Stereoselective Synthesis of the Core Structure of the Nephritogenoside Glycopeptide

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A new strategy for the construction of the *O*-glycoside bond in the nephritogenoside unit using the phenylsulfenyl method is reported. The readily accessible phenylsulfinyl glycoside proved to be an excellent glycosyl donor, leading to high yields and good selectivity. The extremely mild conditions utilized in glycosylation reactions allow trityl and other sensitive protecting groups to be used for temporary protection. The fact that phenyl thioglycosides function as glycosyl acceptors during the coupling reaction and can easily be transformed into glycosyl donors by conversion to phenylsulfinyl glycosides, enables complex oligosaccharides to be prepared in a highly convenient manner.

The discovery of numerous physiologically active glycosides, such as aminocyclitol antibiotics, glycolipids, glycoproteins and immunoactive oligo- and polysaccharides of bacterial cell-walls, has greatly increased the interest in glycoside synthesis.

Many methods have been developed for the preparation of glycosides[1]. One of the classical approaches, the Koenigs-Knorr glycosylation[2], is based on the use of glycosyl halides as glycosyl donors. Trichloroacetimidates[3], pent-4-enyl glycosides[4], isopropenyl glycosides[5], phosphorus derivatives[6], silicon reagents[7], fluoride donors[8], as well as glycal derivatives[9] are also currently used as glycosyl donors in practical, selective syntheses of complex oligosaccharides and glycoconjugates. Thioglycosides[10], which are stable under a wide range of reaction conditions, have been used as glycosyl donors in recent synthetic work; various methods have been developed for activation of 1-thioglycosides by thiophilic promoting agents. In spite of the developments in this area, the application of phenylsulfinyl glycosyl donors[11] has gained new impetus since it was found that rather inactive nucleophiles can be effectively glycosylated in the presence of triflic anhydride. More recently, it was shown that the glycosylation of a phenyl thioglycoside with a phenylsulfinyl glycoside occurs selectively and offers some remarkable advantages for oligosaccharide synthesis[12][13].

Nephritogenoside, isolated from the glomerular basement membrane of rats, is a glycopeptide[14] that shows activity in the induction of glomerulonephritis in homologous animals. This glycopeptide is composed of three D-glucose units and 21 amino acids, and the reducing α-D-glucose unit is linked *N*-glycosylically to an *N*-terminal asparagine unit, i.e. α-Glc-(1→6)-β-Glc(1→6)-α-Glc(1→Asn−peptide)[15]. The synthesis of this model glycopeptide is important because of its unusual structure and its significant biological properties. Several syntheses[16] of nephritogenoside have been described. Here, an efficient and stereocontrolled synthesis of the nephritogenoside core structure using phenylsulfinyl glycosides as glycosyl donors is presented.

Our method is profiled in Scheme 1. It employs the phenyl thioglycoside as a glycosyl acceptor and the phenyl thioglycosyl sulfoxide as a glycosyl donor. The starting material, phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside sulfoxide (**2**), is readily obtained by oxidation of the corresponding sulfide **1** with *m*-chloroperbenzoic acid (*m*CPBA) (96% yield). Phenyl 2,3,4-tri-*O*-pivaloyl-1-thio-β-D-glucopyranoside (**4**) was prepared as follows: Phenyl 1-thio-β-D-glucopyranoside[17] was treated first with trityl chloride and then with pivaloyl chloride in pyridine, to give phenyl 2,3,4-tri-*O*-pivaloyl-6-*O*-triphenylmethyl-1-thio-β-D-glucopyranoside (**3**). This was then detritylated and converted to **4**. Glycosidation of **2** and **4** was carried out in dichloromethane/diethyl ether (1:4) using triflic anhydride (Tf_2O) and 2,6-di-*tert*-butylpyridine (D*t*BP) under nitrogen at −78°C. After gradually warming to 0°C, the reaction mixture was poured into aqueous hydrogen carbonate solution and worked-up to yield the α- and β-linked disaccharides **6α** and **6β** in 68% and 17% yield, respectively, as a result of S_N2 displacement at the anomeric center, which governs the stereochemical outcome of the reaction with the β-glycosyl donor in the absence of neighbouring group participation.

It should be noted that the above glycosidation reaction gives high yields and this suggests that the anomeric phenyl thioglycosides are stable under the conditions used for the activation. Further proof of the selective activation of phenyl thioglycoside sulfoxides over phenyl thioglycosides is provided by the following reaction (Scheme 2): Phenyl 2,3,4-tri-*O*-pivaloyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (**3**) and phenyl 2,3,4-tri-*O*-pivaloyl-6-*O*-trityl-1-thio-β-D-glucopyranoside sulfoxide (**5**) were treated separately with the acceptor 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranoside

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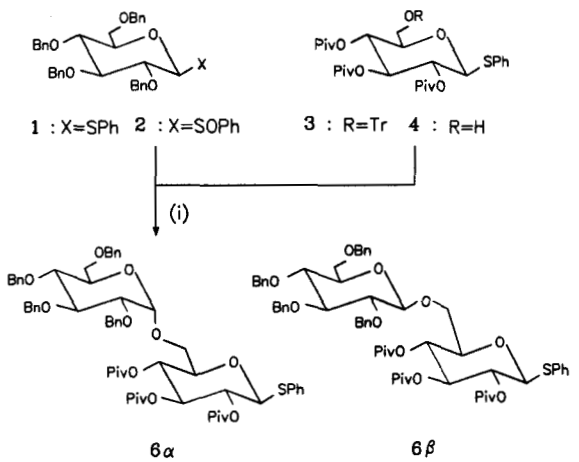
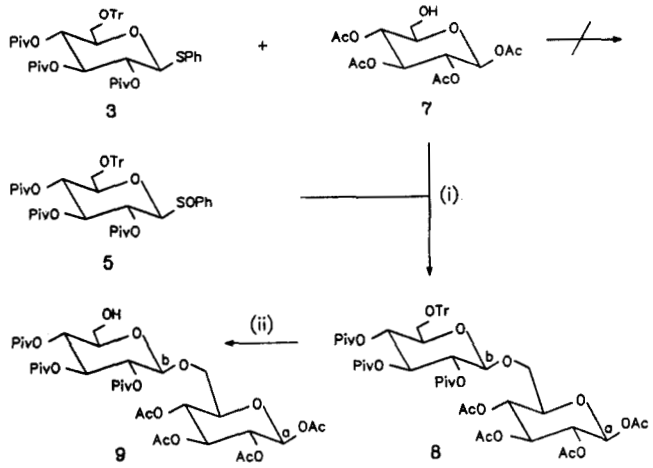
Scheme 1



Reagents: (i) D*t*BP, Tf_2O, DCM/Et_2O (1:4); −78 °C to 0 °C.

(**7**)[18] in the presence of two equivalents of D*t*BP and one equivalent of triflic anhydride. As expected, **5** and **7** yielded stereoselectively 81% of the protected disaccharide **8**, while no coupling was observed between **3** and **7**. It is worthwhile mentioning that the trityl group was not removed under these glycosidation conditions. Therefore, other similar acid-labile protecting groups can also be used for these glycosidation reactions. It should be noted that in the presence of one equivalent of D*t*BP, removal of the trityl group was observed and a complex mixture of products was obtained. Treatment of **8** with 50% trifluoroacetic acid in dichloromethane at 0 °C yielded the disaccharide **9**. The phenyl thioglycosides proved to be stable under the conditions of this acid deprotecting step. The disaccharide **9** could be used as a new glycosyl acceptor for further oligosaccharide synthesis.

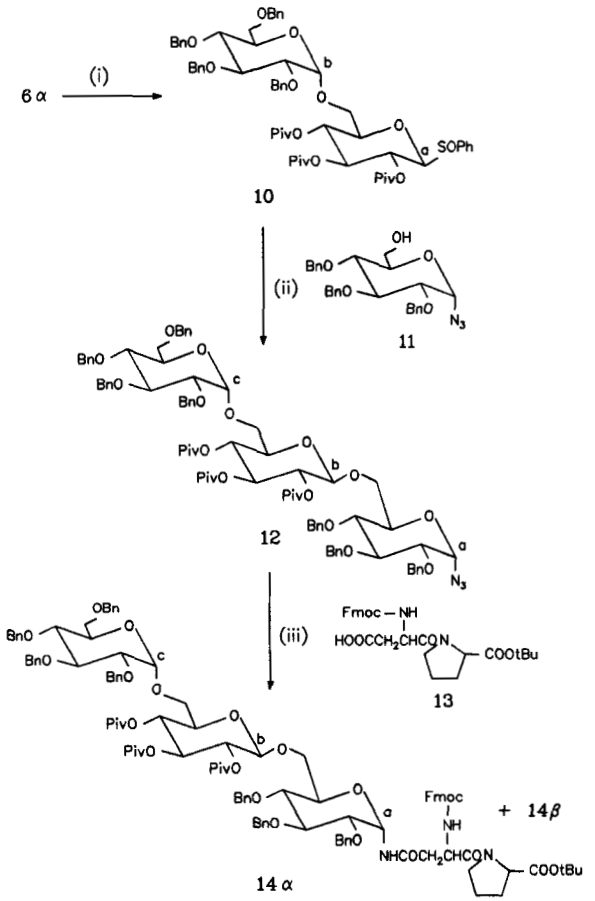
Scheme 2



Reagents: (i) D*t*BP, Tf_2O, DCM; −78 °C to 0 °C. (ii) 50% TFA/DCM; 0 °C.

On the basis of the armed/disarmed concept[4d], changing the *C*-substituent from *O*-acyl to *O*-alkyl would be required in order to activate the disaccharide derivative for further coupling. However, the high yield of **8** resulting from the reaction of **5** and **7** demonstrates that glycosyl sulfoxides can be activated for glycosylation at −78 °C, even in the presence of pivaloyl-disarmed substituents. Therefore, we were able to use neighbouring group participation of **6α** to obtain the β-linked trisaccharide **12**. As depicted in Scheme 3, the phenylthio group of **6α** functions as a glycosyl acceptor in the final coupling reaction, and can then be easily converted to the corresponding phenyl thioglycoside sulfoxide **10**, thereby becoming a new glycosyl donor. The obtained sulfoxide **10** underwent coupling with **11** in the presence of triflic anhydride and D*t*BP in CH_2Cl_2 at −78 °C to give trisaccharide **12** in 78% yield, with 100% β-selectivity as expected. The α configuration at C-1a, β configuration at C-1b and α configuration at C-1c of **12** were assigned on the basis of the ^{13}C-NMR resonances at δ = 87.93, 100.45 and 97.32, respectively.

Scheme 3



Reagents: (i) *m*CPBA, DCM; −78 °C to 10 °C. (ii) D*t*BP, Tf_2O, DCM; −78 °C to 0 °C. (iii) H_2 (2 atm), Lindlar's catalyst, NEt_3, THF/MeOH; 16 h; room temp.

To establish the required asparagine linkage, Jeanloz's methodology[19] was used. Here, a glycosyl azide is reduced to the corresponding glycosylamine and coupled to a suitably protected Asp derivative using dehydrating agents[20]. Reduction of the trisaccharide **12** in the presence of Lindlar's catalyst[21] in 1:1 tetrahydrofuran/methanol and triethylamine, followed by coupling with the dipeptide, N^{α}-(9-fluorenylmethoxycarbonyl)-L-aspartyl-L-proline *tert*-butyl ester (**13**) in the presence of TBTU, gave **14** in 76% yield,

with **14α** as the major isomer (α/β, 5:1). After removal of the *tert*-butyl ester group with TFA and deprotection of the pivaloyl groups under basic conditions this synthon is now ready after reintroduction of the Fmoc group, for further coupling with a nonadecapeptide on a solid support to yield the complete nephritogenside glycopeptide[22].

The methodology described herein offers several advantages: Synthesis of both α- and β-glycosidic linkages has been achieved in high yield. The extremely mild conditions used for the glycosylation reactions make it possible to use trityl and other sensitive protecting groups for temporary protection. The fact that phenyl thioglycosides function as glycosyl acceptors during the coupling reaction, and can be easily converted to the phenyl thioglycoside sulfoxides, i.e. glycosyl donors, enables us to prepare complex oligosaccharides in a highly convergent manner. This strategy should be of valuable utility for the synthesis of oligo- and polysaccharides.

Experimental Section

Solvents were purified using standard procedures; the petroleum ether used had a boiling range of 30–50°C. – Melting points are uncorrected. – ^{1}H- and ^{13}C-NMR spectra: Bruker AC-250, Bruker WM-400, internal standard tetramethylsilane (TMS). – Column chromatography: Silica gel 60 (Merck 0.063–0.200 mm). – Thin-layer chromatography (TLC): DC-plates, silica gel 60 F_{254} (Merck, layer thickness 0.2 mm). – Elemental analyses: Heraeus CHN-O-Rapid, Perkin-Elmer 240 B. – Optical rotations: Zeiss OLD-5-polarimeter. – FD- and FAB-MS: Varian MAT-711 (Finnigan MAT-711).

Phenyl 2,3,4,6-Tetra-O-benzyl-1-thio-β-D-glucopyranoside (**1**)[23]: To a stirred suspension of NaH (0.60 g, 15.0 mmol of a 60% dispersion in oil, previously washed with dry petroleum ether) in dry dimethyl sulfoxide (10 ml) under an atmosphere of nitrogen, a solution of phenyl 1-thio-β-D-glucopyranoside[17] (1.00 g, 3.67 mmol) in dry dimethyl sulfoxide (10 ml) was added dropwise. The resulting mixture was stirred for 1 h at room temp. Benzyl bromide (2.60 ml, 3.75 g, 22.0 mmol) was then added dropwise. The mixture was stirred for a further 3 h, poured into ice-water (300 ml) and extracted with diethyl ether (3 × 50ml). The combined ether layers were washed with water (3 × 50 ml), dried with sodium sulfate, filtered and concentrated. Chromatography of the residue with petroleum ether/ethyl acetate (10:1 → 7:1) gave 1.82 g of **1** (78.4 % yield). – TLC (petroleum ether/ethyl acetate, 7:1): R_f = 0.63. – $[\alpha]_D$ = +1.8 (*c* = 3.6, chloroform). – FD-MS; *m/z*: 633.2 [M^+]. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.65–7.22 (m, 25 H, 5 Ph), 4.97–4.51 (m, 9 H, 1-H, 4 CH_2Ph), 3.86–3.42 (m, 6 H, 2-H, 3-H, 4-H, 5-H, 6-H, 6′-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.49–127.47 (m, aromatic C), 87.53 (1-C), 86.83, 80.95, 79.18, 77.91, 75.86, 75.45, 75.08, 73.48, 69.12 (9 C, 2-C, 3-C, 4-C, 5-C, 6-C, 4 CH_2Ph). – $C_{40}H_{40}O_5S$ (632.8): calcd. C 75.92, H 6.37; found C 76.63, H 6.52.

Phenyl 2,3,4,6-Tetra-O-benzyl-1-thio-β-D-glucopyranoside Sulfoxide (**2**)[23]: To a solution of **1** (100 mg, 0.158 mmol) in dichloromethane (1 ml) at −78°C, a solution of *m*CPBA (55%, 50 mg, 0.159 mmol) in dichloromethane (1 ml) was added. The mixture was warmed to 0°C, quenched with a saturated sodium hydrogen carbonate solution containing 5% sodium sulfite (1 ml) and extracted with dichloromethane (3 × 10 ml). The combined extracts were washed with water, dried with sodium sulfate, filtered and concentrated. Chromatography of the residue with dichloromethane/ethyl acetate (15:1) gave **2α,β** as a mixture of anomers in 96% yield (98 mg). The anomers were separated by column chromatography (dichloromethane/ethyl acetate, 15:1) to afford **2α** and **2β** in a 1:1 ratio. **2α**: TLC (dichloromethane/ethyl acetate, 9:1): R_f = 0.59. – FD-MS; *m/z*: 649.6 [M^+], 1298.6 [2 M^+], 1172.0 [2 M^+ − SOPh]. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.12 (m, 25 H, 5 Ph), 4.94–4.13 (m, 8 H, 4 CH_2Ph), 4.05 (t, *J* = 9.3 Hz, 1 H, 3-H), 3.92 (d, *J* = 9.8 Hz, 1 H, 1-H), 3.75 (t, *J* = 9.0 Hz, 1 H, 4-H), 3.53 (dd, *J* = 9.7, 9.1 Hz, 1 H, 2-H), 3.45–3.40 (m, 2 H, 6-H, 6′-H), 3.26–2.22 (ddd, *J* = 9.7, 4.7, 2.2 Hz, 1 H, 5-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.50–125.53 (m, aromatic C), 93.74 (1-C), 86.82, 80.92, 77.82, 77.07, 76.05, 75.89, 75.34, 73.72, 69.07 (9 C, 2-C, 3-C, 4-C, 5-C, 6-C, 4 CH_2Ph). – $C_{40}H_{40}O_6S$ (648.8): calcd. C 74.05, H 6.21; found C 74.21, H 6.41. **2β**: TLC (dichloromethane/ethyl acetate, 9:1): R_f = 0.47. – FD-MS; *m/z*: 1298.4 [2 M^+]. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.43–125.90 (m, aromatic C), 95.77 (1-C), 86.44, 79.53, 77.49, 76.54, 75.56, 75.07, 74.21, 73.78, 68.82 (9 C, 2-C, 3-C, 4-C, 5-C, 6-C, 4 CH_2Ph). – $C_{40}H_{40}O_6S$ (648.8): calcd. C 74.05, H 6.21; found C 74.21, H 6.31.

Phenyl 2,3,4-Tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranoside (**3**): A solution of phenyl 1-thio-β-D-glucopyranoside[17] (1.00 g, 3.67 mmol) and trityl chloride (1.10 g, 3.94 mmol) in pyridine (10 ml) was stirred at 50°C for 16 h. Then, pivaloyl chloride (1.7 ml, 13.8 mmol) was added and the mixture was stirred at room temp. for one week. The reaction mixture was poured into 100 ml water and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml), dried with sodium sulfate and concentrated in vacuo to give an oily product, which was purified by column chromatography (petroleum ether/dichloromethane, 1:1 → 1:2) to give 2.3 g of **3** (81.7% yield). – TLC (petroleum ether/dichloromethane, 1:2): R_f = 0.34. – FD-MS; *m/z*: 767.0 [M^+], 1533.5 [2 M^+]. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.12 (m, 20 H, 4 Ph), 5.25 (t, *J* = 9.2 Hz, 1 H), 5.06 (t, *J* = 9.6 Hz, 1 H), 4.94 (t, *J* = 9.8 Hz, 1 H), 4.78 (d, *J* = 10.1 Hz, 1 H, 1-H), 3.70–3.65 (ddd, *J* = 9.4, 7.3, 1.7 Hz, 1 H, 5-H), 3.22 (dd, *J* = 10.4, 7.3 Hz, 1 H, 6-H), 2.94 (dd, *J* = 10.4, 1.7 Hz, 1 H, 6′-H), 1.15, 1.00, 0.76 [3 s, 27 H, 3 (CH_3)$_3$C]. – $C_{46}H_{54}O_8S$ (767.0): calcd. C 72.04, H 7.10; found C 72.80, H 7.20.

Phenyl 2,3,4-Tri-O-pivaloyl-1-thio-β-D-glucopyranoside (**4**): The crude product **3** (2.0 g, 2.61 mmol) was dissolved in dichloromethane (10 ml) at 0°C and 10 ml of 50% TFA in dichloromethane was added. The mixture was stirred at 0°C for 10 min, then poured into 100 ml water and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with 7% aqueous sodium carbonate solution (2 × 50 ml), water (2 × 50 ml), dried with sodium sulfate, and concentrated in vacuo. Chromatography of the residue with dichloromethane/ethyl acetate (30:1 → 15:1) gave **4** in 84.8% yield (1.16 g), m.p. 168.5–169.5°C. – TLC (dichloromethane/ethyl acetate, 15:1): R_f = 0.49. – $[\alpha]_D$ = −23.2 (*c* = 3.2, chloroform). – FD-MS; *m/z*: 524.4 [M^+], 1048.7 [2 M^+]. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 5 H, Ph), 5.33 (t, *J* = 9.3 Hz, 1 H), 4.98 (t, *J* = 9.4 Hz, 1 H), 4.97 (t, *J* = 9.2 Hz, 1 H), 4.70 (d, *J* = 10.1 Hz, 1 H, 1-H), 3.65–3.44 (m, 3 H, 5-H, 6-H, 6′-H), 1.14, 1.10, 1.04 [3 s, 27 H, 3 (CH_3)$_3$C]. – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.18, 176.95, 176.23 [3 C, 3 (CH_3)$_3$C*C*O], 132.48–128.16 (m, aromatic C), 86.25 (1-C), 78.26, 72.95, 69.59, 68.16, 61.53 (5 C, 2-C, 3-C, 4-C, 5-C, 6-C), 38.68 [3 C, 3 *C*(CH_3)$_3$], 27.00 [9 C, 3 C(*C*H_3)$_3$]. – $C_{27}H_{40}O_8S$ (524.7): calcd. C 61.81, H 7.68; found C 62.15, H 7.74.

Phenyl 2,3,4-Tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranoside Sulfoxide (**5**): To a solution of **3** (1.24 g, 1.62 mmol) and di-*tert*-butylpyridine (377 mg, 1.97 mmol) in dichloromethane (30 ml) at

−78°C, *m*CPBA (55%, 0.509 g, 1.62 mmol) in dichloromethane (8 ml) was added. After warming to 10°C, the reaction mixture was diluted with saturated sodium hydrogen carbonate solution containing 5% sodium sulfite (10 ml) and extracted with dichloromethane. The organic layers were washed with water (2 × 30 ml), dried with sodium sulfate, filtered and evaporated. Chromatography with dichloromethane/ethyl acetate (35:1) gave 1.13 g of **5α** and **β** (89.5% yield) as a 1:1 mixture of anomers, which was directly used in the next step. **5α**: FD-MS; *m/z*: 782 [M$^+$]. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.70−7.05 (m, 20 H, 4 Ph), 5.15 (t, *J* = 8.9 Hz, 1 H), 5.10 (t, *J* = 8.9 Hz, 1 H), 4.77 (t, *J* = 9.5 Hz, 1 H), 4.37 (d, *J* = 9.7 Hz, 1 H, 1-H), 3.55 (ddd, *J* = 10.1, 5.6, 1.9 Hz, 1 H, 5-H), 2.97 (dd, *J* = 10.6, 1.9 Hz, 1 H, 6-H), 2.89 (dd, *J* = 10.6, 5.7 Hz, 1 H, 6′-H), 1.07, 0.93, 0.65 [3 s, 27 H, 3 (CH_3)$_3$C]. − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.28, 176.98, 176.11 [3 C, 3 (CH_3)$_3$C*C*O], 143.59−126.98 (m, aromatic C), 92.94 (1-C), 86.79 (*C*Ph$_3$), 78.80, 73.81, 68.90, 67.79, 61.63 (5 C, 2-C, 3-C, 4-C, 5-C, 6-C), 38.78 [3 C, 3 *C*(CH_3)$_3$], 27.10 [9 C, 3 C(*C*H$_3$)$_3$]. − $C_{46}H_{54}O_9S$ (783.0): calcd. C 70.56, H 6.95; found C 70.11, H 7.34. **5β**: FD-MS; *m/z*: 783 [M$^+$]. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.70−7.05 (m, 20 H, 4 Ph), 5.41 (t, *J* = 9.5 Hz, 1 H), 5.24 (t, *J* = 9.1 Hz, 1 H), 4.77 (t, *J* = 9.4 Hz, 1 H), 4.20 (d, *J* = 9.2 Hz, 1 H, 1-H), 3.50 (m, 1 H, 5-H), 3.16 (dd, *J* = 10.5, 8.3 Hz, 1 H, 6-H), 2.62 (dd, *J* = 10.5, 1.3 Hz, 1 H, 6′-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.55, 176.60, 176.32 [3 C, 3 (CH_3)$_3$C*C*O], 143.62−125.28 (m, aromatic C), 91.68 (1-C), 86.84 (*C*Ph$_3$), 79.25, 73.63, 68.31, 67.82, 62.94 (5 C, 2-C, 3-C, 4-C, 5-C, 6-C), 38.53 [3 C, 3 *C*(CH_3)$_3$], 27.00 [9 C, 3 C(*C*H$_3$)$_3$]. − $C_{46}H_{54}O_9S$ (783.0): calcd. C 70.56, H 6.95; calcd. C 70.50, H 6.80.

Phenyl 2,3,4-Tri-O-pivaloyl-6-O-(2,3,4,6-tetra-O-benzyl-α- and β-D-glucopyranosyl)-1-thio-D-glucopyranoside (**6α** and **6β**): To a solution of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside sulfoxide (**2**) (100 mg, 0.154 mmol), 2,6-di-*tert*-butylpyridine (32.4 mg, 0.169 mmol) and phenyl 2,3,4-tri-*O*-pivaloyl-1-thio-β-D-glucopyranoside (**4**) (88.9 mg, 0.169 mmol) in 4 ml of dichloromethane/diethyl ether (1:4) under nitrogen at −78°C, triflic anhydride (43.5 mg, 0.154 mmol) was added dropwise over a period of 10 min. The reaction mixture was gradually allowed to warm to 0°C. Then, 3 ml of a saturated $NaHCO_3$ solution was added. The mixture was poured into water (30 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were washed with water (2 × 30 ml), dried with sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate, 40:1) to give 138 mg of **6α** and **6β** (85% yield, **α/β**, 4:1). **6α**: TLC (dichloromethane/ethyl acetate, 40:1): R_f = 0.52. − $[\alpha]_D$ = +7.2 (*c* = 2.5, chloroform). − FD-MS; *m/z*: 1046.6 [M$^+$], 2094.8 [2 M$^+$]. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40−7.00 (m, 25 H, 5 Ph), 5.23−3.25 (m, 22 H, 1a-H, 2a-H, 3a-H, 4a-H, 5a-H, 6a-H, 6a′-H, 1b-H, 2b-H, 3b-H, 4b-H, 5b-H, 6b-H, 6b′-H, 4 C*H*$_2$Ph), 1.14, 1.09, 1.03 [3 s, 27 H, 3 (CH_3)$_3$C]. − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.57, 175.04, 174.99 [3 C, 3 (CH_3)$_3$C*C*O], 137.45, 137.01, 136.67, 136.53 (Cq, 4 C, aromatic C), 131.59−123.58 (m, aromatic C), 95.80 (1b-C), 85.72 (1a-C), 80.55, 78.61, 76.25, 75.20, 74.22, 73.38, 72.05, 71.91, 71.84, 68.72, 68.19, 67.12, 66.95, 65.68 (14 C, 2a-C, 3a-C, 4a-C, 5a-C, 6a-C, 2b-C, 3b-C, 4b-C, 5b-C, 6b-C, 4 *C*H$_2$Ph), 37.25 [3 C, 3 *C*(CH_3)$_3$], 25.66, 25.64, 25.57 [9 C, 3 C(*C*H$_3$)$_3$]. − $C_{61}H_{74}O_{13}S$ (1047.3): calcd. C 69.96, H 7.12; found C 70.50, H 7.31. **6β**: m.p. 142.5−143.5°C. − TLC (dichloromethane/ethyl acetate, 40:1): R_f = 0.42. − $[\alpha]_D$ = −3.13 (*c* = 3.5, chloroform). − FD-MS; *m/z*: 1047.3 [M$^+$], 2095.6 [2 M$^+$]. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51−6.94 (m, 25 H, 5 Ph), 5.13−3.19 (m, 22 H, 1a-H, 2a-H, 3a-H, 4a-H, 5a-H, 6a-H, 6a′-H, 1b-H, 2b-H, 3b-H, 4b-H, 5b-H, 6b-H, 6b′-H, 4 C*H*$_2$Ph), 1.00, 0.94, 0.91 [3 s, 27 H, 3 (CH_3)$_3$C]. − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.28, 177.01, 176.60 [3 C, 3 (CH_3)$_3$C*C*O], 138.88, 138.70, 138.42, 138.25 (Cq, 4 C aromatic C), 133.25−126.75 (m, aromatic C), 104.09 (1b-C), 86.27 (1a-C), 84.81, 82.52, 78.42, 75.96, 75.20, 75.06, 75.01, 73.80, 73.56, 70.29, 69.80, 69.05, 68.92, 68.55 (14 C, 2a-C, 3a-C, 4a-C, 5a-C, 6a-C, 2b-C, 3b-C, 4b-C, 5b-C, 6b-C, 4 *C*H$_2$Ph), 39.00 [3 C, 3 *C*(CH_3)$_3$], 27.39−27.29 [9 C, 3 C(*C*H$_3$)$_3$]. − $C_{61}H_{74}O_{13}S$ (1047.3): calcd. C 69.96, H 7.12; found C 70.67, H 7.24.

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4-tri-O-pivaloyl-6-O-trityl-β-D-glucopyranosyl)-β-D-glucopyranoside (**8**): To phenyl 2,3,4-tri-*O*-pivaloyl-6-*O*-trityl-1-thio-β-D-glucopyranoside sulfoxide (**5**) (232 mg, 0.30 mmol) in dichloromethane (3 ml) under nitrogen at −78°C, a solution of D*t*BP (114.8 mg, 0.60 mmol) in dichloromethane (3 ml) was added. Subsequently, triflic anhydride (84.6 mg, 0.30 mmol) was introduced into the reaction vessel. After warming to −65°C, 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranoside (**7**) (116 mg, 0.33 mmol) was added and the mixture was allowed to warm to 0°C. After addition of 2 ml of a saturated $NaHCO_3$ solution, the mixture was poured into 30 ml water and extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with water (2 × 30 ml), dried with sodium sulfate, filtered and concentrated. Chromatography of the residue with dichloromethane/ethyl acetate (30:1) on a silica gel column gave 240 mg of **8** (80.6% yield). − FD-MS; *m/z*: 1005 [M$^+$]. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.06 (m, 15 H, 3 Ph), 5.64 (d, *J* = 8.3 Hz, 1 H, 1a-H), 5.20−4.83 (m, 6 H), 4.55 (d, *J* = 8.1 Hz, 1 H, 1b-H), 4.00−3.55 (m, 6 H), 1.93, 1.91, 1.90, 1.87 (4 s, 12 H, 4 C*H*$_3$CO), 1.06, 0.96, 0.73 [3 s, 27 H, 3 (CH_3)$_3$C*C*O]. − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.32, 176.73, 176.38 [3 C, 3 (CH_3)$_3$C*C*O], 170.16, 169.82, 169.46, 168.73 (4 C, 4 CH_3*C*O), 143.82 (Cq, aromatic C), 128.98−127.18 (m, aromatic C), 100.52 (1b-C), 91.79 (1a-C), 91.64 (CPh$_3$), 86.79−60.53 (10 C, 2a-C, 3a-C, 4a-C, 5a-C, 6a-C, 2b-C, 3b-C, 4b-C, 5b-C, 6b-C), 38.90, 38.86, 38.62 [3 C, 3 *C*(CH_3)$_3$], 27.40−26.99 [9 C, 3 C(*C*H$_3$)$_3$], 21.18, 20.85, 20.70, 20.53 [4 C, 4 *C*H$_3$CO]. − $C_{54}H_{68}O_{18}$ (1005.1): calcd. C 64.53, H 6.82; found C 64.20, H 7.00.

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4-tri-O-pivaloyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**9**): To a solution of **8** (195 mg, 0.194 mmol) in 5 ml dichloromethane at 0°C, 5 ml 50% TFA in dichloromethane was added. After stirring at 0°C for 20 min, the mixture was poured into ice-water (20 ml). The organic layer was washed with saturated aq. $NaHCO_3$ (10 ml), water (2 × 10 ml) and dried with sodium sulfate. After concentration, the residue was purified by chromatography (dichloromethane/ethyl acetate, 10:1 → 4:1) to give 130 mg of **9** in 87% yield. − FD-MS; *m/z*: 763 [M$^+$]. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (d, *J* = 8.1 Hz, 1 H, 1a-H), 4.34 (d, *J* = 8.0 Hz, 1b-H), 1.83, 1.78, 1.74, 1.73 (4 s, 12 H, 4 C*H*$_3$CO), 0.88, 0.86, 0.83 [3 s, 27 H, 3 (CH_3)$_3$CCO]. − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.40, 177.28, 176.70 [3 C, 3 (CH_3)$_3$C*C*O], 170.21, 170.24, 169.42, 169.00 (4 C, 4 CH_3*C*O), 100.58 (1b-C), 91.81 (1a-C), 38.95, 38.90, 38.70 [3 C, 3 *C*(CH_3)$_3$], 27.50−27.01 [9 C, 3 C(*C*H$_3$)$_3$], 21.21, 20.90, 20.76, 20.60 [4 C, 4 *C*H$_3$CO]. − $C_{35}H_{54}O_{18}$ (762.8): calcd. C 55.11, H 7.14; found C 55.42, H 7.10.

Phenyl 2,3,4-Tri-O-pivaloyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside Sulfoxide (**10**): To a solution of the sulfide **6α** (175 mg, 0.167 mmol) in 5 ml of dichloromethane at −78°C, a solution of *m*CPBA (55%, 52.3 mg, 0.167 mmol) in 5 ml of dichloromethane was added. The reaction mixture was allowed to warm to 10°C and then quenched with a saturated $NaHCO_3$ solution containing 5% sodium sulfite (2 ml). The aqueous layer was extracted with dichloromethane (3 × 20 ml), and the

combined extracts were washed with water (3 × 20 ml), dried with sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (dichloromethane/ethyl acetate, 15:1) to give 165 mg of **10** (93% yield) as a mixture of sulfoxide isomers. – TLC (dichloromethane/ethyl acetate, 10:1): R_f = 0.44 and 0.55. This material was immediately used for the next step.

2,3,4-Tri-O-benzyl-α-D-glucopyranosyl Azide (**11**): A solution of α-D-glucopyranosyl azide[24] (1.0 g, 4.87 mmol) and trityl chloride (1.36 g, 4.87 mmol) in pyridine (10 ml) was stirred at 50°C for 16 h and then poured into 100 ml water. The resulting mixture was extracted with dichloromethane (3 × 50 ml), the combined extracts were washed with water (3 × 50 ml), dried with sodium sulfate and concentrated in vacuo. The obtained product was then dissolved in dry dimethyl sulfoxide (10 ml) and added dropwise to a suspension of oil-free sodium hydride (0.5 g, 12.0 mmol of 60%) in dry dimethyl sulfoxide (10 ml) under nitrogen. The solution was stirred for 1 h at room temp., and then benzyl bromide (2.1 ml, 3.0 g, 17.5 mmol) was added dropwise. The resulting mixture was stirred for a further 3 h, poured into ice-water (300 ml), and extracted with diethyl ether (3 × 50ml). The combined ether layers were washed with water (3 × 50 ml), dried with sodium sulfate, filtered and concentrated. The crude product was then dissolved in dichloromethane (10 ml) and 10 ml of 50% TFA in dichloromethane was added. The mixture was stirred at 0°C for 10 min, then poured into 100 ml water and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with 7% aqueous sodium carbonate solution (2 × 50 ml), water (2 × 50 ml), dried with sodium sulfate, and concentrated in vacuo. Chromatography of the residue with dichloromethane/ethyl acetate (15:1) gave 1.25 g of **11** (54 % yield), m.p. 68–69°C. – TLC (dichloromethane/ethyl acetate, 15:1): R_f = 0.39. – $[\alpha]_D$ = +96.87 (*c* = 2.6, chloroform). – FD-MS; *m/z*: 475.1 [M^+], 951.5 [2 M^+]. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 15 H, aromatic H), 5.07 (d, *J* = 4.1 Hz, 1 H, 1-H), 4.87–4.53 (m, 6 H, 3 C*H*$_2$Ph), 3.84–3.41 (m, 6 H, 2-H, 3-H, 4-H, 5-H, 6-H, 6′-H), 1.65 (s, 1 H, OH). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.54, 138.05, 137.68 (Cq, 3 C, aromatic C), 128.70–127.77 (m, aromatic C), 87.98 (1-C), 81.67–73.36 (7 C, 2-C, 3-C, 4-C, 5-C, 3 *C*H$_2$Ph), 61.50 (6-C). – $C_{27}H_{29}O_5N_3$ (475.5): calcd. C 68.18, H 6.15, N 8.84; found C 68.53, H 6.10, N 8.71.

O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-O-pivaloyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranosyl Azide (**12**): To a solution of the sulfoxide **10** (200 mg, 0.188 mmol) and 2,6-di-*tert*-butylpyridine (36 mg, 0.188 mmol) in dichloromethane (5 ml) at –78°C, triflic anhydride (53 mg, 0.188 mmol) was added. The resulting mixture was stirred at –65°C for 10 min and then a solution of 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl azide (**11**) (82 mg, 0.172 mmol) in dichloromethane (2 ml) was added dropwise over a period of 5 min. The mixture was gradually allowed to warm to 0°C. The reaction was monitored carefully until completion and then quenched with saturated aq. $NaHCO_3$ (5 ml). The aqueous layer was extracted with dichloromethane (3 × 10 ml) and the combined organic extracts were dried with sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (dichloromethane/ethyl acetate, 30:1) to give 190 mg of the trisaccharide **12** (78% yield). – TLC (dichloromethane/ethyl acetate, 30:1): R_f = 0.39. – $[\alpha]_D$ = +38.9 (*c* = 3.5, chloroform). – FD-MS; *m/z*: 1412.6 [M^+]. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.02 (m, 35 H, aromatic H), 5.05 (d, *J* = 4.0 Hz, 1 H, 1a-H), 1.07, 1.06, 1.03 [3 s, 27 H, 3 $(CH_3)_3CCO$]. – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.48, 176.79, 176.64 [3 C, 3 $(CH_3)_3CCO$], 139.10, 138.85, 138.69, 138.45, 138.29, 138.18, 137.83 (Cq, 7 C, aromatic C), 128.90–127.81 (m, aromatic C), 100.45 (1b-C), 97.32 (1c-C), 87.93 (1a-C), 82.19–68.75 (22 C, 2a-C, 3a-C, 4a-C, 5a-C, 6a-C, 2b-C, 3b-C, 4b-C, 5b-C, 6b-C, 2c-C, 3c-C, 4c-C, 5c-C, 6c-C, 7 CH_2Ph), 39.01 [3 C, 3 $C(CH_3)_3$], 27.43 [9 C, 3 $C(CH_3)_3$]. – $C_{82}H_{97}O_{18}N_3$ (1412.7): calcd. C 69.72, H 6.92, N 2.97; found C 69.59, H 6.92, N 2.68.

N^{α}-(9-Fluorenylmethoxycarbonyl)-L-aspartyl-L-proline tert-Butyl Ester (**13**): To a solution of 4-benzyl-N^{α}-(9-fluorenylmethoxycarbonyl)-L-aspartate (988.5 mg, 2.22 mmol), TBTU (712.5 mg, 2.22 mmol) and DIEA (286.8 mg, 2.22 mmol) in dichloromethane/*N,N*-dimethylformamide (10:1, 10 ml) at 0°C, L-proline *tert*-butyl ester (380µl, 2.22 mmol) was added. After 12 h, the mixture was poured into water and extracted with ethyl acetate (100 ml). The organic extract was washed successively with saturated aq. $NaHCO_3$ (2 × 50 ml), 10 % citric acid (2 × 50 ml), water, dried with sodium sulfate, filtered and concentrated (yield: 1.27 g, 95.6%). The obtained [4-benzyl-N^{α}-(9-fluorenylmethoxycarbonyl)-L-aspart-1-oyl]-L-proline *tert*-butyl ester was then dissolved in 10% acetic acid in methanol (10 ml) and hydrogenated in the presence of 10% Pd/C (100 mg) under 1.5 atm. pressure for 2 h. The catalyst was filtered off and the filtrate was concentrated to dryness. Chromatography of the residue with dichloromethane/methanol (8:1) gave 0.73 g of **13** (64.7% yield). – TLC (dichloromethane/methanol, 8:1): R_f = 0.35. – $[\alpha]_D$ = –52.34 (*c* = 2.0, chloroform). – FD-MS; *m/z*: 509.2 [M^+]. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.72–7.22 (m, 8 H, aromatic H), 6.37 (d, *J* = 7.9 Hz, 1 H, Fmoc-N*H*), 2.86–2.67 (dd, *J* = 15.6, 6.70 Hz, 2 H, COC*H*$_2$CH), 1.41 [s, 9 H, (C*H*$_3$)$_3$CO]. – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.78, 170.76, 169.92, 156.20 (4 C, 4 C=O), 81.73 [1 C, $(CH_3)_3CO$], 49.56 (1 C, $COCH_2CH$), 37.45 (1 C, $COCH_2CH$), 27.91 [3 C, $(CH_3)_3CO$]. – $C_{28}H_{32}N_2O_7$ (508.6): calcd. C 66.13, H 6.34, N 5.51; found C 66.18, H 6.46, N 5.72.

O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)-(1→6)-O-(2,3,4-tri-O-pivaloyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-1-N-[N^{α}-(9-fluorenylmethoxycarbonyl)-L-aspart-1-oyl-(L-proline tert-butyl ester)-4-oyl]-α- and -β-D-glucopyranosylamine (**14α** and **14β**): A solution of **12** (141.3 mg, 0.1 mmol) in THF/methanol (1:1, 10 ml) was hydrogenated under 2 atm. pressure in the presence of Lindlar's catalyst (70 mg) and triethylamine (130 mg, 1.25 mmol) for 16 h at room temp. The catalyst was filtered off and the filtrate was concentrated to dryness to give a α,β mixture of the trisaccharide glycosylamine. This mixture was dissolved in dichloromethane/*N,N*-dimethylformamide (9:1, 2 ml) and then added to a solution of dipeptide **13** (61 mg, 0.12 mmol), TBTU (38.5 mg, 0.12 mmol), HOBT (18.4 mg, 0.12 mmol) and DIEA (15.5 mg, 0.12 mmol) in dichloromethane/*N,N*-dimethylformamide (9:1, 5 ml). The resulting mixture was stirred at 0°C for 1 h, then left at room temp. for 12 h, diluted with dichloromethane, washed with water, 10% citric acid, further water, dried and concentrated. Chromatography of the residue on silica gel with dichloromethane/ethyl acetate (10:1) gave 142 mg (75.6% yield) of **14α** and **14β** (α/β, 5:1). **14α**: TLC (dichloromethane/ethyl acetate, 6:1): R_f = 0.47. – $[\alpha]_D$ = +22.8 (*c* = 0.5, chloroform). – FD MS; *m/z*: 1876.8 [M^+]. – ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.96 (d, *J* = 6.2 Hz, 1 H), 5.70 (t, *J* = 6.2 Hz, 1 H), 5.18 (t, *J* = 9.4 Hz, 1 H), 5.08 (t, *J* = 9.4 Hz, 1 H), 4.90 (t, *J* = 8.7 Hz, 1 H), 2.73–2.50 (dd, *J* = 15.4, 6.0 Hz, 2 H, $COCH_2CH$), 1.32 [s, 9 H, $(CH_3)_3CO$], 1.05, 1.03, 1.01 [3 s, 27 H, 3 $(CH_3)_3CCO$]. – ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ = 176.83, 176.17, 175.98 [3 C, 3 $(CH_3)_3CCO$], 170.54, 170.08, 168.69, 156.02 (4 C, 4 C=O), 100.36 (1 C, 1b-C), 97.00 (1c-C), 81.18 (1a-C), 81.01–65.72 (24 C), 59.90 (1 C, C-Pro), 49.80 (1 C, $COCH_2CH$), 46.94, 46.80 (2 C, C-Pro, CH-Fmoc), 40.20 (1 C, $COCH_2CH$), 38.42 [3 C, 3 $(CH_3)_3CCO$], 28.84 (1 C, C-Pro), 27.55 [3 C, $(CH_3)_3CO$], 26.82 [9 C, 3 $(CH_3)_3CCO$], 24.67 (1 C, C-Pro). – $C_{110}H_{129}O_{24}N_3$ (1877.2):

calcd. C 70.38, H 6.93, N 2.24; found C 69.86, H 7.09, N 2.53. **14β**: TLC (dichloromethane/ethyl acetate, 6:1): R_f = 0.38. – $[\alpha]_D$ = +6.77 (*c* = 0.4, chloroform). – FD-MS; *m/z*: 1876.8 [M^+]. – ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.85 (d, *J* = 8.2 Hz, 1 H), 5.12 (t, *J* = 9.1 Hz, 1 H), 5.03 (t, *J* = 9.2 Hz, 1 H), 4.98 (t, *J* = 9.7 Hz, 1 H), 2.56–2.42 (dd, *J* ≈ 14.7, 5.4 Hz, 2 H, $COCH_2CH$), 1.37 [s, 9 H, $(CH_3)_3CO$], 1.08, 1.07, 1.04 [3 s, 27 H, 3 $(CH_3)_3CCO$]. – ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ = 176.72, 176.22, 176.14 [3 C, $(CH_3)_3CCO$], 171.15, 169.42, 169.16, 155.60 (4 C, 4 C=O), 100.40 (1b-C), 96.69 (1c-C), 85.40 (1a-C), 81.37–65.57 (24 C), 59.90 (1 C, C-Pro), 49.80 (1 C, $COCH_2CH$), 46.94, 46.80 (2 C, C-Pro, CH-Fmoc), 40.20 (1 C, $COCH_2CH$), 38.42 [3 C, 3 $(CH_3)_3CCO$], 28.85 (1 C, C-Pro), 27.55 [3 C, $(CH_3)_3CO$], 26.82, 26.75, 26.67 [9 C, 3 $(CH_3)_3CCO$], 24.68 (1 C, C-Pro). – $C_{110}H_{129}O_{24}N_3$ (1877.2): calcd. C 70.38, H 6.93, N 2.24; found C 69.96, H 7.05, N 2.34.

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