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Synthesis of S-linked thiooligosaccharide analogues of Nod factors: synthesis of new protected thiodisaccharide and thiotrisaccharide intermediates☆

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Abstract

We are investigating the synthesis of thioanalogues of nodulation factors that will be resistant to degradation by chitinases. To study the influence of our protecting group strategy, the glycosylation of 1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**7**) with two trichloroacetimidate glycosyl donors carrying an azido group at C-2 and either benzyl or benzoyl protecting groups on O-3 and O-4 was first attempted under catalysis with $BF_3 \cdot Et_2O$ in toluene. While glycosylation with the benzoylated glycosyl donor gave only a poor yield (27%) of the disaccharide, a similar reaction with the benzylated donor gave the corresponding disaccharide in good yield (77%). Although both products were obtained as anomeric mixtures, the benzylated donor led to improved stereoselectivity in favor of the desired β-anomer (α:β 3:7). Based on these results, a novel thiotrisaccharide was synthesized via the coupling of **7** with 6-*O*-acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-α-D-glucopyranosyl trichloroacetimidate (**25**) also newly synthesized. After optimization of the reaction conditions, the desired thiotrisaccharide 4-*O*-[6-*O*-acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-β-D-glucopyranosyl]-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**26β**) was obtained in 57% yield. These conditions led to an anomeric mixture in favor of the desired β-anomer (α:β 1:4.7) that was separated from the α-anomer by normal-phase HPLC on a PrepNova Pack® silica gel cartridge. The work described here shows that thiodisaccharide glycosyl donors behave quite differently from the analogous O-disaccharide used previously to synthesize nodulation factors.

Keywords: Nodulation factors; Analogues; Thiooligosaccharides; Glycosylation

1. Introduction

Various soil bacteria of the genera *Rhizobium*, *Bradyrhizobium* or *Azorhizobium* can enter in a specific symbiotic association[2] with leguminous plants. This association allows the plant to use atmospheric nitrogen previously fixed and metabolized into ammonia and alanine[3] by the bacteria residing in root nodules. This biological process is of considerable interest to agriculture since it could provide an alternative to the use of fertilizers (e.g., nitrates). The key step of the infection is the production by the bacteria of extracellular messenger molecules called nodulation factors (Nod factors) that will induce deformations and nodule organogenesis on the plant roots.[4] Nod factors have been shown[2] in all cases to be lipooligosaccharides constituted of a tetra- (ABCD) or penta- (ABCDE) saccharidic backbone of chitin variably substituted as represented on Fig. 1 (**1**). Although only very small concentrations (10^{-6}–10^{-12} mol/L) of Nod factors are required to trigger nodulation, the activity of these oligosaccharides is limited by

☆ Part 3 of a series. For Part 2 see Ref. 1.

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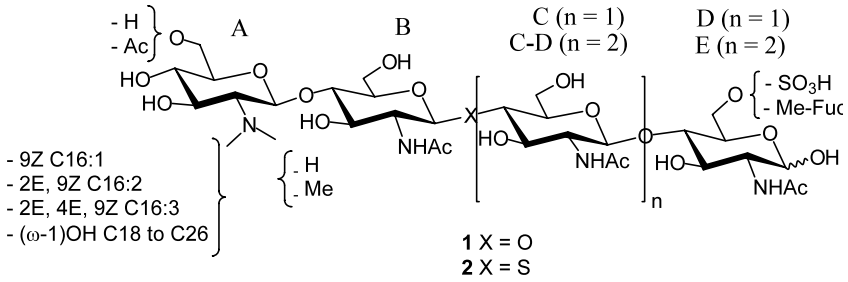
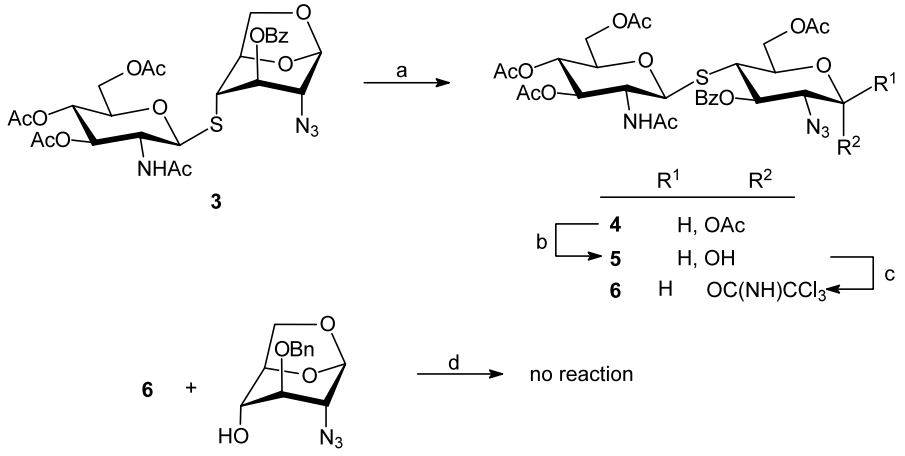


Fig. 1. Natural nodulation factors (**1**) and thioanalogues of nodulation factors (**2**).

the action of enzymes named chitinases that cleave the B–C interglycosidic linkage.[5] It is known[6] that glycosidase enzymes cleave thio-interglycosidic bonds more slowly than the corresponding oxygen interglycosidic bonds. Thus, to increase the resistance of our analogues to chitinases, our research aims at preparing analogues of Nod factors in which the interglycosidic oxygen atom between the sugar units B and C is replaced by a sulfur atom (Fig. 1, **2**). We previously reported the synthesis of various thiodisaccharides by nucleophilic displacement of a 1,6-anhydrotriflate by an anomeric thiolate[7] and, in turn, described the preparation of a thiotrisaccharide intermediate.[1] We report here the synthesis of new thiodi- and thiotri-saccharide precursors of larger structures.

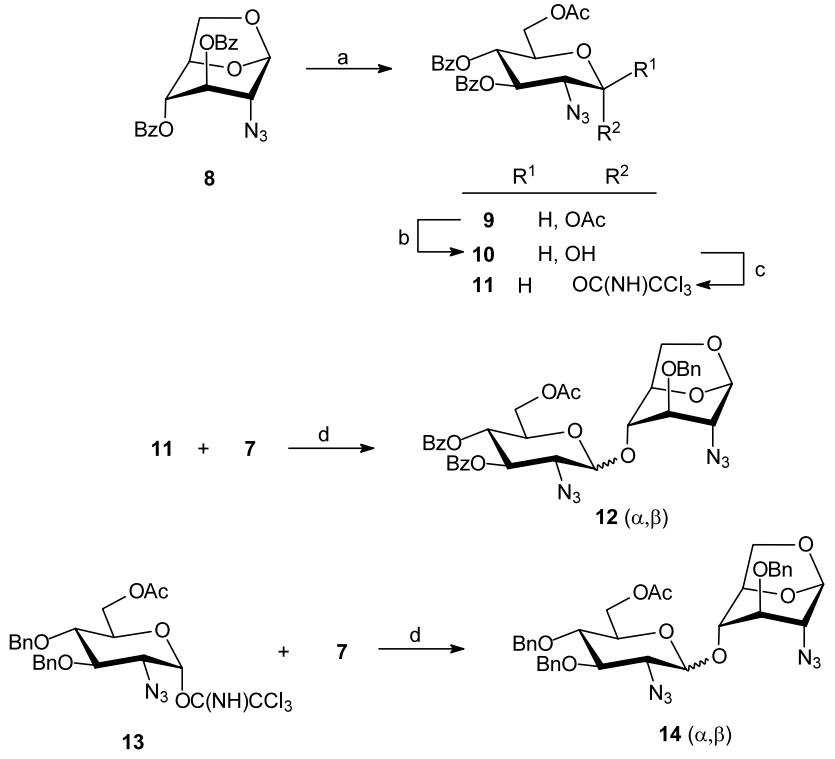
2. Results and discussion

Relying on the results obtained by Tailler and co-workers,[8] our synthetic strategy is based on the use of 2-azido trichloroacetimidate glucosaminyl donors prepared from the thiodisaccharides that we reported previously.[7] To favor the formation of a β-glycosidic linkage,[9] all the trichloroacetimidate glycosyl donors used in our work were prepared as α-anomers. Thus, the 1,6-anhydro disaccharide **3**[7] was converted in three steps to the trichloroacetimidate glycosyl donor **6**. The 1,6-anhydro bridge was submitted to acetolysis with acetic anhydride and trifluoroacetic acid to yield an anomeric mixture of **4** (79%). Selective O-deacetylation at the anomeric position with hydrazine acetate in *N*,*N*-dimethylformamide led to the hemicetal **5** (82%) that was converted to the trichloroacetimidate **6** (Cl_3CCN/DBU). The glycosyl donor **6** was obtained in 85% yield as an anomeric mixture largely in favor of the α-anomer (>90%) as expected when using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base.[9] Glycosylation of the known[10] acceptor **7** with the thiodisaccharide imidate **6** was then attempted according to the conditions described by Tailler and co-workers[8] using $BF_3 \cdot Et_2O$ as a promoter in toluene (Scheme 1). However, these conditions failed to give the desired trisaccharide. Similarly, addition of the more active catalyst, triethylsilyl trifluoromethanesulfonate, to the reaction mixture led to the degradation of the glycosyl donor without formation of the expected trisaccharide. Since the acceptor **7** had been used successfully[10] as a glycosyl acceptor, we concluded that the protecting group strategy devised for donor **6** was incompatible with its coupling to acceptor **7**. Thus, we investigated the reaction of donors **11** and **13** with acceptor **7**. The 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose[10] was converted to the dibenzoate **8** and then submitted to



Scheme 1. (a) 9:1 Ac_2O–TFA, 65 °C (79%); (b) $H_2NNH_2 \cdot AcOH$ in DMF (82%); (c) Cl_3CCN, DBU in CH_2Cl_2 (85%); (d) $BF_3.Et_2O$, $PhCH_3$ (no reaction).

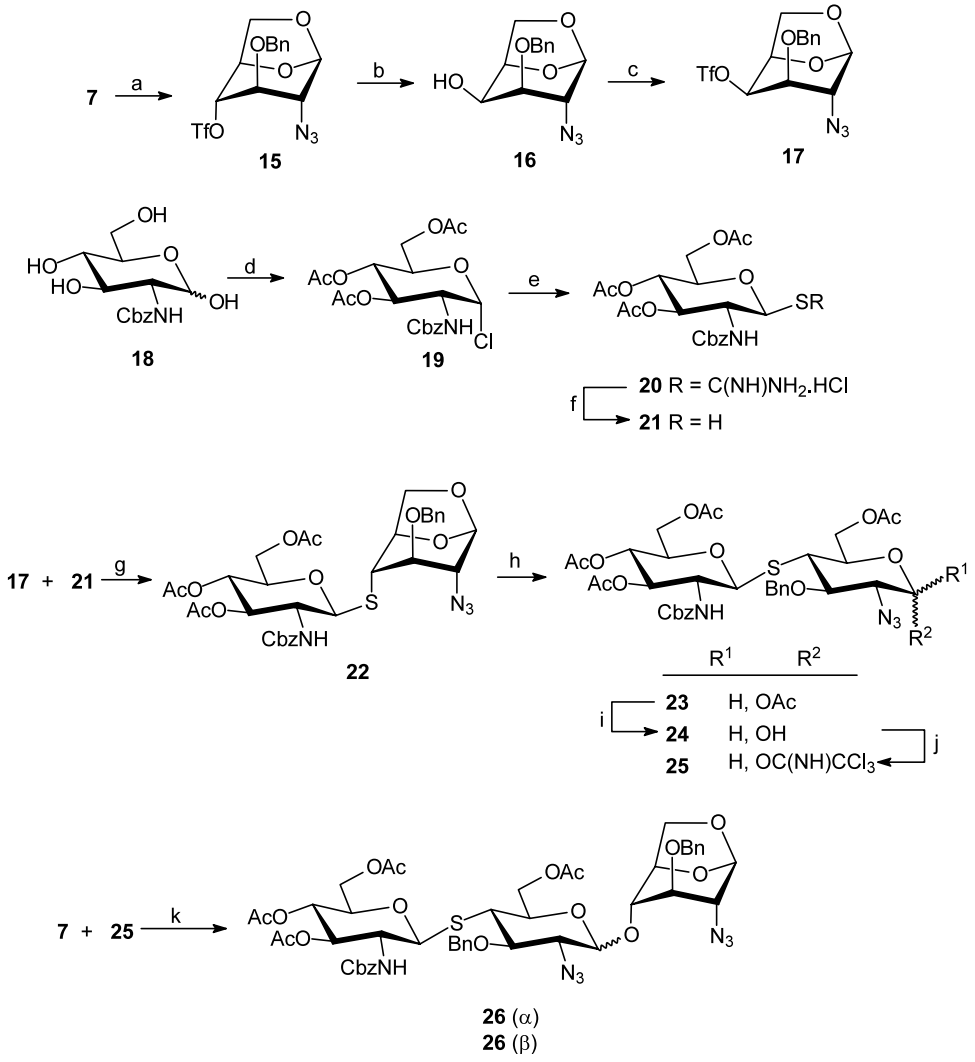
acetolysis (Ac_2O–TFA) to give diacetate **9** (90%) as an anomeric mixture. The anomeric acetyl group in **9** was selectively removed with hydrazine acetate, and the hemiacetal **10** was converted to the trichloroacetimidate **11** (Cl_3CCN/DBU). Once again, the α:β ratio obtained for the donor **11** was estimated by ^1H NMR spectroscopy to be largely in favor of the α-anomer (> 90%). Similarly, the dibenzylated trichloroacetimidate **13** was prepared from the corresponding hemiacetal.[11] Glycosylation of acceptor **7** with donors **11** and **13** (Scheme 2) was then attempted using the reaction conditions that had previously failed to promote its coupling to imidate **6** ($BF_3 \cdot Et_2O$ in toluene). Thus, glycosylation of excess (1.3 equiv) **7** with the benzoylated glycosyl donor **11** gave only a poor yield (27%) of disaccharide **12** that was isolated as an anomeric mixture only slightly in favor of the β-anomer (α:β 4:6). In contrast, coupling of **7** with the benzylated analogue **13** gave disaccharide **14** in good yield (77%) and with an improved stereoselectivity towards the β-anomer (α:β 3:7). Although this selectivity was not as pronounced as expected when using trichloroacetimidate glycosyl donors bearing nonparticipating groups at C-2,[9,10] the yield obtained with the benzylated donor **13** prompted us to investigate the efficiency of the thiodisaccharide **25** as a glycosyl donor to prepare thiotrisaccharide **26** (Scheme 3). Therefore, we prepared thiodisaccharide **22** following the strategy that we established previously[7] to synthesize N-protected-S-linked chitobiose derivatives. The gluco derivative **7** was first converted to the triflate **15** (Tf_2O–pyridine in dichloromethane), and the triflyl group was subsequently displaced with nitrite ions in anhydrous *N*,*N*-dimethylformamide[12] to give the nitrite ester that underwent hydrolysis during workup to afford **16** in 68% yield. The configurations of the 1,6-anhydro derivatives **15** and **16** were confirmed by ^1H NMR coupling constants measured between H-3 and H-4 (~ 1 and 5.5 Hz, respectively, for the gluco and galacto configurations). The galacto derivative **16** was then treated with triflic anhydride to give the triflate derivative **17** in 94% yield, which was ready to undergo nucleophilic displacement with the thiol **21**. Thus, the known[13] hemiacetal **18** was treated with acetyl chloride to give in one step the acetylated glucosyl chloride **19**,[14] which was immediately converted (thiourea, acetone) to the pseudothiourea hydrochloride **20** following the procedure of Horton and Wolfrom.[15] Finally, treatment of **20** with sodium sulfite in a mixture of acetone and water led efficiently to the corresponding anomeric thiol **21** (81%). Reaction of thiol **21** with sodium hydride led to the corresponding thiolate, which was in turn condensed with the triflate derivative **17** to afford the thiodisaccharide **22** in excellent yield (88%). Conversion of the 1,6-anhydro thiodisaccharide **22** to the glycosyl donor



Scheme 2. (a) 9:1 Ac_2O–TFA, 20 °C (90%); (b) $H_2NNH_2 \cdot AcOH$ in DMF (83%); (c) Cl_3CCN, DBU in CH_2Cl_2 (31%); (d) $BF_3.Et_2O$, $PhCH_3$, −50 °C, 1.3 equiv of **7** [27% for **12** (α:β 4:6), 77% for **14** (α:β 3:7)].

25 was then accomplished in three steps: opening of the 1,6-anhydro ring (TFA–Ac_2O), O-deacetylation at the anomeric position (hydrazine acetate) and reaction with trichloroacetonitrile in the presence of DBU (Scheme 3). Thus, trichloroacetimidate **25** was obtained from the hemiacetal **24** in 82% yield and as an anomeric mixture largely in favor of the α-anomer (α:β 8:2) as established from its ^1H NMR spectrum.

Glycosidation of donor **25** with 2 molar equiv of alcohol **7** was then attempted under $BF_3 \cdot Et_2O$ catalysis in toluene using the conditions (Table 1, Entry 1) that were successful for the synthesis of the model disacchar-



Scheme 3. (a) Tf_2O, C_6H_5N–CH_2Cl_2, −15 °C (quant); (b) $NaNO_2$, DMF, 20 °C then aqueous workup (68%); (c) Tf_2O in C_6H_5N–CH_2Cl_2, −15 °C (94%); (d) AcCl; (e) H_2NCSNH_2, acetone [47% over (d) and (e)]; (f) Na_2SO_3, acetone–water (81%); (g) NaH with **21** in DMF at 0 °C then **17** at 20 °C (88%); (h) 9:1 Ac_2O–TFA, 20 °C (96%, α:β 75:25); (i) $H_2NNH_2 \cdot AcOH$ in DMF (81%, α:β 6:4); (j) Cl_3CCN, DBU in CH_2Cl_2 (82%, α:β 8:2); (k) see Table 1 for details.

Table 1
Glycosidation of thiodisaccharide trichloroacetimidate glycosyl donor **25** by alcohol **7**

Entry	Catalyst	Solvent	Temperature (°C)	Yield (%)	α/β ratio
1	$BF_3 \cdot Et_2O$	$PhCH_3$	−78–−20	24	3:1
2	TESOTf	$PhCH_3$	−78–−20	20	2:1
3	TESOTf	CH_3CN	−30–−10	29	1:2
4	$BF_3 \cdot Et_2O$	CH_2Cl_2	−78–−20	57	1:4.7

ide **14**. However, the results were in contrast with those obtained for the preparation of **14** since only 24% of the trisaccharide **26** was isolated after chromatography. In addition, careful examination of the ^{1}H NMR spectrum showed that **26** was obtained as an anomeric mixture in which, surprisingly, the α-anomer was the major product formed (α:β 3:1). As can be seen from Table 1, replacing $BF_3{\cdot}Et_2O$ with triethylsilyl triflate in toluene or acetonitrile did not increase the yield of thiotrisaccharide **26**. However, these conditions gave a better selectivity in favor of the β-anomer than $BF_3{\cdot}Et_2O$ (in toluene): the ratio α:β decreased to 2:1 in toluene (Entry 2) and to 1:2 in acetonitrile (Entry 3). Finally, to favor an S_N2 displacement of the trichloroacetimidate group in **25**, we attempted to use the less polar solvent dichloromethane under catalysis with $BF_3{\cdot}Et_2O$ (Table 1, Entry 4). These conditions turned out to be successful since thiotrisaccharide **26** was isolated in 57% yield based on the imidate **25**, which was used as the limiting reagent. Most importantly, these conditions led to an anomeric mixture considerably in favor of the wanted β-anomer (α:β 1:4.7). The two anomers, which could not be separated by conventional chromatography using various solvent systems and column sizes, were eventually obtained pure by normal-phase HPLC on a PrepNova Pack® silica gel cartridge (Waters) using a mixture of ethyl acetate and hexane as the mobile phase.

The formation of β-glycosidic linkages of glucosamine typically relies on the use of donors carrying participating groups such as phthalimide or alkylcarbamates at C-2.[16,17] However, these glycosyl donors have limited reactivity especially when coupled to poorly reactive acceptors such as the 4-hydroxyl group of a glucosamine acceptor. To circumvent these limitations, alternative synthetic strategies have used 2-azido-α-trichloroacetimidates[9,10] and α-phosphates as glycosyl donors.[18] While α-trichloroacetimidates were reported to give β-anomers with very good selectivity,[9,10] α-phosphates were reported to give a 1:4 mixture of α and β-anomers.[18] In fact, the synthesis of nodulation factors through coupling of 2-azido trichloroacetimidate glucosamine glycosyl donors to the known acceptor **7** were reported[10] to give β-glycosidic linkages in good yields and with high stereoselectivity. In contrast, our results show that this synthetic strategy applied to the coupling of the 2-azido trichloroacetimidate thiodisaccharide glycosyl donor **25** to acceptor **7** was less selective in favor of a β-glycosidic linkage. Based on the results described here, we conclude that thiodisaccharide trichloroacetimidate glycosyl donors (like **25**) behave quite differently from the analogous O-disaccharides used previously extensively and successfully to synthesize[10] nodulation factors. In fact, our results are similar to those obtained when coupling a 2-azido α-phosphate glycosyl donor to the more reactive 2-OH and 6-OH groups of glucose acceptors.[18] However, the thiotrisaccharide **26β** could be prepared in sufficient amount to allow investigation towards extension at the reducing end. Thus, it is now undergoing further studies to provide access to the first thiotetrasaccharide analogue of nodulation factor.

3. Experimental

3.1. General methods

Melting points were determined with a Büchi B-450 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker AC 400 NMR or an Avance 400 NMR for solutions in $CDCl_3$, $(CD_3)_2SO$ or CD_3OD (internal standard, for ^{1}H: residual $CHCl_3$ δ_H 7.27 ppm, Me_2SO δ_H 2.49 ppm or MeOH δ_H 3.31 ppm, for ^{13}C: $CDCl_3$ δ_C 77.0). First-order chemical shifts and coupling constants (J Hz) were obtained from one-dimensional spectra. Assignments of proton and carbon resonances were based on COSY and ^{13}C–^{1}H heteronuclear correlated experiments. TLC was performed on precoated aluminium plates with Silica Gel 60 F254 (E. Merck), and products were detected with UV light and/or by charring with 10% H_2SO_4 solution in EtOH. Solvents were distilled and dried according to standard procedures,[19] and organic solutions were dried over Na_2SO_4 and concentrated below 40 °C under reduced pressure. Compounds were purified by atmospheric pressure chromatography with Silica Gel (70–120) mesh or neutral aluminium oxide (50–200 μm). Elemental analyses were performed at the 'Service Central d'Analyses du CNRS', Lyon. High-resolution mass spectrometry analyses were performed at the 'Centre Régional de Mesures Physiques de l'Ouest', Rennes.

3.2. 4-*S*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-1,6-di-*O*-acetyl-2-azido-3-*O*-benzoyl-2-deoxy-4-thio-α,β-D-glucopyranoside (4)

Anhydro **3**[7] (250 mg, 0.636 mmol) was dissolved in 9:1 Ac_2O–TFA (30 mL), and the solution was stirred for 14 h at room temperature (rt) and for 6 h at 65 °C. Solvents were evaporated, and residual traces of acid were co-evaporated with toluene. Chromatography (hexane–EtOAc, gradient 1:2 to 1:6, followed by EtOAc) of the dry residue gave the anomeric mixture of diacetate **4** (200 mg, 79%); ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 55:45; ^{1}H NMR ($CDCl_3$): δ 8.09 (m, 2 Hα, 2 Hβ, aromatics), 7.55 (m, 1 Hα, 1 Hβ, aromatic), 7.50 (m, 2 Hα, 2 Hβ, aromatics), 6.40 (d, 1 Hα, $J_{1,2}$ 3.5 Hz, H-1Bα), 5.71 (t, 1 Hα, $J_{2,3+3,4}$ 20.6 Hz, H-3Bα), 5.65 (d, 1 Hα, $J_{NH,2}$ 9.8 Hz, NHAα), 5.58 (d, 1 Hβ, $J_{1,2}$ 8.8 Hz, H-1Bβ), 5.53 (d, 1 Hβ, $J_{NH,2}$ 9.8 Hz, NHAβ), 5.32 (t, 1 Hβ,

$J_{2,3+3,4}$ 20.6 Hz, H-3Bβ), 5.16 (t, 1 Hα, $J_{2,3+3,4}$ 19.2 Hz, H-3Aα), 5.09 (t, 1 Hβ, $J_{2,3+3,4}$ 19.7 Hz, H-3Aβ), 5.01–4.94 (m, 1 Hα, 1 Hβ, H-4Aα, H-4Aβ), 4.91 (d, 1 Hα, $J_{1,2}$ 10.3 Hz, H-1Aα), 4.87 (d, 1 Hβ, $J_{1,2}$ 10.8 Hz, H-1Aβ), 4.64–4.55 (m, 1 Hα, 1 Hβ, H-6′Bα, H-6′Bβ), 4.50 (m, 1 Hβ, H-6Bβ), 4.46–4.38 (m, 2 Hα, H-5Bα, H-6Bα), 4.29–4.13 (m, 2 Hα, 3 Hβ, H-6Aα, H-6Aβ, H-2Aα, H-2Aβ, H-5Bβ), 4.04 (dd, 1 Hα, $J_{5,6'}$ 7.4, $J_{6,6'}$ 12.3 Hz, H-6′Aα), 3.96 (dd, 1 Hβ, $J_{5,6'}$ 7.4 Hz, $J_{6,6'}$ 12.3 Hz, H-6′Aβ), 3.90–3.70 (m, 2 Hα, 2 Hβ, H-2Bα, H-2Bβ, H-5Aα, H-5Aβ), 3.13 (dd, 1 Hα, $J_{3,4+4,5}$ 21.2 Hz, H-4Bα), 3.05 (dd, 1 Hβ, $J_{3,4+4,5}$ 21.6 Hz, H-4Bβ) 2.25 (s, 3 Hα, CH_3COα), 2.20 (s, 3 Hβ, CH_3COβ), 2.25 (s, 3 Hβ, CH_3COβ), 2.09 (s, 3 Hα, CH_3COα), 2.08 (s, 3 Hβ, CH_3COβ), 2.07–2.03 (m, 9 Hα, 6 Hβ, 3 × CH_3COα, 2 × CH_3COβ), 2.01 (s, 3 Hα, CH_3COα), 2.00 (s, 3 Hβ, CH_3COβ). HRMS Calcd for $C_{31}H_{38}N_4O_{15}S$ $[M+Na]^+$: 761.1952. Found: 761.1948.

3.3. 4-*S*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-*O*-acetyl-2-azido-3-*O*-benzoyl-2-deoxy-4-thio-α,β-D-glucopyranose (5)

Hydrazine acetate (74 mg, 0.803 mmol) was added to a solution of the diacetate **4** (489 mg, 0.661 mmol) in DMF (6 mL). The reaction mixture was stirred for 1 h at rt and diluted with EtOAc (25 mL). The solution was washed successively with brine (2 × 15 mL) and water (2 × 15 mL). The washings were re-extracted with EtOAc (2 × 15 mL), and the combined organic extracts were dried and concentrated. Chromatography of the residue (1:1, then 2:3 and 3:7 toluene–EtOAc) afforded the anomeric mixture of the hemiacetal **5** (377 mg, 82%); ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 75:25; ^{1}H NMR ($CDCl_3$): δ 8.15 (m, 2 Hα, 2 Hβ, aromatics), 7.65 (m, 1 Hα, 1 Hβ, aromatic), 7.50 (m, 2 Hα, 2 Hβ, aromatics), 5.82 (dd, 1 Hα, $J_{2,3+3,4}$ 21.2 Hz, H-3Bα), 5.68 (d, 1 Hα, $J_{NH,2}$ 9.8 Hz, NHAα), 5.57 (d, 1 Hβ, $J_{NH,2}$ 9.8 Hz, NHAβ), 5.48 (d, 1 Hα, $J_{1,2}$ 2.9 Hz, H-1Bα), 5.24 (dd, 1 Hβ, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 10.8 Hz, H-3Bβ), 5.14–4.99 (m, 2 Hα, 2 Hβ, H-3Aα, H-3Aβ, H-4Aα, H-4Aβ), 4.96 (d, 1 Hα, $J_{1,2}$ 10.8 Hz, H-1Aα), 4.89 (d, 1 Hβ, $J_{1,2}$ 10.3 Hz, H-1Aβ), 4.78 (d, 1 Hβ, $J_{1,2}$ 7.9 Hz, H-1Bβ), 4.65–4.47 (m, 3 Hα, 2 Hβ, H-5Bα, H-6Bα, H-6Bβ, H-6′Bα, H-6′Bβ), 4.25–4.15 (m, 2 Hα, 2 Hβ, H-2Aα, H-2Aβ, H-6′Aα, H-6′Aβ), 4.05–3.98 (m, 1 Hα, 2 Hβ, H-5Bβ, H-6Aα, H-6Aβ), 3.80–3.71 (m, 1 Hα, 1 Hβ, H-5Aα, H-5Aβ), 3.68–3.60 (m, 1 Hα, 1 Hβ, H-2Bα, H-2Bβ), 3.05 (t, 1 Hα, *J* 10.8 Hz, H-4Bα), 3.02 (t, 1 Hβ, *J* 10.8 Hz, H-4Bβ), 2.11 (s, 3 Hα, CH_3COα), 2.10 (s, 3 Hα, 3 Hβ, CH_3COα, CH_3COβ), 2.08 (s, 3 Hβ, CH_3COβ), 2.05 (m, 6 Hα, 6 Hβ, 2 × CH_3COα, 2 × CH_3COβ), 2.00 (2 s, 3 Hα, 3Hβ, CH_3COα, CH_3COβ). HRMS Calcd for $C_{29}H_{36}N_4O_{14}S$ $[M+Na]^+$: 719.1846. Found: 719.1842.

3.4. 4-*S*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-*O*-acetyl-2-azido-3-*O*-benzoyl-2-deoxy-4-thio-α,β-D-glucopyranosyl trichloroacetimidate (6)

Trichloroacetonitrile (1 mL, 10 mmol) and DBU (20 μL, 0.134 mmol) were added to a solution of the hemiacetal **5** (350 mg, 0.502 mmol) in anhyd CH_2Cl_2 (12 mL), and the reaction mixture was stirred for 2 h under Ar at rt. Solvents were evaporated off, and the residue was purified by chromatography (7:3 toluene–EtOAc) to give the imidate **6** (360 mg, 85%) as a glass; ^{1}H NMR spectroscopy in $CDCl_3$ showed the α-anomer to be in large majority (90%); ^{1}H NMR ($CDCl_3$) for α-anomer: δ 8.84 (s, 1 H, NHB), 8.07 (m, 2 H, aromatics), 7.65 (m, 1 H, aromatic), 7.50 (m, 2 H, aromatics), 6.59 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1B), 5.81 (dd, 1 H, $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 10.8 Hz, H-3B), 5.67 (d, 1 H, $J_{NH,2}$ 9.8 Hz, NHA), 5.12–5.02 (m, 2 H, H-3A, H-4A), 4.89 (d, 1 H, $J_{1,2}$ 10.7 Hz, H-1A), 4.65 (dd, 1 H, $J_{5,6}$ 2.9 Hz, $J_{6,6'}$ 11.8 Hz, H-6B), 4.55–4.45 (m, 2 H, H-5B, H-6′B), 4.25–4.19 (m, 1 H, H-2A), 4.13–3.95 (m, 3 H, H-2B, H-6A, H-6′A), 3.65–3.57 (m, 1 H, H-5A), 3.19 (t, 1 H, *J* 10.8 Hz, H-4B), 2.08, 2.05, 2.04 and 2.00 (4 s, 15 H, 5 × CH_3CO).

3.5. Preparation of 1,6-anhydro-2-azido-3,4-di-*O*-benzoyl-2-deoxy-β-D-glucopyranose (8)

Benzoyl chloride (845 μL, 7.28 mmol) was added to a solution of 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose (400 mg, 2.14 mmol)[10] in anhyd pyridine (7 mL). The reaction mixture was stirred for 2 h at rt. Methanol (10 mL) was added to the mixture, solvents were evaporated, and the residue dissolved in CH_2Cl_2 (20 mL) was washed with 1 M HCl (2 × 15 mL), satd aq $NaHCO_3$ (2 × 15 mL) and water (2 × 15 mL). The washings were re-extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were dried and concentrated. Chromatography (7:1 then 4:1 cyclohexane–EtOAc) of the residue gave the dibenzoate **8** (738 mg, 87%) as white crystals: mp 109 °C, lit.[1] 108–109 °C; ^{1}H NMR ($CDCl_3$): δ 7.45–7.30 (m, 10 H, aromatics), 5.66 (br s, 1 H, H-3), 5.37 (m, 1 H, H-4), 5.11 (br s, 1 H, H-1), 4.87 (br d, 1 H, H-5), 4.36 (d, 1 H, $J_{6,6'}$ 8 Hz, H-6′), 3.98 (dd, 1 H, $J_{5,6}$ 5.8 Hz, H-6), 3.48 (br s, 1 H, H-2).

3.6. 1,6-Di-*O*-acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-α,β-D-glucopyranose (9)

Anhydro **8** (700 mg, 1.77 mmol) was dissolved in 4.6:1 Ac_2O–TFA (49.2 mL), and the solution was stirred for 6 h at rt. Solvents were evaporated, and residual traces of acid were co-evaporated with toluene. Chromatography (7:1, 5:1, 3:1 and 1:1 cyclohexane–EtOAc) of the dry residue gave an anomeric mixture of diacetate **9** (790

mg, 90%); ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 8:2; ^{1}H NMR ($CDCl_3$): δ 8.00–7.85 (m, 4 Hα, 4 Hβ, aromatics), 7.55–7.50 (m, 2 Hα, 2 Hβ, aromatics), 7.45–7.35 (m, 4 Hα, 4 Hβ, aromatics), 6.45 (d, 1 Hα, $J_{1,2}$ 3.6 Hz, H-1α), 5.94 (dd, 1 Hα, $J_{2,3+3,4}$ or $J_{3,4+4,5}$ 20.1 Hz, H-3α or H-4α), 5.75 (d, 1 Hβ, $J_{1,2}$ 8.4 Hz, H-1β), 5.61–5.48 (m, 1 Hα, 2 Hβ, H-3α or H-4α, H-3β, H-4β), 4.32–4.14 (m, 3 Hα, 2 Hβ, H-5α, H-6α, H-6′α, H-6β, H-6′β), 4.04 (m, 1 Hβ, H-5β), 3.90 (dd, 1 Hβ, $J_{2,3}$ 9.7 Hz, H-2β), 3.83 (dd, 1 Hα, $J_{2,3}$ 10.5 Hz, H-2α), 2.30 (s, 3 Hα, CH_3COα), 2.25 (s, 3 Hβ, CH_3COβ), 2.10 (s, 3 Hα, 3 Hβ, CH_3COα, CH_3COβ). HRMS Calcd for $C_{24}H_{23}N_3O_9$ $[M+Na]^+$: 520.1332. Found: 520.1330.

3.7. 6-*O*-Acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-α,β-D-glucopyranose (10)

Hydrazine acetate (164 mg, 1.79 mmol) was added to a solution of the diacetate **9** (740 mg, 1.49 mmol) in DMF (10 mL). The reaction mixture was stirred for 2 h at rt, and additional hydrazine acetate (42 mg, 0.456 mmol) was added. The mixture was stirred for 1 h at rt and diluted with EtOAc (40 mL), and the solution was washed successively with brine (2 × 20 mL) and water (2 × 20 mL). The washings were re-extracted with EtOAc (2 × 20 mL), and the combined organic extracts were dried and concentrated. Chromatography of the residue (1:1, then 2:3 and 3:7 toluene–EtOAc) gave an anomeric mixture of the hemiacetal **10** (560 mg, 83%); ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 7:3; ^{1}H NMR ($CDCl_3$): δ 8.00–7.85 (m, 4 Hα, 4 Hβ, aromatics), 7.55 (m, 2 Hα, 2 Hβ, aromatics), 7.38 (m, 4 Hα, 4 Hβ, aromatics), 6.02 (dd, 1 Hα, $J_{3,4}$ 10.1 Hz, $J_{4,5}$ 9.5 Hz, H-4α), 5.55–5.48 (m, 2 Hα, 2 Hβ, H-1α, H-3α, H-3β, H-4β), 4.95 (d, 1 Hβ, $J_{1,2}$ 7.7 Hz, H-1β), 4.52 (m, 1 Hα, H-5α), 4.30–4.20 (m, 2 Hα, 2-Hβ, H-6α, H-6′α, H-6β, H-6′β), 3.95 (m, 1 Hβ, H-5β), 3.72 (dd, 1 Hβ, $J_{2,3}$ 10.2 Hz, H-2β), 3.58 (dd, 1 Hα, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 10.5 Hz, H-2α), 2.09 and 2.05 (2 s, 3 Hα, 3 Hβ, CH_3COα, CH_3COβ). HRMS Calcd for $C_{22}H_{21}N_3O_8$ $[M+Na]^+$: 478.1226. Found: 478.1232.

3.8. 6-*O*-Acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-α,β-D-glucopyranosyl trichloroacetimidate (11)

Trichloroacetonitrile (2.29 mL, 22.85 mmol) and a solution of DBU in CH_2Cl_2 (0.67 M, 494 μL, 0.296 mmol) were added to a solution of the hemiacetal **10** (520 mg, 1.14 mmol) in anhyd CH_2Cl_2 (15 mL), and the reaction mixture was stirred for 1 h under Ar at rt. After concentration, the residue was purified by chromatography on silica gel packed with NEt_3-containing solvent and eluted with a gradient of cyclohexane–EtOAc (7:1, 5:1 then 3:1) to give the imidate **11** (213 mg, 31%) as a glass; ^{1}H NMR spectroscopy in $CDCl_3$ showed the α-anomer to be the major anomer (90%); ^{1}H NMR ($CDCl_3$) for α-anomer: δ 8.90 (s, 1 H, NH), 8.00–7.40 (m, 10 H, aromatics), 6.64 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 6.01 (t, 1 H, $J_{2,3+3,4}$ or $J_{3,4+4,5}$ 19.7 Hz, H-3 or H-4), 5.62 (t, 1 H, $J_{2,3+3,4}$ or $J_{3,4+4,5}$ 19.8 Hz, H-3 or H-4), 4.44 (m, 1 H, H-5), 4.25 (m, 2 H, H-6, H-6′), 3.95 (dd, 1 H, $J_{2,3}$ 10.8 Hz, H-2), 2.02 (s, 3 H, CH_3CO).

3.9. 4-*O*-(6-*O*-Acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-α,β-D-glucopyranosyl)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (12)

A suspension of the alcohol **7** (120 mg, 0.434 mmol) and the imidate **11** (186 mg, 0.310 mmol) in dry toluene (10 mL) containing 4 Å activated molecular sieves (450 mg) was stirred under Ar at rt for 30 min. The reaction mixture was cooled to −50 °C, and a solution of $BF_3\cdot Et_2O$ in CH_2Cl_2 (0.16 M, 196 μL, 0.031 mmol) was added. The reaction was monitored by TLC (2:1 cyclohexane–AcOEt) and more $BF_3\cdot Et_2O$ in CH_2Cl_2 (0.16 M, 300 μL and 196 μL, 0.077 mmol) was added portionwise over 6 h. Triethylamine (100 μL) was added, and the reaction mixture was stirred for 14 h at rt. The molecular sieves were decanted and washed with CH_2Cl_2. The supernatant and washings were combined, diluted with CH_2Cl_2 (40 mL) and washed with water (2 × 30 mL). The organic layer was dried and concentrated, and the residue was purified by chromatography (7:1, 5:1 then 4:1 toluene–EtOAc) to give an anomeric mixture of disaccharide **12** (60 mg, 27%) as a glass; ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 4:6; ^{1}H NMR ($CDCl_3$): δ 7.99–7.87 (m, 4 Hα, 4 Hβ, aromatics), 7.56–7.48 (m, 2 Hα, 2 Hβ, aromatics), 7.44–7.32 (m, 9 Hα, 9 Hβ, aromatics), 6.09 (dd, 1 Hα, $J_{2,3}$ 10.8 Hz, $J_{3,4}$ 9.2 Hz, H-3Aα), 5.65 (br s, 1 Hα, H-1Bα), 5.55 (br s, 1 Hβ, H-1Bβ), 5.53–5.42 (m, 1 Hα, 2 Hβ, H-3Aβ, H-4Aα, H-4Aβ), 5.14 (d, 1 Hα, $J_{1,2}$ 3.7 Hz, H-1Aα), 4.99 (m, 1 Hα, H-5Bα), 4.80–4.72 (m, 1 Hα, 2 Hβ, C*H*Phα, C*H*Phβ, H-5Bβ), 4.70–4.58 (m, 2 Hα, 2 Hβ, C*H*Phα, C*H*Phβ, H-1Aβ, H-5Aα), 4.30 (dd, 1 Hα, $J_{5,6}$ 2.6 Hz, $J_{6,6'}$ 12.3 Hz, H-6Aα), 4.25–4.12 (m, 2 Hα, 3 Hβ, H-6Aβ, H-6′Aα, H-6′Aβ, H-6Bα, H-6Bβ), 4.03 (br s, 1 Hβ, H-4Bβ), 3.93 (br s, 1 Hα, H-4Bα), 3.88–3.73 (m, 1 Hα, 4 Hβ, H-3Bβ, H-2Aβ, H-5Aβ, H-6′Bα, H-6′Bβ), 3.68 (br s, 1 Hα, H-3Bα), 3.44 (dd, 1 Hα, H-2Aα), 3.28 (br s, 1 Hβ, H-2Bβ), 3.18 (br s, 1 Hα, H-2Bα), 2.07 (s, 3 Hα, CH_3COα), 1.97 (s, 3 Hβ, CH_3COβ). HRMS Calcd for $C_{35}H_{34}N_6O_{11}$ $[M+Na]^+$: 737.2183. Found: 737.2186.

3.10. 6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranosyl trichloroacetimidate (13)

Reaction of 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranose (545 mg, 1.28 mmol)[11] with trichloroacetonitrile (2.56 mL, 25.5 mmol) and

DBU (solution in CH_2Cl_2, 0.67 M, 442 μL, 0.333 mmol), as well as work-up of the reaction and purification by chromatography, were carried out using the same conditions than those described above for the preparation of imidate **11**. The imidate **13** (670 mg, 83%) was obtained pure as a glass, and ^{1}H NMR spectroscopy in $CDCl_3$ showed the α-anomer to be formed in large majority (>95%); ^{1}H NMR ($CDCl_3$) for α-anomer: δ 8.76 (s, 1 H, N*H*CCl$_3$), 7.44–7.28 (m, 10 H, aromatics), 6.42 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.96 (s, 2 H, CH_2Ph), 4.89 (m, 1 H, C*H*Ph), 4.61 (m, 1 H, C*H*Ph), 4.33–4.24 (m, 2 H, H-6, H-6′), 4.05 (m, 2 H, H-3 or H-4, H-5), 3.70 (m, 2 H, H-2, H-3 or H-4), 2.05 (s, 3 H, CH_3CO).

3.11. 4-*O*-(6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranosyl)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (14)

A suspension of alcohol **7** (240 mg, 0.864 mmol) and imidate **13** (380 mg, 0.665 mmol) in dry toluene (15 mL) containing 4 Å activated molecular sieves (650 mg) was treated as described for synthesis of the compound **12** using 0.1 equiv of $BF_3{\cdot}Et_2O$ (solution in CH_2Cl_2, 0.16 M, 421 μL). The residue was purified by column chromatography (7:1, 5:1 then 4:1 toluene–AcOEt) to afford the disaccharide **14** (350 mg, 77%) as a glass; ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 3:7; ^{1}H NMR ($CDCl_3$): δ 7.40–7.25 (m, 15 Hα, 15 Hβ, aromatics), 5.56 (br s, 1 Hα, H-1Bα), 5.50 (br s, 1 Hβ, H-1Bβ), 4.93 (d, 1 Hα, 1 Hβ, *J* 10.7 Hz, C*H*Phα, C*H*Phβ), 4.89–4.84 (m, 3 Hα, 1 Hβ, 2 × C*H*Phα, C*H*Phβ, H-1Aα), 4.82 (d, 1 Hβ, *J* 10.7 Hz, C*H*Phβ), 4.77 (m, 1 Hα, H-5Bα), 4.74–4.69 (m, 1 Hα, 2 Hβ, C*H*Phα, C*H*Phβ, H-5Bβ), 4.62 (d, 1 Hα, 1 Hβ, *J* 10.7 Hz, C*H*Phα, C*H*Phβ), 4.59 (d, 1Hα, 1 Hβ, *J* 10.7 Hz, C*H*Phα, C*H*Phβ), 4.36 (d, 1 Hβ, $J_{1,2}$ 8 Hz, H-1Aβ), 4.35–4.28 (m, 1 Hα, 1 Hβ, H-6Aα, H-6Aβ), 4.21–4.06 (m, 4 Hα, 2 Hβ, H-3Aα, H-5Aα, H-6′Aα, H-6′Aβ, H-6Bα, H-6Bβ), 3.97 (br s, 1 Hβ, H-4Bβ), 3.83–3.77 (m, 2 Hα, 1 Hβ, H-6′Bα, H-6′Bβ, H-3Bα), 3.75 (br s, 1 Hβ, H-3Bβ), 3.58–3.49 (m, 2 Hα, 2 Hβ, H-2Aβ, H-4Aα, H-4Aβ, H-4Bα), 3.41 (t, 1 Hβ, *J* 9.1 Hz, H-3Aβ), 3.38–3.31 (m, 1 Hα, 1 Hβ, H-2Aα, H-5Aβ), 3.25 (br s, 1 Hβ, H-2Bβ), 3.18 (br s, 1 Hα, H-2Bα), 2.02 (s, 3 Hα, $CH_3COα$), 1.97 (s, 3 Hβ, $CH_3COβ$). HRMS Calcd for $C_{35}H_{38}N_6O_9$ $[M+Na]^+$: 709.2598. Found: 709.2599.

3.12. 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-trifluoromethanesulfonyl-β-D-glucopyranoside (15)

A solution of anhyd pyridine (3 mL) in freshly distilled CH_2Cl_2 (10 mL), cooled at −15 °C, was added dropwise to a solution of triflic anhydride (2.3 mL, 13.9 mmol) in CH_2Cl_2 (15 mL) cooled at −15 °C. This mixture was added to a solution of 1,6-anhydro **7** (2.56 g, 9.24 mmol) in CH_2Cl_2 (15 mL) cooled at −15 °C, and the reaction mixture was stirred at −15 °C for 1 h. The solution was warmed to 20 °C, diluted with CH_2Cl_2 (100 mL) and washed successively with 5% HCl, satd aq $NaHCO_3$ and water. The aq layers were re-extracted with CH_2Cl_2 (50 mL), and the combined organic layers were dried and concentrated to give the triflate **15** (3.78 g, quant.); $[\alpha]_D^{22}$ +25° (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45–7.30 (m, 5 H, aromatics), 5.57 (br s, 1 H, H-1), 4.81 (br s, 1 H, H-4), 4.76 (d, 1 H, $J_{5,6'}$ 5.9 Hz, H-5), 4.69 (br s, 2 H, CH_2Ph), 4.19 (d, 1 H, $J_{6,6'}$ 8.2 Hz, H-6), 3.85 (dd, 1H, H-6′), 3.77 (br s, 1 H, H-3), 3.37 (br s, 1 H, H-2). Anal. Calcd for $C_{14}H_{14}F_3N_3O_6S$: C, 41.08; H, 3.45; N, 10.27. Found: C, 41.25; H, 3.48; N, 10.21.

3.13. 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-galactopyranoside (16)

Triflate **15** (3.78 g, 9.24 mmol) was dissolved in anhyd DMF (30 mL) containing $NaNO_2$ (6.38 g, 92.4 mmol). The reaction mixture was stirred at 20 °C for 20 h, the DMF was removed under reduced pressure, and the residual solvent was co-evaporated with toluene. The residue was diluted with CH_2Cl_2 (100 mL) and washed successively with brine and water. The aqueous layers were re-extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried and concentrated. Chromatography (98:2 $CHCl_3$–EtOAc) of the residue gave the alcohol **16** (1.75 g, 68%) as a glass; $[\alpha]_D^{22}$ +28° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45–7.30 (m, 5 H, aromatics), 5.45 (br s, 1 H, H-1), 4.75 (d, 1 H, *J* 11.3 Hz, C*H*Ph), 4.53 (d, 1 H, *J* 11.3 Hz, C*H*Ph), 4.45 (m, 1 H, H-5), 4.25 (d, 1 H, $J_{6,6'}$ 7.5 Hz, H-6), 4.04 (m, 1 H, H-4), 3.85 (d, 1 H, $J_{3,4}$ 5.4 Hz, H-3), 3.68 (dd, 1 H, $J_{5,6'}$ 6 Hz, H-6′), 3.53 (br s, 1 H, H-2), 3.05 (d, 1 H, $J_{4,OH}$ 9.6 Hz, OH). Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.25; H, 5.39; N, 14.99.

3.14. 1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-trifluoromethanesulfonyl-β-D-galactopyranoside (17)

A solution of anhyd pyridine (1.6 mL) in freshly distilled CH_2Cl_2 (5 mL) was added dropwise at −15 °C to a solution of triflic anhydride (1.55 mL, 9.41 mmol) in freshly distilled CH_2Cl_2 (10 mL). This mixture was added to a solution of 1,6-anhydro **16** (1.7 g, 6.14 mmol) in CH_2Cl_2 (10 mL) kept at −15 °C. After being stirred for 1 h at −15 °C and warmed to 20 °C, the mixture was diluted with CH_2Cl_2 (100 mL) and washed successively with 5% HCl, satd aq $NaHCO_3$ and water. The aqueous layers were re-extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried and concentrated. Chromatography (98:2 $CHCl_3$–EtOAc) of the residue gave the triflate **17** (2.35 g, 94%) as a glass; $[\alpha]_D^{22}$ +32° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45–7.30 (m,

5 H, aromatics), 5.48 (br s, 1 H, H-1), 5.09 (t, 1 H, J 4.4 Hz, H-4), 4.71 (d, 1 H, J 11.8 Hz, C*H*Ph), 4.65–4.60 (m, 2 H, H-5, C*H*Ph), 4.58 (d, 1 H, $J_{6,6'}$ 7.9 Hz, H-6), 4.00 (m, 1 H, H-3), 3.79 (dd, 1 H, $J_{5,6'}$ 5 Hz, H-6′), 3.66 (br s, 1 H, H-2). HRMS Calcd for $C_{14}H_{14}F_3N_3O_6S$ $[M+Na]^+$: 432.0453. Found: 432.0448.

3.15. 2-*S*-(3,4,6-Tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-pseudothiourea hydrochloride (20)

A mixture of the known carbamate[13] (10.7 g, 34.15 mmol) **18** and acetyl chloride (40 mL) was stirred at 20 °C for 20 h. The mixture was diluted with CH_2Cl_2 (150 mL) and washed successively with a cooled satd aq solution of $NaHCO_3$ and brine. The aqueous layers were re-extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were dried and concentrated to give the known chloride **19**.[14] The syrup (12.8 g, 27.9 mmol) was dissolved in anhydrous acetone (130 mL), and thiourea was added (4 g, 52.5 mmol). The mixture was refluxed for 7 h, cooled to 20 °C, and the pseudothiourea **20** was filtered off as a white solid and washed with acetone (8.5 g, 47%); $[\alpha]_D^{22}$ −5° (*c* 1, MeOH); ^{1}H NMR (MeOD): δ 7.38–7.28 (m, 5 H, aromatics), 5.56 (d, 1 H, $J_{1,2}$ 10.7 Hz, H-1), 5.31 (t, 1 H, $J_{2,3+3,4}$ 19.1 Hz, H-3), 5.16 (d, 1 H, J 12.4 Hz, C*H*Ph), 5.13–5.01 (m, 2H, C*H*Ph, H-4), 4.29 (dd, 1 H, $J_{6,6'}$ 12.4 Hz, $J_{5,6'}$ 4.9 Hz, H-6′), 4.21 (dd, 1H, $J_{5,6}$ 2.2 Hz, H-6), 4.08 (m, 1H, H-5), 3.88 (dd, 1H, $J_{1,2+2,3}$ 20.2 Hz, H-2), 2.08 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO) and 1.90 (s, 3H, CH_3CO). Anal. Calcd for $C_{21}H_{28}ClN_3O_9S$: C, 47.24; H, 5.29; N, 7.87. Found: C, 46.80; H, 5.36; N, 7.74.

3.16. 3,4,6-Tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-1-thio-β-D-glucopyranose (21)

Sodium sulfite (3.98 g, 31.6 mmol) was added to a solution of the pseudothiourea **20** (8.25 g, 15.8 mmol) in a mixture of acetone and water (35 mL/210 mL). The mixture was stirred at 20 °C for 22 h. The pH was adjusted to 5 by adding 5% HCl, and the solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and water (100 mL). The aqueous layers were re-extracted with CH_2Cl_2 (2 × 100 mL) and the organic layers were combined, dried and concentrated. The crude product was recrystallized from EtOH to afford the pure thiol **21** (5.67 g, 81%) as a white powder: mp 128 °C; $[\alpha]_D^{22}$ +7° (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.53 (d, 1 H, $J_{NH,2}$ 9.7 Hz, NH), 7.40–7.27 (m, 5 H, aromatics), 5.11–4.98 (m, 3 H, CH_2Ph, H-4), 4.85 (t, 1 H, J 9.6 Hz, H-3), 4.75 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.14 (dd, 1 H, $J_{6,6'}$ 12.2 Hz, $J_{5,6'}$ 4.8 Hz, H-6′), 3.99 (m, 1 H, H-6), 3.81 (m, 1 H, H-5), 3.54 (ddd, 1 H, H-2), 2.01, 1.95 and 1.84 (3 s, 3 × CH_3CO). Anal. Calcd for $C_{20}H_{25}NO_9S$: C, 52.74; H, 5.53; N, 3.08. Found: C, 52.39; H, 5.46; N, 3.17.

3.17. 4-*S*-(3,4,6-Tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-thio-β-D-glucopyranoside (22)

NaH (55% in oil, 459 mg, 10.5 mmol) was added to a solution of thiol **21** (4.6 g, 10.1 mmol) DMF (90 mL) stirred at 0 °C. The mixture was stirred for 10 min at 0 °C, 10 min at 20 °C and was, in turn, added to the triflate **17** (3.45 g, 8.42 mmol). The reaction mixture was stirred for 1 h at 20 °C, and the reaction was quenched by addition of HOAc (8 mL), followed by stirring for a further 30 min at rt. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (7:1 to 1:1 toluene–EtOAc) to furnish the thiodisaccharide **22** (5.32 g, 88%); $[\alpha]_D^{22}$ −13° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.29 (m, 10 H, aromatics), 5.44 (s, 1 H, H-1B), 5.27 (t, 1 H, J 9.7 Hz, H-3A), 5.13 (d, 1 H, J 12.2 Hz, C*H*Ph), 5.18–4.96 (m, 3 H, C*H*Ph, NHA, H-4A), 4.89 (d, 1 H, $J_{1,2}$ 11.1 Hz, H-1A), 4.74–4.58 (m, 3 H, CH_2Ph, H-5B), 4.22 (d, 1 H, $J_{6,6'}$ 7.3 Hz, H-6B), 4.18 (dd, 1 H, $J_{6,6'}$ 12.3 Hz, $J_{5,6'}$ 4.5 Hz, H-6′A), 4.11 (dd, 1 H, $J_{5,6}$ 2.1 Hz, H-6A), 3.84 (s, 1 H, H-3B), 3.76 (dd, 1 H, $J_{5,6'}$ 5.5 Hz, H-6′B), 3.74–3.60 (m, 2 H, H-2A, H-5A), 3.52 (s, 1 H, H-2B), 3.19 (s, 1 H, H-4B), 2.01, 2.02 and 1.95 (3 s, 9 H, 3 × CH_3CO). Anal. Calcd for $C_{33}H_{38}N_4O_{12}S$: C, 55.46; H, 5.36; N, 7.84. Found: C, 55.70; H, 5.34; N, 7.45.

3.18. 1,6-Di-*O*-acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-α,β-D-glucopyranose (23)

The thiodisaccharide **22** (5.31 g, 0.074 mmol) was dissolved in Ac_2O–TFA (9:1, 80 mL), and the solution was stirred for 4 h at rt. Solvents were evaporated under reduced pressure, and residual traces of acid were eliminated by repeated evaporation with toluene. Chromatography (9:1, 8:1, 7:1, 6:1 then 5:1 toluene–acetone) of the dry residue gave compound **23** (5.84 g, 96%) as an anomeric mixture; ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 75:25; ^{1}H NMR ($CDCl_3$): δ 7.45–7.20 (m, 10 Hα, 10 Hβ, aromatics), 6.27 (d, 1 Hα, $J_{1,2}$ 3.2 Hz, H-1Bα), 5.45 (d, 1 Hβ, $J_{1,2}$ 7.3 Hz, H-1Bβ), 5.33 (m, 1 Hα, 1 Hβ, H-3Aα, H-3Aβ), 5.02–4.84 (m, 6 Hα, 6 Hβ, 2 × CH_2Phα, 2 × CH_2Phβ, H-4Aα, H-4Aβ, H-1Aα, H-1Aβ), 4.47 (dd, 1 Hα, 1 Hβ, $J_{6,6'}$ 12.4 Hz, $J_{5,6'}$ 4.2 Hz, H-6′Bα, H-6′Bβ), 4.38 (d, 1 Hα, 1 Hβ, H-6Aα, H-6Aβ), 4.15 (dd, 1 Hα, 1 Hβ, $J_{6,6'}$ 12.3 Hz, $J_{5,6'}$ 4.6 Hz, H-6′Aα, H-6′Aβ), 4.01 (m, 2 Hα, 1 Hβ, H-6Aα, H-6Aβ, H-5Bα), 3.80–3.72 (m, 1 Hα, 1 Hβ, H-3Bα, H-5Bβ), 3.65–3.55 (m, 3 Hα, 3 Hβ, H-2Bα, H-2Bβ, H-2Aα, H-2Aβ, H-5Aα,

H-5Aβ), 3.40 (m, 1 Hβ, H-3Bβ), 2.99 (t, 1 Hα, $J_{3,4+4,5}$ 20.8 Hz, H-4Bα), 2.96 (m, 1 Hβ, H-4Bβ), 2.19, 2.07, 2.03, 2.01 and 1.91 (5 s, 15 H, 5 × CH_3CO). HRMS Calcd for $C_{37}H_{44}N_4O_{15}S$ $[M+Na]^+$: 839.2422. Found: 839.2424.

3.19. 6-*O*-Acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-α,β-D-glucopyranose (24)

Hydrazine acetate (920 mg, 9.99 mmol) was added to a solution of the diacetate **23** (5.84 g, 7.15 mmol) in DMF (70 mL). The reaction mixture was stirred for 5 h at rt, the solvent was evaporated under reduced pressure and residual traces of DMF were eliminated by repeated evaporation with toluene. The residue was diluted with EtOAc (150 mL), and the solution was washed successively with brine (2 × 100 mL) and water (2 × 100 mL). The washings were re-extracted with EtOAc (100 mL), and the combined organic extracts were dried and concentrated. Chromatography of the residue (3:1, 2:1, 1:1 toluene–EtOAc) gave the anomeric mixture of hemiacetal **24** (4.5 g, 81%); ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 6:4; ^{1}H NMR ($CDCl_3$): δ 7.43 (m, 2 Hα, 2 Hβ, aromatics), 7.35–7.28 (m, 6 Hα, 6 Hβ, aromatics), 7.24 (m, 2 Hα, 2 Hβ, aromatics), 5.37 (br s, 1 Hα, H-1Bα) 5.32–5.25 (m, 1 Hα, 1 Hβ, H-3Aα, H-3Aβ), 5.08–4.83 (m, 7 Hα, 7 Hβ, 2 × CH_2Phα, 2 × CH_2Phβ, H-1Aα, H-1Aβ, H-4Aα, H-4Aβ, NHα, NHβ), 4.60 (m, 2 Hβ, H-1Bβ, H-6Bβ), 4.53–4.40 (m, 2 Hα, H-6Bα, H-6′Bα), 4.32 (dd, 1 Hβ, $J_{6,6'}$ 11.8 Hz, $J_{5,6'}$ 5.4 Hz, H-6′Bβ), 4.27 (ddd, 1 Hα, $J_{4,5}$ 11.2 Hz, $J_{5,6'}$ 4.1 Hz, $J_{5,6}$ 3.1 Hz, H-5Bα), 4.18–4.03 (m, 2 Hα, 2 Hβ, H-6Aα, H-6Aβ, H-6′Aα, H-6′Aβ), 3.90 (t, 1 Hα, $J_{2,3+3,4}$ 19.8 Hz, H-3Bα), 3.70–3.58 (m, 2 Hα, 3 Hβ, H-5Bβ, H-2Aα, H-2Aβ, H-5Aα, H-5Aβ), 3.49 (dd, 1 Hα, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 9.6 Hz, H-2Bα), 3.41 (dd, 1 Hβ, $J_{1,2}$ 8 Hz, $J_{2,3}$ 9.3 Hz, H-2Bβ), 3.31 (dd, 1 Hβ, $J_{3,4}$ 10,5 Hz, H-3Bβ), 2.95 (t, 1 Hα, $J_{4,5}$ 10,5 Hz, H-4Bα), 2.90 (t, 1 Hβ, *J* 10,5 Hz, H-4Bβ), 2.09–2.08 (2 s, 3 Hα, 3 Hβ, $CH_3COα$, $CH_3COβ$), 2.06 (s, 3 Hα, 3 Hβ, $CH_3COα$, $CH_3COβ$), 2.01 (s, 3 Hα, 3 Hβ, $CH_3COα$, $CH_3COβ$), 1.91 (s, 3 Hα, 3 Hβ, $CH_3COα$, $CH_3COβ$). HRMS Calcd for $C_{35}H_{42}N_4O_{14}S$ $[M+Na]^+$: 797.2316. Found: 797.2312.

3.20. 6-*O*-Acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-α-D-glucopyranosyl trichloroacetimidate (25)

Reaction of hemiacetal **24** (4 g, 5.16 mmol) with trichloroacetonitrile (10.3 mL, 103 mmol) and DBU (200 μL, 1.34 mmol), as well as work-up of the reaction, were carried out using the same conditions than those described above for the preparation of imidate **11**. Chromatography on a column of alumina (2:1, 1:1, 1:2 and 1:3 cyclohexane–EtOAc) gave the imidate **25** (3.91 g, 82%) as a glass; ^{1}H NMR in $CDCl_3$ showed a ratio α:β of 80:20; ^{1}H NMR ($CDCl_3$): δ 8.76 (s, 1 Hα, NHBα), 8.73 (s, 1 Hβ, NHBβ), 7.48–7.26 (m, 10 Hα, 10 Hβ, aromatics), 6.47 (d, 1 Hα, $J_{1,2}$ 3.3 Hz, H-1Bα), 5.61 (d, 1 Hβ, $J_{1,2}$ 8.6 Hz, H-1Bβ), 5.33 (m, 1 Hα, 1 Hβ, H-3Aα, H-3Aβ), 5.08–4.08 (m, 7 Hα, 7Hβ, 2 × CH_2Phα, 2 × CH_2Phβ, H-1Aα, H-1Aβ, NHAα, NHAβ, H-4Aα, H-4Aβ), 4.54–4.43 (m, 2 Hα, 2 Hβ, H-6Bα, H-6Bβ, H-6′Bα, H-6′Bβ), 4.22–4.07 (m, 2 Hα, 2 Hβ, H-5Bα, H-5Bβ, H-6′Aα, H-6′Aβ), 4.01 (dd, 1 Hα, $J_{5,6}$ 2.1 Hz, $J_{6,6'}$ 12.3 Hz, H-6Aα), 3.86 (t, 1 Hα, 1 Hβ, $J_{2,3+3,4}$ 19.6 Hz, H-3Bα, H-3Bβ), 3.77–3.70 (m, 1 Hα, 1 Hβ, H-2Bα, H-2Bβ), 3.66–3.52 (m, 2 Hα, 2 Hβ, H-2Aα, H-2Aβ, H-5Aα, H-5Aβ), 3.07 (t, 1 Hα, *J* 10.7 Hz, H-4Bα), 3.00 (t, 1 Hβ, *J* 10.7 Hz, H-4Bβ), 2.12–1.99 (m, 9 Hα, 9 Hβ, 3 × $CH_3COα$, 3 × $CH_3COβ$), 1.94–1.89 (m, 3 Hα, 3 Hβ, $CH_3COα$, $CH_3COβ$).

3.21. 4-*O*-[6-*O*-Acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-β-D-glucopyranosyl]-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (26β) and 4-*O*-[6-*O*-acetyl-4-*S*-(3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-2-azido-3-*O*-benzyl-2-deoxy-4-thio-α-D-glucopyranosyl]-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (26α)

A suspension of the alcohol **7** (1.50 g, 5.41 mmol) and imidate **25** (2.48 g, 2.70 mmol) in dry CH_2Cl_2 (100 mL) containing 3 Å activated molecular sieves (800 mg) was stirred under Ar at rt for 1 h. The reaction mixture was cooled to −78 °C, and $BF_3{\cdot}Et_2O$ (68 μL, 0.540 mmol) was added. The reaction mixture was allowed to warm up to −20 °C over 1 h and was subsequently stirred for 2.5 h at −20 °C. Et_3N (100μL) was added, and the molecular sieves were decanted and washed with CH_2Cl_2. The supernatant and washings were combined, diluted with CH_2Cl_2 (75 mL) and washed with water (2 × 100 mL). The washings were re-extracted with CH_2Cl_2 (2 × 75 mL), and the combined organic layers were dried and concentrated. Chromatography (5:1, 4:1, 3:1 and 2:1, cyclohexane–AcOEt) of the residue gave the trisaccharide **26** (1.59 g, 57%) as an anomeric mixture. The anomers were separated by HPLC (Waters PrepNova Pack® silica 125 Å, 40 × 100 mm, sample concentration 40 mg/mL, volume injected 8 mL, flow rate: 15 mL/min of 65:35 hexane–EtOAc) to give **26α** (276 mg) and **26β** (1.30 g).

3.21.1. Analytical data for 26β. $[\alpha]_D^{23}$ −12° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.48–7.24 (m, 15 H, aromatics), 5.52 (s, 1 H, H-1C), 5.32 (m, 1 H, H-3A), 5.06–4.82 (m,

6 H, 2 × CH_2Ph, H-1A, H-4A), 4.77 (d, 1 H, $J_{NH,2}$ 8 Hz, NHA), 4.75–4.59 (m, 4 H, CH_2Ph, H-5C, H-6B), 4.41 (d, 1 H, $J_{1,2}$ 8 Hz, H-1B), 4.27 (dd, 1 H, $J_{5,6'}$ 5 Hz, $J_{6,6'}$ 12 Hz, H-6′B), 4.20–4.12 (m, 2 H, H-6C, H-6′A), 4.07 (d, $J_{6,6'}$ 12 Hz, H-6A), 3.96 (s, 1 H, H-4C), 3.81 (t, 1 H, J 6.7 Hz, H-6′C), 3.76 (s, 1 H, H-3C), 3.63 (m, 1 H, H-5A), 3.57 (t, 1 H, J 8.7 Hz, H-2B), 3.54–3.41 (m, 2 H, H-2A, H-5B), 3.27–3.20 (m, 2 H, H-2C, H-3B), 2.90 (t, 1 H, J 10.9 Hz, H-4B), 2.04, 2.02, 2.01 and 1.91 (4 s, 12 H, 4 × CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.44, 170.39, 170.23, 169.40 (4 × *CO*CH_3, N*CO*CH_2Ph), 137.61 (C*ipso* aromatic), 101.68 (C-1B), 100.68 (C-1C), 82.23 (C-1A), 79.37 (C-3B), 77.22 (C-3C, C-4C), 75.84 (C-5A), 75.11 (2 × *C*H_2Ph), 74.71 (C-5B), 74.53 (C-5C), 72.51 (*C*H_2Ph, C-3A), 68.48 (C-4A), 67.00 (C-2B), 65.00 (C-6C), 64.12 (C-6B), 62.12 (C-6A), 59.23 (C-2C), 55.99 (C-2A), 45.76 (C-4B). Anal. Calcd for $C_{48}H_{55}N_7O_{17}S$: C, 55.75; H, 5.36; N, 9.48. Found: C, 55.93; H, 5.41; N, 9.19.

3.21.2. Analytical data for 26α. $[\alpha]_D^{23}$ +14° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42–7.25 (m, 15 H, aromatics), 5.56 (s, 1 H, H-1C), 5.20 (m, 1 H, H-3A), 5.07 (t, 1 H, J 9.6 Hz, H-4A), 5.02–4.92 (m, 3 H, 2 × C*H*Ph, H-1A), 4.90 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1B), 4.85–4.74 (m, 3 H, C*H*Ph, H-5C, NHA), 4.72 (d, 1 H, J 11.9 Hz, C*H*Ph), 4.63 (m, 2 H, H-6′B, C*H*Ph), 4.57 (d, 1 H, J 10.4 Hz, C*H*Ph), 4.43–4.33 (m, 2 H, H-5B, H-6B), 4.22–4.14 (m, 2 H, H-6A, H-6′C), 4.11 (m, 1 H, H-6C), 4.01 (t, 1 H, J 10 Hz, H-3B), 3.87 (s, 1 H, H-4C), 3.83–3.64 (m, 3 H, H-5A, H-2A, H-6′A), 3.53 (s, 1 H, H-3C), 3. 31 (dd, 1 H, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 9.7 Hz, H-2B), 3.14 (s, 1 H, H-2C), 2.88 (t, 1 H, J 10.9 Hz, H-4B), 2.06, 2.04, 2.02 and 1.87 (4 s, 12 H, 4 × CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.65, 170.42, 169.39 (4 × *CO*CH_3, N*CO*CH_2Ph), 137.50, 136.80, 135.96 (C*ipso* aromatic), 101.04 (C-1B), 100.75 (C-1C), 81.92 (C-1A), 78.69 (C-3C), 77.45 (C-4C), 75.92 (C-3B), 75.63 (*C*H_2Ph), 74.86 (C-5A, C-5C) 73.19 (C-3A), 72.93 (*C*H_2Ph), 70.30 (C-5B), 68.18 (C-4A), 67.00 (*C*H_2Ph), 64.82 (C-2B), 64.73 (C-6A), 63.89 (C-6B), 61.84 (C-6C), 58.37 (C-2C), 55.43 (C-2A), 47.26 (C-4B). Anal. Calcd for $C_{48}H_{55}N_7O_{17}S$: C, 55.75; H, 5.36; N, 9.48. Found: C, 55.86; H, 5.56; N, 9.18.

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