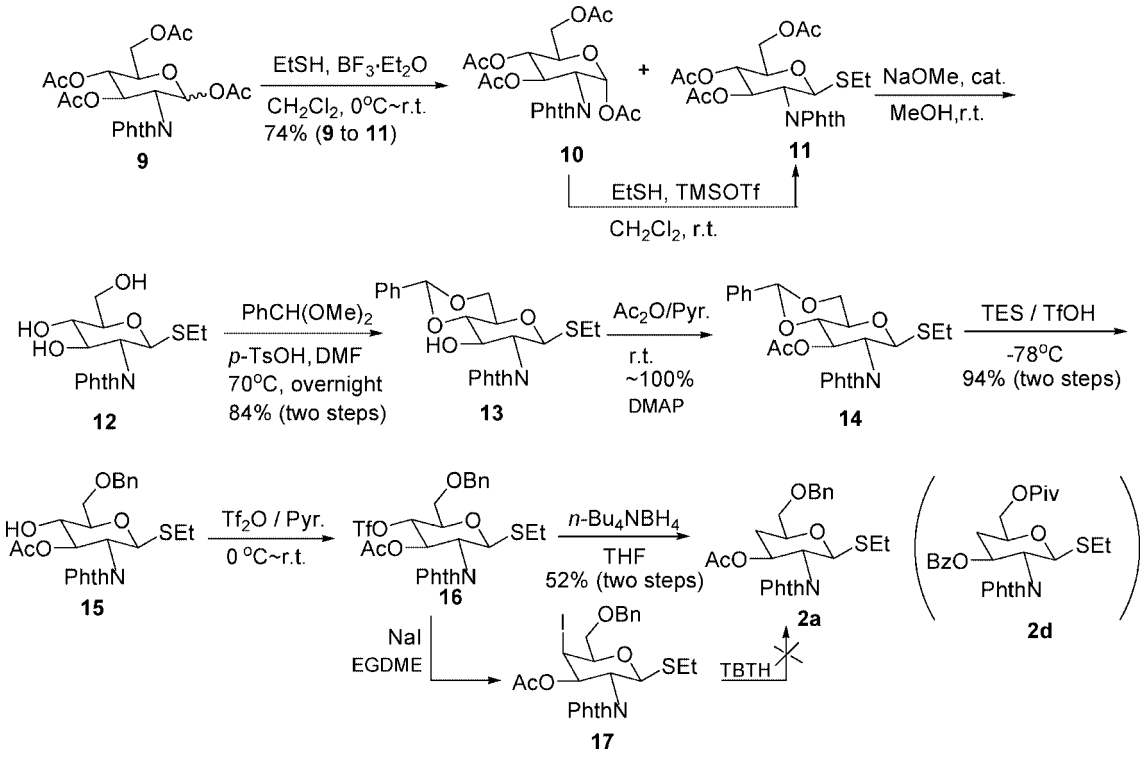
Several methods for *O*-glycosylation have been developed of which the thioglycoside methodology is one of the most versatile and widespread.[12,17,18] This methodology employs a thioglycoside donor (e.g., having an alkylthio aglycon) which is *O*-glycosylated with a carbohydrate acceptor in the presence of a thiophilic agent, which is generated by a promoter system and transforms the aglycon into a good leaving group. There are several promoter systems for thioglycoside activation.[19–23] In our case the ICl/AgOTf method did not give the desired product and NIS/AgOTf afforded the disaccharide in yields lower than 30%. The NIS/



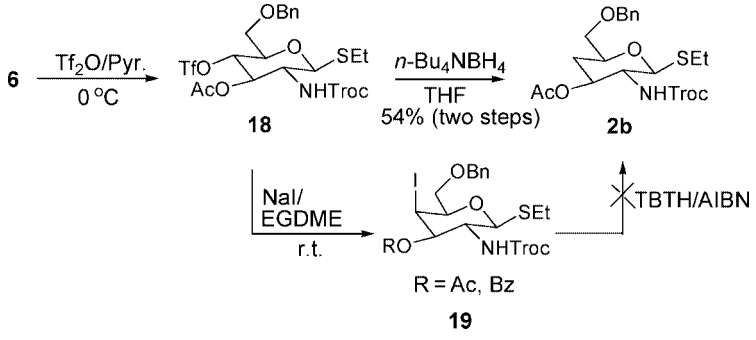
Scheme 1. Retrosynthetic analysis for the synthesis of the deoxygenated lipid II precursors.



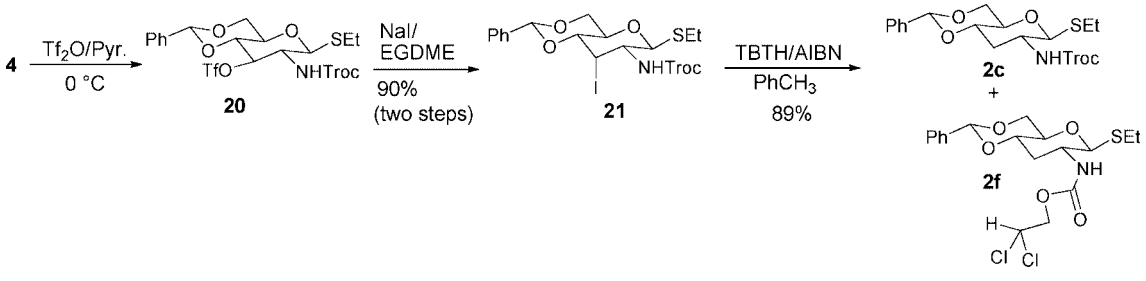
Scheme 2. Attempts to obtain the deoxygenated sugars by the Barton reaction.



Scheme 3. Synthesis of the 4-deoxyglucosamine building block with a Phth protecting group at the amino function.



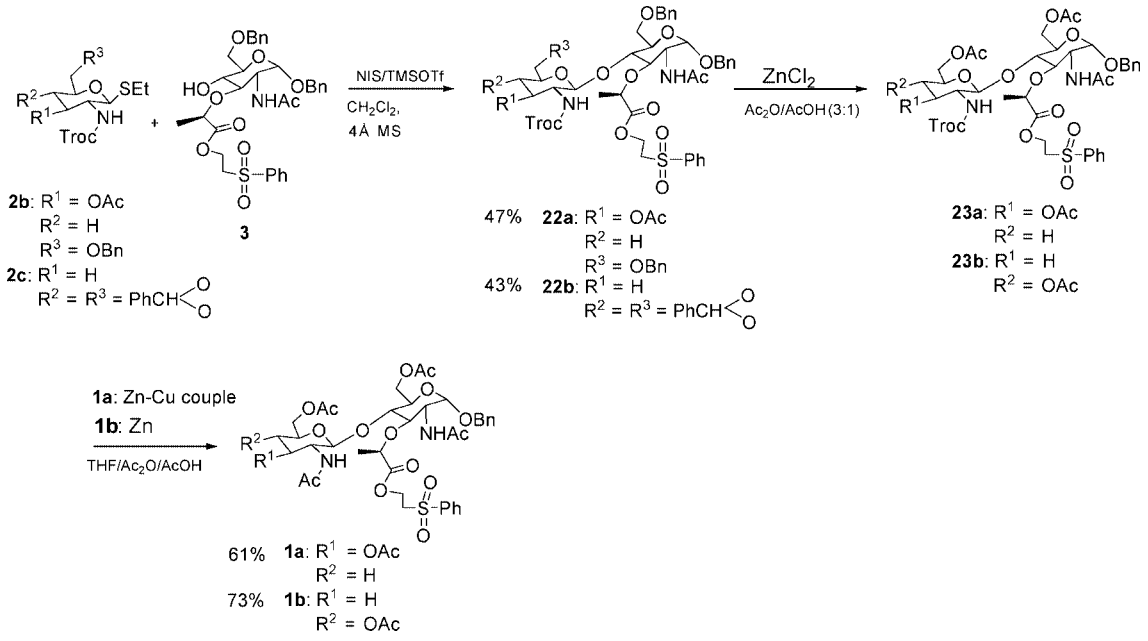
Scheme 4. Synthesis of the 4-deoxyglucosamine building block with a Troc protecting group at the amino function.



Scheme 5. Synthesis of the 3-deoxyglucosamine building block with a Troc protecting group at the amino function.

TMSOTf system gave yields of 43–47% (Scheme 6) in the coupling reaction between different donors and the acceptor under controlled reaction conditions (Table 1).

When the coupling reaction was carried out at –78 °C, yields lower than 40% were obtained (entry 1). Therefore, the reaction was studied at the higher temperature of



Scheme 6. Synthesis of 3- and 4-deoxygenated lipid II precursors through coupling reaction promoted by NIS/TMSOTf.

Table 1. Study of the coupling reactions between the donors **2b** and **2c** and acceptor **3**.

Entry	Equiv. of acceptor (mmol)	Equiv. of donor	Equiv. of promoter system			% Yield[c]
			TMSOTf	NIS	Temp. (time)	
1	1.0	3.0[a]	0.2	3.5	–78 °C (3 h), r.t. (16 h)	34
2	1.0 (0.5)	1.5[a]	0.2	2.0	–45 °C (20 min), 4 °C (10 h), r.t. (10 h)	54 (79)
3	1.0 (1.0)	1.5[a]	0.2	2.0	–45 °C (20 min), 4 °C (12 h), r.t. (11 h)	43 (64)
4	1.0 (2.0)	1.5[a]	0.1	2.0	–45 °C (20 min), 4 °C (7 h), r.t. (15 h)	43 (59)
5	1.0 (4.0)	1.5[a]	0.1	2.0	–45 °C (30 min), 4 °C (10 h), r.t. (10 h)	36 (68)
6	1.0 (1.2)	1.5[b]	0.2	2.0	–45 °C (30 min), –10 °C (10 h), r.t. (20 h)	18 (27)
7	1.0 (2.4)	1.3[b]	0.3	2.0	–45 °C (1 h), –10 °C (7 h), r.t. (9 h)	41 (85)
8	1.0 (4.5)	1.3[b]	0.3	1.3	–45 °C (2 h), –10 °C (14 h)	47 (61)

[a] Donor: **2c**. [b] Donor: **2b**. [c] Yields obtained after purification by column chromatography on silica; values in parentheses were calculated on the basis of the amount of recovered acceptor.

–45 °C. Based on the amount of acceptor, 1.3–1.5 equiv. of the donor, 1.3–2.0 equiv. of the activator (NIS) and 0.1–0.3 equiv. of the promoter (TMSOTf) were used (entries 2–8). The potential side-reaction (transesterification between the protecting group of donor and acceptor caused by the presence of TMSOTf) could be avoided by performing the reaction for a longer period at a lower temperature (entry 8). The 6-benzylated derivative **3** was used for the coupling reaction because this reaction did not work well when the 6-position of the acceptor was protected with an acetyl group.[6]

The 6-*O*-benzyl and 4′,6′-*O*-benzylidene acetal groups in compound **22b** were removed using anhydrous zinc chloride in Ac_2O/AcOH[24] and the free hydroxy groups generated were acetylated in situ. Without isolation of the intermediate **23b**, zinc dust was added to the reaction mixture to cleave the Troc group from the deoxygenated glucosamine. The free amino group was then acetylated to afford target compound **1b** in 73% yield. This one-pot reaction procedure gave a much lower yield (lower than 30%) of target compound **1a**. The zinc chloride should be strictly anhydrous otherwise the deprotection of the benzyl group would not go to completion. After the first stage of the deprotection procedure to remove the 6- and 6′-*O*-benzyl groups to generate **23a**, removal of the residual zinc chloride was necessary to avoid a side-reaction during the next step. Compound **23a** was then treated with a zinc/copper couple in a solution of THF/Ac_2O/AcOH to cleave the Troc group. Acetylation in situ gave the target compound **1a** in 61% yield.

Conclusions

Synthetic strategies have been developed to obtain three protected deoxygenated glucosamine donors **2a**, **2b** and **2c**. The 4-deoxy and 3-deoxy donors **2c** and **2b**, respectively, were employed in a coupling reaction promoted by TMSOTf/NIS to give the desired disaccharides **1a** and **1b** in moderate yields. The target compounds will be used to prepare deoxygenated lipid II analogs.

Experimental Section

All reactions using air- or moisture-sensitive reagents were conducted in an inert nitrogen atmosphere. Anhydrous solvents were

distilled prior to use. THF, toluene, 1,4-dioxane and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2 and CH_3CN were distilled from CaH_2, DMF was distilled from P_2O_5 and Pyr from KOH. Precoated SIL G/UV254 plates were used for TLC and spots were examined with UV light and $Ce(SO_4)_2/(NH_4)_6MoO_4$ spray. Silica (200–425 mesh) was used for column chromatography. Exact mass spectra were acquired with a quadrupole time-of-flight mass spectrometer equipped with a standard electrospray ionization (ESI) interface. NMR spectra were recorded with 200 and 500 MHz spectrometers at 25 °C. ^1H and ^{13}C resonances are referenced to TMS; coupling constants (*J*) are reported in hertz (Hz). NMR splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br. (broad). The acceptor **3** was prepared by a route based on the improved procedure of Lioux et al.[6] Compounds **4**,[8] **5**,[8] **6**[8] and **9**[11] were prepared according to literature procedures.

Ethyl 3,4,6-Tri-*O*-Acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (11): $BF_3{\cdot}Et_2O$ (3.8 mL, 29.1 mmol) was added dropwise to a solution of **9** (10.0 g, 20.9 mmol, β/α = 1.6:1) in EtSH (2.2 mL, 29.1 mmol) and anhydrous CH_2Cl_2 (100 mL) at 0 °C. Then the reaction was stirred for 50 min at the same temperature and then at room temperature for 4 h. The solution was evaporated under vacuum to give a mixture of **10** and **11** as a brown-red slurry. This mixture was dissolved in anhydrous CH_2Cl_2 (100 mL) and then EtSH (2.7 mL, 36.0 mmol) and TMSOTf (1.6 mL, 8.4 mmol) were added successively at room temperature. After being stirred for 1.5 h, Et_3N (5 mL) was added to quench the reaction. The solution was evaporated under vacuum and the residue purified by chromatography (SiO_2, 1:1 *n*-hexane/ethyl acetate) to give **11**[12a] (7.4 g, 74% based on recovered **10**); 0.43 g of **10** (the unreacted α isomer of **9**) was recovered.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.87 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.62–2.73 (m, 2 H, SCH_2), 3.87–3.91 (m, 1 H, 2-H), 4.14–4.36 (m, 2 H, 6,6′-H), 4.40 (t, *J* = 10.2 Hz, 1 H, 5-H), 5.18 (t, *J* = 9.8 Hz, 1 H, 3-H), 5.49 (d, *J* = 10.6 Hz, 1 H, 1-H), 5.84 (t, *J* = 10.2 Hz, 1 H, 4-H), 7.70–7.90 (m, 4 H, Phth) ppm.

Ethyl 4,6-*O*-Benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (13): A solution of **11** (4.8 g, 10.0 mmol) in MeOH (100 mL) was treated with NaOMe (30 wt.-% in MeOH, 115.0 μL, 2.0 mmol) at room temperature. After being stirred for 2 h, dry ice was added to quench the reaction. Then the solution was concentrated in vacuo to give **12** as a white solid which was used in the next step without further purification. Crude **12** was dissolved in DMF (50 mL), then treated with *p*TsOH·H_2O (0.46 g, 2.4 mmol) and α,α-dimethoxytoluene (4.7 mL, 30.0 mmol). The reaction mixture was stirred overnight at 70 °C. The solvent was evaporated under vacuum and the residue dissolved in ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ and brine. The organic layer was dried with anhydrous Na_2SO_4, concentrated in vacuo and the residue purified by chromatography (SiO_2, 2:1 *n*-hexane/ethyl acetate) to afford **13**[25] (3.71 g, 84%) as white foam. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.4 Hz, 3 H, CH_3), 2.67–2.73 (m, 2 H, SCH_2), 2,782 (d, *J* = 3.2 Hz, 1 H, OH) 3.53–3.70 (m, 2 H, 6,6′-H), 3,798 (t, *J* = 9.4 Hz, 1 H, 2-H), 4.25–4.45 (m, 2 H, 3-H, 4-H), 4.62 (m, 1 Hz, 5-H), 5.39 (d, *J* = 10.6 Hz, 1 H, 1-H), 5.59 (s, 1 H, PhCH), 7.35–7.53 (m, 5 H, Ph), 7.68–7.85 (m, 4 H, Phth) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.7 (CH_3), 24.0 (CH_2), 55.3 (C-2), 68.6 (C-6), 69.5 (C-3), 70.3 (C-5), 81.8 (C-1), 82.1 (C-4), 101.8 (PhCH), 123.3, 123.8, 126.3, 128.3, 129.3, 131.6, 134.2, 136.9 (C_{arom}), 168.2 (2×CO) ppm.

Ethyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (14): A solution of **13** (1.33 g, 3.0 mmol) and DMAP (20 mg) in Ac_2O (15 mL) and pyridine (9 mL) was stirred at room temperature for 1 h. The mixture was evaporated and co-evaporated with toluene under vacuum to give **14**[26] as a white solid. The solid was dried under high vacuum and used in the next step without further purification. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 2.63–2.76 (m, 2 H, CH_2), 3.77–3.84 (m, 3 H, 2-H, 6,6′-H), 4.32–4.44 (m, 2 H, 4-H, 5-H), 5.55 (s, 1 H, PhCH), 5.58 (d, *J* = 11 Hz, 1 H, 1-H), 5.93 (t, *J* = 9.4 Hz, 1 H, 3-H), 7.34–7.49 (m, 5 H, Ph), 7.72–7.91 (m, 4 H, Phth) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.8 (CH_3), 20.5 ($CH_3C{=}O$), 24.3 (SCH_2), 54.2 (C-2), 68.6 (C-6), 70.5 (C-3, C-5), 79.2 (C-4), 81.7 (C-1), 101.6 (PhCH), 123.1, 126.9, 128.3, 129.2, 131.2, 131.7, 134.2, 134.4, 136.9 (C_{arom}), 167.5, 167.9 (2×CO, Phth), 170.2 (Ac_{CO}) ppm.

Ethyl 3-*O*-Acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-1-thio-β-D-glucopyranoside (15): A mixture of crude **14** and 4-Å molecular sieves (MS) (3 g) in anhydrous CH_2Cl_2 (60 mL) was stirred at room temperature for 30 min. The mixture was cooled to –78 °C and then TES (1.34 mL, 9.0 mmol) and TfOH (0.54 mL, 6.0 mmol) were added successively. After being stirred for 1 h at –78 °C, TLC showed the reaction was complete. The reaction mixture was quenched with $NaHCO_3$ and a few drops of MeOH, then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (SiO_2, 3:1 *n*-hexane/ethyl acetate) to give **15**[27] (1.37 g, 94% for two steps). ^1H NMR (500 MHz, $CDCl_3$), δ = 1.22 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.91 (s, 3 H, $CH_3C{=}O$), 2.61–2.74 (m, 2 H, SCH_2), 3.30 (br. s, 1 H, OH), 3.81–3.84 (m, 4 H, 2-H, 5-H, 6,6′-H), 4.31 (t, *J* = 10.5 Hz, 1 H, 4-H), 4.63 (AB pattern, ^2J = 13.5 Hz, 2 H, OCH_2Ph), 5.54 (d, *J* = 10.5 Hz, 1 H, 1-H), 5.73 (t, *J* = 10 Hz, 1 H, 3-H), 7.29–7.36 (m, 5 H, Ph), 7.69–7.84 (m, 4 H, Phth) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.8 (CH_3), 20.5 ($CH_3C{=}O$), 24.1 (SCH_3), 53.7 (C-2), 70.1 (C-6), 70.9 (C-4), 73.5 (OCH_2Ph), 74.2 (C-5), 78.5 (C-3), 80.7 (C-1), 123.4, 127.6, 127.6, 128.3, 131.1, 131.5, 134.0, 134.2, 137.7 (C_{arom}), 167.3, 167.7 (2×CO), 171.0 (Ac_{CO}) ppm. MS: calcd. for $C_{25}H_{27}NO_7S$ [M + Na] 508.1406; found 508.1407.

Ethyl 3-*O*-Acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-(trifluoromethylsulfonyl)-1-thio-β-D-glucopyranoside (16): Tf_2O (0.6 mL, 3.6 mmol) was added dropwise to a solution of pyridine (0.58 mL, 7.2 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 °C. After being stirred for 10 min at the same temperature, a solution of **15** (0.87 g, 1.79 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise. The reaction was stirred for another 30 min at 0 °C; TLC showed the starting material had been completely consumed. Then the reaction mixture was diluted with CH_2Cl_2 and washed with 0.1 N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give **16** as a brown oil which was dried under high vacuum and used in the next step without further purification. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.93 (s, 3 H, $CH_3C{=}O$), 2.57–2.74 (m, 2 H, SCH_2), 3.70–4.0 (m, 3 H, 2-H, 6,6′-H), 4.38 (t, *J* = 9.6 Hz, 1 H, 5-H), 4.53–4.68 (AB, *J* = 11.8 Hz, 2 H, OCH_2), 5.25 (t, *J* = 9.6 Hz, 1 H, 4-H), 5.52 (d, *J* = 10.6 Hz, 1 H, 1-H), 5.95 (t, *J* = 9.6 Hz, 1 H, 3-H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.8 (CH_3), 20.1 ($CH_3C{=}O$), 24.1 (SCH_2), 54.0 (C-2), 67.6 (C-6), 70.7 (C-3), 73.5 (OCH_2), 76.6 (C-4), 79.5 (C-5), 81.0 (C-1), 123.8, 125.3, 127.8, 128.2, 128.4, 129.0, 131.0, 134.4, 137.5 (C_{arom}), 167.1 (2×CO), 169.9 (Ac_{CO}) ppm.

Ethyl 3-*O*-Acetyl-6-*O*-benzyl-2,4-dideoxy-2-phthalimido-1-thio-β-D-xylopyranoside (2a): Crude **16** was dissolved in anhydrous THF (60 mL) and treated with 4-Å MS (3 g) and *n*Bu_4NBH_4 (1.41 g,

5.37 mmol). The reaction mixture was stirred at room temperature for 5 h until TLC showed the starting material **16** had been completely consumed. The reaction mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate and then washed with cold water and brine. The organic layer was dried with Na_2SO_4, concentrated in vacuo and the residue purified by chromatography (SiO_2, 3:1 *n*-hexane/ethyl acetate) to give **2a** (0.44 g, 52%) as a slightly yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.8 Hz, 3 H, CH_3), 1.69 (q, J = 11.72 Hz, 1 H, 4ax-H), 2.26–2.36 (m, 1 H, 4eq-H), 2.58–2.78 (m, 2 H, SCH_3), 3.52–3.70 (m, 2 H, 6,6′-H), 3.88–3.96 (m, 1 H, 5-H), 4.25 (t, J = 10.3 Hz, 1 H, 2-H), 4.60 (s, 2 H, OCH_2), 5.43 (d, J = 10.8 Hz, 1 H, 1-H), 5.66–5.79 (dt, 1 H, 3-H), 7.30–7.32 (m, 5 H, Ph), 7.77–7.88 (m, 4 H, Phth) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.7 (CH_3), 20.6 (CH_3C=O), 23.9 (SCH_2), 33.8 (C-4), 54.3 (C-2), 69.0 (C-3), 71.9 (C-6), 73.2 (OCH_2), 74.9 (C-5), 80.98 (C-1), 123.4, 127.5, 128.3, 131.3, 131.6, 134.1, 137.9 (C_{arom}), 167.7 (2×CO), 170.06 (Ac_{CO}) ppm. MS: calcd. for $C_{25}H_{27}NO_6S$ [M + Na] 492.1457; found 492.1465.

Ethyl 3-*O*-Acetyl-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-4-*O*-(trifluoromethylsulfonyl)-1-thio-β-D-glucopyranoside (18): Tf_2O (2.0 mL, 12.0 mmol) was added dropwise to a solution of pyridine (2.0 mL, 24.0 mmol) in anhydrous CH_2Cl_2 (30 mL) at –10 to –15 °C. After being stirred for 5 min at the same temperature, a solution of **6** (4.23 g, 8.0 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise at the same temperature. The reaction was stirred for another 30 min at 0 °C until TLC showed the reaction to be complete. The solution was diluted with CH_2Cl_2 and washed with 0.1 N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried with anhydrous Na_2SO_4, concentrated in vacuo to give **18** as a pink solid, which was dried under high vacuum for 2 h and used in the next step without further purification.

Ethyl 3-*O*-Acetyl-6-*O*-benzyl-2,4-dideoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1-thio-β-D-xylopyranoside (2b): Crude **18** was dissolved in anhydrous THF (180 mL, freshly distilled) and treated with nBu_4NBH_4 (6.1 g, 23.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h until TLC showed the starting material **18** had been completely consumed. The reaction solution was added to a cold saturated NaCl solution, the organic layer was separated and the aqueous phase extracted four times with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4, the solvents evaporated under vacuum and the residue purified by chromatography (SiO_2, 3:2 *n*-hexane/ethyl acetate) to give **2b** (2.2 g, 53.6%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.5 Hz, 3 H, CH_3), 1.63 (q, J = 12 Hz, 1 H, 4ax-H), 2.03 (s, 3 H, CH_3C=O), 2.15–2.17 (m, 1 H, 4eq-H), 2.68–2.76 (m, 2 H, SCH_2), 3.49 (dd, J = 5 and 10 Hz, 1 H, 6-H), 3.61 (dd, J = 5 and 10 Hz, 1 H, 6′-H), 3.68 (q, J = 10 Hz, 1 H, 2-H), 3.71–3.73 (m, 1 H, 5-H), 4.50 (d, J = 10 Hz, 1 H, 1-H), 4.56 (s, 2 H, OCH_2CCl_3), 4.67 and 4.81 (AB, J = 12 Hz, OCH_2Ph), 5.03 (m, 1 H, 3-H), 5.41 (d, J = 10 Hz, 1 H, NH), 7.28–7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.7 (CH_3), 20.8 (CH_3C=O), 23.8 (SCH_2), 33.6 (C-4), 55.4 (C-2), 71.4 (C-3), 71.9 (C-6), 73.3 (OCH_2CCl_3), 74.3 (OCH_2Ph), 74.9 (C-5), 84.4 (C-1), 95.4 (CCl_3), 127.4, 127.5, 128.2, 137.8 (C_{arom}), 154.2 (NCOO), 170.7 (Ac_{CO}) ppm. MS: calcd. for $C_{20}H_{26}Cl_3NO_6S$ [M + Na] 536.0444; found 536.0452.

Ethyl 4,6-*O*-Benzylidene-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3-*O*-(trifluoromethylsulfonyl)-1-thio-β-D-glucopyranoside (20): Tf_2O (7.0 mL, 40.0 mmol) was added dropwise to a solution of pyridine (6.5 mL, 80.0 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C. After being stirred for 15 min, a solution of compound **4** (9.72 g, 20.0 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise. Then the mixture was stirred at the same temperature for an additional 30 min until TLC showed the starting material had been completely consumed. The reaction mixture was evaporated and co-concentrated with toluene below 30 °C in vacuo to give **20** as a white solid, which was dried under high vacuum for 2 h and used in the next reaction without further purification.

Ethyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-iodo-2-(2,2,2-trichloroethoxycarbonylamino)-1-thio-β-D-glucopyranoside (21): Crude **20** was dissolved in anhydrous ethylene glycol dimethyl ether (200 mL), and treated with NaI (15.0 g, 100.0 mmol). The mixture was stirred at room temperature overnight until TLC showed the starting material **20** had been completely consumed. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with saturated $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, concentrated in vacuo and the residue purified by chromatography (SiO_2, 4:1 *n*-hexane/ethyl acetate) to give **21** (10.78 g, 90.4% for two steps) as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.4 Hz, 3 H, CH_3), 2.7–2.8 (q, J = 7.4 Hz, 2 H, SCH_2), 3.08 (dd, J = 3.2 and 8.4 Hz, 1 H, 4-H), 3.50 (dt, J = 3.5 and 9.3 Hz, 1 H, 2-H), 3.84–4.09 (m, 2 H, 5-H, 6′-H), 4.38 (dd, J = 4.4 and 9.5 Hz, 1 H, 6-H), 4.72–4.86 (m, 3 H, OCH_2CCl_3 and 1-H), 5.08 (t, J = 3.3 Hz, 1 H, 3-H), 5.38 (d, J = 9.2 Hz, 1 H, NH), 5.70 (s, 1 H, PhCH), 7.35–7.55 (m, 5 H, Ph) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.7 (CH_3), 24.1 (SCH_2), 41.6 (C-3), 52.0 (C-2), 68.3 (C-6), 69.8 (C-4), 74.7 (OCH_2CCl_3), 76.1 (C-5), 84.0 (C-1), 95.1 (CCl_3), 101.4 (PhCH), 126.4, 128.4, 129.4, 136.8 (C_{arom}), 153.6 (O=CN) ppm. MS: calcd. for $C_{18}H_{21}Cl_3NO_5S$ [M + H] 595.9331; found 595.9320.

Ethyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1-thio-β-D-xylopyranoside (2c): A solution of TBTH (4.8 mL, 17.2 mol) in anhydrous toluene (5 mL) was slowly added dropwise to a solution of **21** (7.89 g, 13.2 mmol) and AIBN (80 mg) in anhydrous toluene (750 mL) at 115–120 °C under nitrogen. The reaction was refluxed for 1.8 h. Then the solvent was removed under vacuum to give a mixture of **2c** and **2f**, which was recrystallized from *n*-hexane/ethyl acetate (6:1) to give **2c** (4.03 g, 89% based on recovered **21**) as a white solid. From the mother liquor of *n*-hexane/ethyl acetate, 2.15 g of **21** was recovered. Data for main product **2c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.4 Hz, 3 H, CH_3), 1.79 (q, J = 11.8 Hz, 1 H, 3ax-H), 2.61 (m, 1 H, 3eq-H), 2.74 (AB, J = 7.4 Hz, 2 H, SCH_2), 3.45–3.52 (m, 1 H, 2-H), 3.62–3.84 (m, 3 H, 4-H, 5-H and 6-H), 4.348 (dd, J = 4.6 and 10.6 Hz, 1 H, 6′-H), 4.49 (d, J = 10.2 Hz, 1 H, 1-H), 4.77 (s, 2 H, OCH_2), 5.06 (d, J = 8 Hz, 1 H, NH), 5.56 (s, 1 H, PhCH), 7.36–7.51 (m, 5 H, Ph) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.8 (CH_3), 24.1 (SCH_3), 36.2 (C-3), 50.6 (C-2), 68.9 (C-6), 73.9 (C-4), 74.6 (OCH_2CCl_3), 75.9 (C-5), 86.5 (C-1), 95.3 (CCl_3), 101.6 (PhCH), 126.1, 128.4, 129.2, 137.1 (C_{arom}), 153.8 (O=CN) ppm. MS: calcd. for $C_{18}H_{22}Cl_3NO_5S$ [M + Na] 492.0182; found 492.0190.

Benzyl *O*-[3-*O*-Acetyl-6-*O*-benzyl-2,4-dideoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-xylopyranosyl]-(1→4)-2-acetylamino-6-benzyl-2-deoxy-3-*O*-[D-1-(2-phenylsulfonylethyloxycarbonyl)ethyl]-α-D-glucopyranoside (22a): A mixture of **2b** (3.0 g, 5.84 mmol), **3** (2.9 g, 4.50 mmol) and 4-Å MS (3 g) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature under nitrogen for 30 min and then the mixture was cooled to –45 °C. NIS (1.31 g, 5.84 mmol) was added in one portion, followed by dropwise addition of TMSOTf (0.26 mL, 1.35 mmol). After being stirred for an additional 2 h at the same temperature, the reaction was kept at 0 °C for 14 h. Then the reaction mixture was treated with saturated $Na_2S_2O_3$ (10 mL). After being stirred until the brown color had

disappeared, the mixture was diluted with CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ and brine. The organic layer was dried with anhydrous Na_2SO_4, concentrated in vacuo and the residue purified by chromatography (SiO_2, 1:4 ethyl acetate/dichloromethane) to give **22a** (2.32 g, 47.2%) as a white foam (0.65 g of **3** was recovered). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.169 (d, J = 6.6 Hz, 3 H, CH_3), 1.500 (q, J = 12.1 Hz, 1 H, 4′A-H), 1.97 (s, 3 H, 2-Ac_{Me}), 2.02 (s, 3 H, 3′-Ac_{Me}), 2.12 (dd, J = 5.4 and 12.1 Hz, 1 H, 4′B-H), 3.37 (m, 1 H, 6A-H), 3.40–3.53 (m, 5 H, 2′-H, 6′A-H, 3-H, CH_2-S), 3.57 (m, 2 H, 5-H and 6′B-H), 3.66 (m, 2 H, 6B-H and NHCOO), 3.78 (m, 1 H, 2-H), 3.91 (t, J = 9.3 Hz, 1 H, 4-H), 4.11 (d, J = 8.5 Hz, 1 H, 1′-H), 4.34 (d, J = 12.2 Hz, 1 H, $Troc_A$), 4.36–4.52 (m, 7 H, 3-OCH, 3′-H, 5′-H, $Troc_B$, 1-Bn_A, OCH_2-C), 4.57 (m, 2 H, 1-Bn_B and 6′-Bn_A), 4.63 (d, J = 12.2 Hz, 1 H, 6-Bn_A), 4.71 (d, J = 12.5 Hz, 1 H, 6-Bn_B), 4.83 (d, J = 12.0 Hz, 1 H, 6′-Bn_B), 5.36 (d, J = 3.4 Hz, 1 H, 1-H), 7.24–7.69 (m, 18 H, 3 × Bn, Ph_m, Ph_p), 7.90 (d, J = 7.5 Hz, 2 H, Ph_o), 8.94 (br., 1 H, NHAc) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 18.2 (CH_3), 20.8 (3′-Ac_{Me}), 22.9 (2-Ac_{Me}), 33.4 (C-4′), 54.1 (C-2), 54.7 (CH_2-S), 56,3 (C-2′), 58.0 (O-CH_2-C), 67.2 (C-6), 70.0 (C-5), 70.2 (1-Bn-CH_2), 70.4 (C-3′), 70.6 (C-5′), 71.7 (C-6′), 73.3 (Troc-CH_2), 73.6 (6′-Bn-CH_2), 74.2 (6-Bn-CH_2), 74.6 (3-OCH), 75.3 (C-3), 77.2 (C-4), 95.7 (CCl_3), 96.4 (C-1), 100.5 (C-1′), 127.5, 127.6, 127.7, 127.9, 128.2, 128.3, 128.9, 129.3, 129.4, 134.0, 137.1, 137.5, 137.6, 138.9 (C_{arom}), 154.1 (NCOO), 170.2 (2-Ac_{CO}), 170.6 (3′-Ac_{CO}), 175.5 (COO) ppm. MS: calcd. for $C_{51}H_{59}Cl_3N_2O_{16}S$ [M + H] 1093.2729; found 1093.2750.

Benzyl *O*-[4,6-*O*-Benzylidene-2,3-dideoxy-2-(2,2,2-trichloroethoxycarbonylamino)-1-β-D-xylopyranosyl]-(1→4)-2-acetylamino-6-benzyl-2-deoxy-3-*O*-[D-1-(2-phenylsulfonylethyloxycarbonyl)ethyl]-α-D-glucopyranoside (22b): A mixture of **2c** (0.71 g, 1.5 mmol), **3** (0.64 g, 1.0 mmol) and 4-Å MS (3 g) in anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature under nitrogen for 20 min and then the mixture was cooled to –45 °C. NIS (0.45 g, 2.0 mmol) was added in one portion and then TMSOTf (40 μL, 0.2 mmol) was added dropwise. After being stirred for an additional 20 min at the same temperature, the reaction was kept at 4 °C for 10 h and then for 11 h at room temperature. Then the reaction mixture was treated with 10% $Na_2S_2O_3$ (10 mL). After being stirred until the brown color had disappeared, the mixture was diluted with $CHCl_3$ (100 mL) and washed with brine. The organic layer was dried with anhydrous Na_2SO_4, concentrated in vacuo and the residue purified by chromatography (SiO_2, 2:3 *n*-hexane/ethyl acetate) to give **22b** (0.45 g, 43%) as a white foam (0.21 g of **3** was recovered). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, J = 6 Hz, 3 H, CH_3), 1.29 (q, J = 11.8 Hz, 1 H, 3′A-H), 1.973 (s, 3 H, 2-Ac_{Me}), 2.25 (dt, J = 4.5 and 12.4 Hz, 1 H, 3′B–H), 3.26 (dt, J = 4.9 and 9.8 Hz, 1 H, 5′-H), 3.41 (dd, J = 3.1 and 10.6 Hz, 1 H, 6A-H), 3.44–3.54 (m, 5 H, 2′-H, 4′-H, 3-H, CH_2-S), 3.58 (td, J = 2.7 and 10.0 Hz, 1 H, 5-H), 6.69 (t, J = 10.3 Hz, 1 H, 6′A-H), 3.70 (obs m, 1 H, 6B-H), 3.79 (dt, J = 11.2 and 3.9 Hz, 1 H, 2-H), 3.86 (t, J = 9.5 Hz, 1 H, 4-H), 4.19 (d, J = 8.0 Hz, 1 H, 1′-H), 4.24 (d, J = 9.5 Hz, 1 H, NHCOO), 4.35 (dd, J = 4.9 and 10.3 Hz, 1 H, 6′B-H), 4.37 (d, J = 12.0 Hz, 1 H, $Troc_A$), 4.40–4.60 (m, 6 H, 3-OCH, 1-Bn_{A+B}, 6-Bn_A, O-CH_2-C), 4.79 (d, J = 12.2 Hz, 1 H, 6-Bn_B), 4.87 (d, J = 12.2 Hz, 1 H, $Troc_B$), 5.35 (d, J = 3.4 Hz, 1 H, 1-H), 5.51 (s, 1 H, O-CH-O), 7.25–7.62 (m, 17 H, 3 × Bn, Ph_m), 7.63–7.68 (m, 2 H, NH-AC, Ph_p), 7.92 (m, 2 H, Ph_o) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 18.5 (CH_3), 23.0 (2-Ac_{Me}), 34.3 (C-3′), 51.2 (C-2’), 54.1 (C-2), 54.8 (CH_2-S), 58.0 (O-CH_2-C), 67.8 (C-6), 68.9 (C-6’), 69.9 (C-5), 70.3 (C-5’, 1-Bn-CH_2), 73.9 (Troc–CH_2), 74.5 (3-OCH, 6-Bn-CH_2), 75.3 (C-4’), 75.8 (C-3), 78.6 (C-4), 95.5 (CCl_3), 96.5 (C-1), 101.7 (O-CH-O), 102.4 (C-1’), 126.1, 127.7, 128.0, 128.3, 128.6, 129.1, 129.4, 129.8, 134.1, 137.0, 137.2, 137.5, 138.9 (C_{arom}), 153.5 (NCOO), 170.5 (2-Ac_{CO}), 175.4 (COO) ppm. MS: calcd. for $C_{49}H_{55}Cl_3N_2O_{15}S$ [M + H] 1049.2467; found 1049.2461.

Benzyl *O*-[(3,6-*O*-Acetyl-2,4-dideoxy-2-acetylamino)-β-D-xylopyranosyl]-(1→4)-2-acetylamino-6-*O*-acetyl-2-deoxy-3-*O*-[D-1-(2-phenylsulfonylethyloxycarbonyl)ethyl]-α-D-glucopyranoside (1a): A mixture of **22a** (2.24 g, 2.05 mmol) and anhydrous $ZnCl_2$ (2.85 g, 20.5 mmol) in a solution of Ac_2O/AcOH (3:1, 36 mL) was stirred at room temperature overnight (15 h). The reaction mixture was co-evaporated with toluene in vacuo to give a brown oil, which was dissolved in CH_2Cl_2 (300 mL) and saturated $NaHCO_3$ (100 mL). Then the organic layer was separated and washed with saturated $NaHCO_3$ (pH > 7) and brine (pH = 7). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give **23a** as a light brown oil as intermediate (MS: calcd. for $C_{41}H_{51}Cl_3N_2O_{18}S$ [M + H] 997.2001; found 997.1990). Compound **23a** was dissolved in a solution of Ac_2O/AcOH/THF (3:2:1, 30 mL) and then treated with a zinc/copper couple (5.0 g, 76.5 mmol). The mixture was stirred at room temperature overnight (26 h). The mixture was filtered through a pad of Celite and washed with acetone. The filtrate was concentrated in vacuo and the residue purified by chromatography (SiO_2, ethyl acetate and 95:5 ethyl acetate/methanol) to afford **1a** (1.08 g, 61%) as a white foam (0.34 g of **23a** was recovered). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.222 (d, J = 7.0 Hz, 3 H, CH_3), 1.60 (q, J = 12.0 Hz, 1 H, 4′A-H), 1.95, 1.99, 2.05, 2.07, 2.12 (5 × s, 15 H, 5 × Ac_{Me}), 2.10 (obs m, 1 H, 4′B-H), 3.48–3.60 (m, 2 H, 3-H, 5-H), 3.62–3.84 (m, 5 H, 2-H, 4-H, 5′-H, CH_2-S), 3.93 (q, J = 8.5 Hz, 1 H, 2′-H), 4.03–4.30 (m, 5 H, 6A-H, 6B-H, 6′A-H, 6′B-H, 14-H), 4.34–4.70 (m, 5 H, O-CH_2-C, 3-OCH, 1-Bn-CH_2), 4.91 (dt, J = 5.0 and 10.8 Hz, 1 H, 3′-H), 5.29 (d, J = 3.2 Hz, 1 H, 1-H), 6.25 (d, J = 7.8 Hz, 1 H, 2′-NHAc), 7.31 (m, 5 H, Bn), 7.60–7.75 (m, 4 H, Ph_{m+p}, 2-NHAc), 7.95 (dd, J = 2.2 and 8.4 Hz, 2 H, Ph_o) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 18.0 (CH_3), 20.5, 20.7, 20.7(3 × OAc_{Me}), 22.8, 22.9 (2 × $NHAc_{Me}$), 32.8 (C-4’), 53.8 (C-2), 54.2 (C-2), 54.6 (CH_2-S), 58.0 (O-CH_2-C), 61.9 (C-6), 65.1 (C-6’), 69.3 (C-5’), 69.5 (C-5), 70.2 (1-Bn-CH_2), 70.5 (C-3′), 74.5 (C-3), 74.8 (3-OCH), 77.7 (C-4), 96.2 (C-1), 101.5 (C-1’), 127.6, 127.8, 128.0, 128.3, 129.5, 134.1, 137.4, 138.9 (C_{arom}), 170.5, 170.5, 170.7, 170.8, 171,3 (5 × Ac_{CO}), 175.4 (COO) ppm. MS: calcd. for $C_{408}H_{52}N_2O_{17}S$ [M + H] 865.3064; found 865.3068.

Benzyl *O*-(4,6-*O*-Acetyl-2,3-dideoxy-2-acetylamino-β-D-xylopyranosyl)-(1→4)-2-acetylamino-6-*O*-acetyl-2-deoxy-3-*O*-[D-1-(2-phenylsulfonylethyloxycarbonyl)ethyl]-α-D-glucopyranoside (1b): A mixture of **22b** (1.05 g, 1.0 mmol) and anhydrous $ZnCl_2$ (1.39 g, 10 mmol) in a solution of Ac_2O/AcOH (3:1, 15 mL) was stirred at room temperature overnight. The reaction mixture was co-evaporated with toluene in vacuo to give **23b** as an oil as intermediate, which was dissolved in a solution of THF/Ac_2O/AcOH (3:2:1, 15 mL) and then treated with zinc dust (2.61 g, 40.0 mmol). The mixture was stirred at room temperature overnight until TLC showed the intermediate **23b** had been completely consumed. The mixture was filtered through a pad of Celite and washed with acetone. The filtrate was concentrated in vacuo and the residue was purified by chromatography (SiO_2, 1:4 *n*-hexane/ethyl acetate and 95:5 ethyl acetate/methanol) to afford **1b** (0.634 g, 73%) as a white foam. ^{1}H NMR (500 MHz, [D_6]acetone): δ = 1.18 (d, J = 7.1 Hz, 3 H, CH_3), 1.77 (q, J = 12.1 Hz, 1 H, 3′A-H), 1.98, 1.20, 2.03, 2.05, 2.09 (5 × s, 15 H, 5 × Ac_{Me}), 2.41 (dt, J = 12.2 and 4.6 Hz, 3′B-H), 3.64–3.77 (m, 4 H, 2-H, 3-H, CH_2-S), 3.80 (dm, J = 9.5 Hz, 1 H, 5′-H), 3.86 (dd, J = 4.7 and 10.0 Hz, 1 H, 5-H), 3.90–4.00 (m, 2 H, 2′-H and 4-H), 4.10 (d, J = 12.2 Hz, 1 H, 6A-H), 4.15 (dd, J = 4.9 and 12.2 Hz, 1 H, 6′A-H), 4.34 (dd, J = 4.8 and 12.2 Hz, 1 H, 6B-H), 4.44–4.60 (m, 5 H, 6′B-H, O-CH_2-C, 3-OCH, 1-Bn_A), 4.66 (d, J =

7.5 Hz, 1 H, 1′-H), 4.68 (d, J = 11.7 Hz, 1 H, 1-Bn_B), 4.84 (dt, J = 4.8 and 10.5 Hz, 1 H, 4′-H), 5.26 (s, 1 H, 1-H), 7.28 (m, 1 H, Bn_p), 7.35 (m, 4 H, Bn_m, Ph_o), 7.53 (d, J = 8.6 Hz, 1 H, 2′-NHAc), 7.72 (t, J = 7.5 Hz, 2 H, Ph_m), 7.98 (d, J = 8.0 Hz, 2 H, Bn_o), 8.24 (br. s, 1 H, 2-NHAc) ppm. ^{13}C NMR (500 MHz, [D$_6$]acetone): δ = 18.5 (CH_3), 20.69, 20.85 (2×), 22.98, 23.17 (5 × Ac_{Me}), 34.54 (C-3′), 50.34 (C-2'), 55.30 (C-2, CH_2-S), 59.59 (O-CH_2-C), 63.0 (C-6), 63.20 (C-6'), 66.9 (C-4'), 70.2 (C-5), 70.3 (1-Bn-CH_2), 75.8 (3-OCH), 75.9 (C-5'), 76.2 (C-3), 77.3 (C-4), 96.5 (C-1), 102.8 (C-1'), 128.4, 128.6, 128.2, 129.1, 130.3, 134.7, 138.6, 140.9 (C_{arom}), 170.1, 170.6, 171.0, 171.3, 172.8 (5 × Ac_{CO}), 176.4 (COO) ppm. MS: calcd. for $C_{40}H_{52}N_2O_{17}S$ [M + H] 865.3064 and [M + Na] 887.2883; found 865.3020 and 887.2853.

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[1] E. D. Brown, G. D. Wright, *Chem. Rev.* **2005**, *105*, 759–774.
[2] a) S. A. Hitchcock, C. N. Eid, J. A. Aikins, M. Zia-Ebrahimi, L. C. Blaszcak, *J. Am. Chem. Soc.* **1998**, *120*, 1916–1917; b) H. B. Men, P. Park, M. Ge, S. Walker, *J. Am. Chem. Soc.* **1998**, *120*, 2484–2485; c) S. Ha, E. Chang, M. C. Lo, H. B. Men, P. Park, M. Ge, S. Walker, *J. Am. Chem. Soc.* **1999**, *121*, 8415–8426; d) P. Cudic, D. C. Behenna, M. K. Yu, R. G. Kruger, L. M. Szewczuk, D. G. McCafferty, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3107–3110; e) S. L. Saha, M. S. Van Nieuwenhuyze, W. J. Hornback, J. A. Aikins, L. C. Blaszczak, *Org. Lett.* **2001**, *3*, 3575–3577.
[3] a) B. Schwartz, J. A. Markwalder, Y. Wang, *J. Am. Chem. Soc.* **2001**, *123*, 11638–11643; b) M. S. Van Nieuwenhuyze, S. C. Mauldin, M. Zia-Ebrahimi, J. A. Aikins, L. C. Blaszczak, *J. Am. Chem. Soc.* **2001**, *123*, 6983–6988; c) X. Y. Ye, M. C. Lo, L. Brunner, D. Walker, D. Kahne, S. Walker, *J. Am. Chem. Soc.* **2001**, *123*, 3155–3156; d) M. S. Van Nieuwenhuyze, S. C. Mauldin, M. Zia-Ebrahimi, B. E. Winger, W. J. Hornback, S. L. Saha, J. A. Aikins, L. C. Blaszczak, *J. Am. Chem. Soc.* **2002**, *124*, 3656–3660.
[4] U. S. Eggert, N. Ruiz, B. V. Falcone, A. A. Branstrom, R. C. Golman, T. J. Silhavy, D. Kahne, *Science* **2001**, *294*, 361–364.
[5] Z. Y. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov, C. H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
[6] T. Lioux, R. Busson, J. Rozenski, M. Nguyen-Distèche, J.-M. Frère, P. Herdewijn, *Collect. Czech. Chem. Commun.* **2005**, *70*, 1615–1641.
[7] a) W. Hartwig, *Tetrahedron* **1983**, *39*, 2609–2645; b) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413–1432, and references therein; c) J. C. Florent, C. Monneret in *Glycoscience* (Eds.: B. Fraser-Reid, K. Tatsuta, J. Thiem), Springer, Heidelberg, Germany, **2001**, vol. 1, pp. 232–251.
[8] a) U. Ellervik, H. Grundberg, G. Magnusson, *J. Org. Chem.* **1998**, *63*, 9323–9338; b) M. Schultz, H. Kunz, *Tetrahedron: Asymmetry* **1993**, *4*, 1205–1220.
[9] *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Marcel Dekker, New York, **1996**, chapter 8, and references cited therein.
[10] Y. Kajihara, H. Kodama, T. Endo, H. Hashimoto, *Carbohydr. Res.* **1998**, *306*, 361–378.
[11] R. P. McGeary, K. Wright, I. Toth, *J. Org. Chem.* **2001**, *66*, 5102–5105.
[12] a) U. Ellervik, G. Magnusson, *Carbohydr. Res.* **1996**, *280*, 251–260; b) H. Lönn, *Carbohydr. Res.* **1985**, *139*, 105–113.
[13] J. Vesely, M. Ledvina, J. Jindrich, D. Saman, T. Trnka, *Collect. Czech. Chem. Commun.* **2003**, *68*, 1264–1274.
[14] M. P. DeNinno, J. B. Etienne, K. C. Duplantier, *Tetrahedron Lett.* **1995**, *36*, 669–672.
[15] Z. D. Shi, B. H. Yang, Y. L. Wu, *Tetrahedron* **2002**, *58*, 3287–3296.
[16] a) M. J. Robins, Z. Guo, M. C. Samano, S. F. Wnuk, *J. Am. Chem. Soc.* **1996**, *118*, 11317–11318; b) A. Berkin, M. A. Szarek, J. Plenkiewicz, W. A. Szarek, R. Kisilevsky, *Carbohydr. Res.* **2000**, *325*, 30–45.
[17] a) Z. Y. Zhang, G. Magnusson, *Carbohydr. Res.* **1996**, *295*, 41–55; b) *Carbohydrate Chemistry* (Ed.: G. J. Boons), 1st ed., Blackie Academic & Professional, London, **1998**, and references therein.
[18] T. Norberg in *Modern Methods in Carbohydrate Synthesis* (Eds.: S. H. Khan, R. A. O'Neill), Harwood Academic, London, **1996**, pp. 82–106.
[19] V. Martichonok, G. M. Whitesides, *J. Org. Chem.* **1996**, *61*, 1702–1706.
[20] E. Dasgupta, P. J. Garegg, *Carbohydr. Res.* **1998**, *306–314*, C13–C17.
[21] T. Ercegovic, A. Meijer, G. Magnusson, U. Ellervik, *Org. Lett.* **2001**, *3*, 913–915.
[22] M. Fridman, D. Solomon, S. Yogev, T. Baasov, *Org. Lett.* **2002**, *4*, 281–283.
[23] a) F. Yang, Y. G. Du, *Carbohydr. Res.* **2003**, *338*, 495–502; b) A. R. Chowdhury, A. Siriwardena, G. J. Boons, *Tetrahedron Lett.* **2002**, *43*, 7805–7807.
[24] G. Yang, X. Ding, F. Kong, *Tetrahedron Lett.* **1997**, *38*, 6725–6728.
[25] a) A. K. Misra, M. Fukuda, O. Hindsgaul, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2667–2670; b) R. I. Ei-Sokkary, B. A. Silwanis, M. A. Nashed, H. Paulsen, *Carbohydr. Res.* **1990**, *203*, 319–323; c) H. Lönn, *Carbohydr. Res.* **1985**, *139*, 105–113.
[26] J. O. Kihlberg, D. A. Leigh, D. R. Bundle, *J. Org. Chem.* **1990**, *55*, 2860–2863.
[27] J. Buskas, P. Konradsson, *J. Carbohydr. Chem.* **2000**, *19*, 25–52.

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