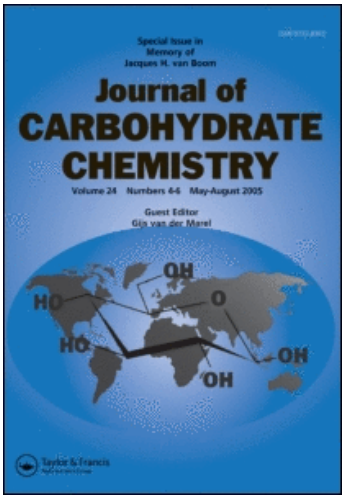

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of Glycosylated Amino Acids for Use in Solid Phase Glycopeptide Synthesis, Part 2: *N*-(9-Fluorenylmethyloxycarbonyl)-3-0-[2,4,6-TRI-*0*-Acetyl-3-0-(2,3,4-TRI-0-Acetyl-α-D-Xylopyranosyl)-β-D-Glucopyranosyl]-L-Serine

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To cite this Article Lüning, Björn , Norberg, Thomas and Tejbrant, Jan(1992) 'Synthesis of Glycosylated Amino Acids for Use in Solid Phase Glycopeptide Synthesis, Part 2: *N*-(9-Fluorenylmethyloxycarbonyl)-3-0-[2,4,6-TRI-*0*-Acetyl-3-0-(2,3,4-TRI-0-Acetyl-α-D-Xylopyranosyl)-β-D-Glucopyranosyl]-L-Serine', Journal of Carbohydrate Chemistry, 11: 7, 933 — 943
To link to this Article: DOI: 10.1080/07328309208018280
URL: http://dx.doi.org/10.1080/07328309208018280

J. CARBOHYDRATE CHEMISTRY, 11(7), 933-943 (1992)

SYNTHESIS OF GLYCOSYLATED AMINO ACIDS FOR USE IN SOLID PHASE GLYCOPEPTIDE SYNTHESIS, PART 2*: *N*-(9-FLUORENYLMETHYLOXYCARBONYL)-3-*O*-[2,4,6-TRI-*O*-ACETYL-3-*O*-(2,3,4-TRI-*O*-ACETYL-α-D-XYLOPYRANOSYL)-β-D-GLUCOPYRANOSYL]-L-SERINE

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Received October 25, 1992 - Final Form July 1, 1992

ABSTRACT

FMOC-serine phenacylester was glycosylated with a derivative of the disaccharide α-D-Xyl*p*-(1→3)-β-D-Glc*p*, and the product was treated with zinc to remove the phenacyl group. The title derivative is useful for synthesis of blood clotting factor IX glycopeptide fragments by the solid-phase approach.

* Part one is reference 1.

INTRODUCTION

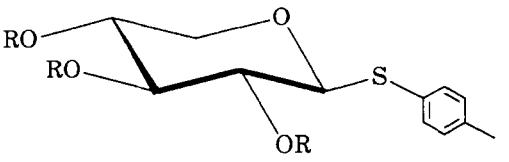
Solid-phase synthesis of glycopeptides, using *N*-(9-fluorenylmethyloxycarbonyl) amino acids carrying protected or unprotected sugar residues, has recently[1-6] been carried out successfully in several laboratories. It appears to be the most generally applicable method known today for obtaining well defined glycopeptides[7] in reasonable amounts. The synthetic glycopeptides obtained have been used in investigations of the effects of glycosylation on biological[8] and conformational[9] properties of proteins and peptides.

In connection with such studies, we needed a glycopeptide fragment of the EGF-like domain[10] of human blood clotting factor IX. This domain contains a serine (53) which carries an O-linked α-D-Xyl*p*-(1-3)-α-D-Xyl*p*-(1-3)-β-D-Glc*p* trisaccharide[11] or an α-D-Xyl*p*-(1-3)-β-D-Glc*p* disaccharide.[12] A symposium report has been given about the synthesis of the trisaccharide connected to serine.[13] We now report synthesis of the corresponding disaccharide amino acid **8**, suitable for use in solid-phase peptide synthesis.

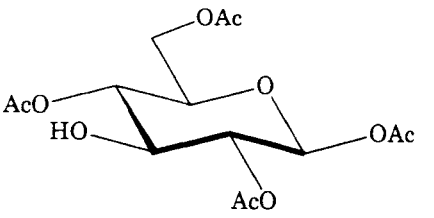
RESULTS AND DISCUSSION

The xylosyl unit **2** was prepared in the following way: 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose[14] was reacted with 4-methylthiophenol and boron trifluoride etherate and the product was deacetylated to give **1** (75 %). Benzylation with benzyl bromide/NaH gave **2** (70 %).

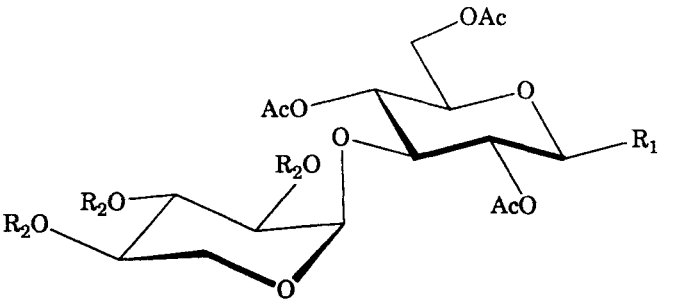
The condensation of **2** with 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**3**) was then investigated. Promotion with dimethyl(methylthio)sulfonium trifluoromethanesulfonate,[15] as well as reaction of the bromide derived from **2** with **3** using tetraethylammonium bromide as promoter, did not produce appreciable amounts of glycosidation product, for unknown reasons. Therefore, although not stereospecific, a silver-triflate promoted reaction was chosen for preparation of the disaccharide. Treatment



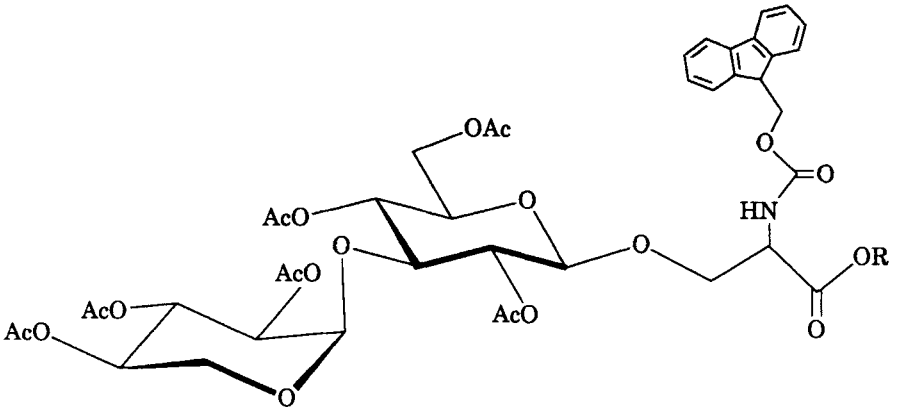
1. R = H
2. R = Bn



3.



4. R_1 = AcO R_2 = Bn
5. R_1 = AcO R_2 = Ac
6. R_1 = SC_2H_5 R_2 = Ac



7. R = $CH_2COC_6H_5$
8. R = H

of **2** with bromine gave the corresponding bromide, which was reacted with **3** and silver triflate to give a mixture of **4** and its β anomer (34 and 57 %, respectively). Compound **4** was subjected to hydrogenolysis and acetylation to give **5** (94 %), subsequent reaction with ethanethiol and boron trifluoride etherate gave the peracetylated ethyl thioglycoside **6** (80 %). Reaction of **6** with *N*-(9-fluorenylmethyloxycarbonyl)-L-serine phenacylester gave **7** (54 %), which was treated with zinc in acetic acid to give the target amino acid derivative **8** in 90 % yield. The use of **8** in solid phase peptide synthesis will be reported in a separate paper.

EXPERIMENTAL

General procedures. Melting points are corrected. Evaporations were performed at <40 °C bath temperature. Optical rotations were recorded at 20 °C (*c*= 0.4-0.7, chloroform) unless otherwise stated, using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded at 30 °C for solutions in $CDCl_3$ unless otherwise stated, using a Bruker AM 500 spectrometer or a JEOL JNM-GSX 270 spectrometer (TMS = δ_H 0.00, $CDCl_3$ = δ_C 77.17). Only selected NMR data are reported. In the assignments of disaccharides the carbons or protons of the 3-linked Xyl carry an apostrophe. The purity (> 95 %) of the prepared compounds was ascertained by NMR spectroscopy and by TLC in at least two different solvent systems. Silica gel 60 F-254 (Merck, Darmstadt, Germany) was used for TLC, detection by UV or by charring with 8% sulfuric acid. Column chromatography was performed on silica gel (Matrex Silica Si, 60Å, 35-70 μ, Amicon). Organic solvents were dried over metallic sodium (toluene, diethyl ether), or over molecular sieves 4Å (heated to 280 °C for >2 weeks, KEBO, Stockholm, Sweden). Powdered molecular sieves, Union Carbide 4Å (Fluka, Buchs, Switzerland, heated to 280 °C for >2 weeks) were used in reactions where so stated.

4-Methylphenyl 1-Thio-β-D-xylopyranoside (1). Boron trifluoride etherate (65 mL, 173 mmol) was added to a stirred solution of 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose[14] (33.0 g, 58.3 mmol) and 4-methylthiophenol (11.6 g, 93.3 mmol) in dichloromethane (50 mL) containing molecular sieves (17 g). After 30 min the reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and washed with aqueous sodium bicarbonate and water. The organic layer was concentrated and the residue was dissolved in methanol (80 mL) containing methanolic sodium methoxide (0.5 M, 20 mL). The reaction mixture was neutralized after 1h with 4M hydrochloric acid, diluted with warm water, washed twice with toluene, and the aqueous layer was concentrated and the residue crystallized from water to give **1** (18.5 g, 72.4 mmol, 75 %) mp 128 °C, $[\alpha]_D$= +35° (methanol). NMR data ($C^2H_3O^2H$): δ 21.1 (Ar-CH_3), 70.4, 70.9, 73.6, 79.2 (C-2,3,4,5), 90.3 (C-1), 130-133 (Ar).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.2; H, 6.3. Found: C, 53.9; H, 6.0. The reason for the low C,H values is unclear, but could be caused by inorganic salt contamination.

4-Methylphenyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-xylopyranoside (2). Sodium hydride (12.0 g, 60% in oil, 300 mmol) was added to a stirred solution of **1** (18.2 g, 71 mmol) in dry *N,N*-dimethylformamide (150 mL). After 1 h, benzyl bromide (29.0 mL, 244 mmol) was added slowly. The reaction mixture was partitioned between water and toluene. The organic layer was dried (magnesium sulfate), concentrated and purified on a silica gel column (toluene/ethyl acetate 95/5) to give **2** (26.2 g, 50 mmol, 70 %). A sample was crystallized from ether-petroleum ether (bp 40-65) to give white needles, mp 56 °C, $[\alpha]_D$= +32°. NMR data: ^{13}C, δ 21.1 (Ar-**C**H_3), 67.5 (C-5), 73.2, 75.4, 75.6 (Ar-**C**H_2-O), 77.8, 80.5, 85.4 (C-2,3,4), 88.7 (C-1), 127-133 (Ar); ^1H, δ 2.32 (s, Ar-C**H**$_3$), 3.21 (dd, $J_{1,2}$=9.6, $J_{2,3}$=11.2 Hz, H-2), 3.40 (m, H-4), 3.61 (m, H-

3,5a), 4.04 (dd, $J_{4,5b}$=4.6, $J_{5a,5b}$=11.5 Hz, H-5b), 4.59 (d, $J_{1,2}$=9.6 Hz, H-1), 4.58-4.91 (Ar-CH_2-O), 7.08-7.43 (Ar-H).

Anal. Calcd for $C_{33}H_{34}O_4S$: C, 75.3; H, 6.5; S, 6.1. Found: C, 75.3; H, 6.5; S, 6.2.

1,2,4,6-tetra-*O*-Acetyl-β-D-glucopyranose (3). 1,2,4,6-Tetra-*O*-acetyl-β-D-glucopyranose was prepared essentially according to Freudenberg and Plankenhorn.[16] NMR data: ^{13}C, δ 20.8 (**C**H_3CO), 62.0 (C-6), 70.4, 72.8, 72.9, 73.6 (C-2,3,4,5), 91.8 (C-1), 169-171 (CH_3**C**O); ^{1}H, δ 2.05 (s, C**H**$_3$CO), 3.75 (m, H-3,5), 4.10 (dd, $J_{5,6a}$=2.3, $J_{6a,6b}$=12.3 Hz, H-6a), 4.28 (dd, $J_{5,6b}$=4.3, $J_{6a,6b}$=12.3 Hz, H-6b), 5.95-5.97 (m, H-2,4), 5.65 (d, $J_{1,2}$ 7.8 Hz, H-1).

Anal. Calcd for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.8. Found: C, 48.3; H, 5.8.

1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl)-β-D-glucopyranose (4) and 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)-β-D-glucopyranose. 4-Methylphenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-xylopyranoside (**2**, 1.58 g, 3.0 mmol) and molecular sieves (3.35 g) were stirred in dry dichloromethane (4 mL) and dry ether (2 mL). Bromine (0.18 mL, 3.50 mmol) was added and the mixture was stirred at room temperature for 30 min. Cyclohexene was added until all bromine color dissappeared. Solid **3** (0.70 g, 2.0 mmol) was then added. The mixture was cooled to -55 °C and silver triflate (1.29 g, 5.0 mmol) in dry toluene (3 mL) was added. After 10 min pyridine (1 mL) was added and the reaction mixture was allowed to attain room temperature. The solids were filtered off and thoroughly washed with dichloromethane. The filtrate was further diluted with dichloromethane, washed with 0.5M aqueous sodium thiosulfate, 0.1 M aqueous hydrochloric acid and water. The organic layer was dried (magnesium sulfate), concentrated and purified by column chromatography (toluene/ethyl acetate 7/3) to give pure **4** (0.10 g, 0.13 mmol, 7%), a mixture of **4** and 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)-β-D-gluco-

pyranose (0.78 g, 1.04 mmol, 52%), and pure 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)-β-D-glucopyranose (0.54 g, 0.72 mmol, 36%). The impure fraction was further fractionated by repeated column chromatography to give pure **4** (0.41 g, 0.55 mmol, 27%) and pure 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)-β-D-glucopyranose (0.32 g, 0.43 mmol, 21%). Thus, **4** was obtained in a total yield of 34 %, and the corresponding β isomer was obtained in 57 %. Compound **4** had $[\alpha]_D$= +22° and NMR data: ^{13}C, δ 20.6-20.9 (**C**H$_3$CO), 61.2, 61.8 (C-6,5'), 67.8, 71.7, 72.9, 73.3, 73.8, 75.8, 76.6, 80.4, 80.7, 81.2 (C-2,3,4,5,2',3',4', Ar-**C**H$_2$-O), 92.0 (C-1), 99.7 (C-1'), 127-139 (Ar), 169-171 (CH$_3$**C**O); ^{1}H, δ 2.05-2.15 (s, C**H**$_3$CO), 3.31 (dd, $J_{1',2'}$=3.1, $J_{2',3'}$=9.4 Hz, H-2'), 3.5-3.6 (m,H-4',5'a,5'b), 3.74 (t, $J_{2,3}$=9.4, $J_{3,4}$=9.3 Hz, H-3), 3.79 (m, H-5,3'), 4.13 (dd, $J_{5,6a}$=2.0, $J_{6a,6b}$=12.2 Hz, H-6a), 4.28 (dd, $J_{5,6b}$=4.7, $J_{6a,6b}$=12.2 Hz, H-6b), 4.58-4.88 (Ar-C**H**$_2$-O), 4.66 (d, $J_{1',2'}$=3.1 Hz, H-1'), 5.12 (dd, $J_{1,2}$=8.6, $J_{2,3}$=9.4 Hz, H-2), 5.19 (dd, $J_{3,4}$=9.4, $J_{4,5}$=10.6 Hz, H-4), 5.61 (d, $J_{1,2}$=8.6 Hz, H-1).

NMR data for 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl)-β-D-glucopyranose: ^{13}C, δ 20.3-20.8 (**C**H$_3$CO), 61.9 (C-6), 63.9 (C-5'), 67.9, 71.9, 73.0, 73.3, 75.3, 75.4, 78.1, 78.3, 81.6, 83.7 (Ar-**C**H$_2$O, C-2,3,4,5,2',3',4'), 92.0 (C-1), 104.4 (C-1').

1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-β-D-glucopyranose (5). A solution of **4** (0.37 g, 0.49 mmol) in a mixture of ethyl acetate (6 mL) and ethanol (2 mL) with Pd-C (0.55 g, 10%) as catalyst was hydrogenated for 16 h at 60 p.s.i. The solids were filtered off and washed with ethanol. The combined solutions were concentrated and the residue was dissolved in a mixture of pyridine (4 mL) and acetic anhydride (2 mL), and heated to 60 °C for two h. The mixture was diluted with toluene, then washed twice with 0.1M hydrochloric acid and once with concentrated aqueous sodium bicarbonate, dried (magnesium

sulfate) and concentrated to give **5** as an amorphous solid (0.28 g, 0.46 mmol, 94%), $[\alpha]_D$= +50°. NMR data: ^{1}H, δ 1.95-2.15 (s,C**H**$_3$-CO), 3.60-3.80 (m, H-5,5'a,5'b), 3.91 (t, $J_{2,3}$=9.2, $J_{3,4}$=9.2 Hz, H-3), 4.07 (dd, $J_{5,6a}$=2.6, $J_{6a,6b}$=12.9 Hz, H-6a), 4.21 (dd, $J_{5,6b}$=5.0, $J_{6a,6b}$=12.9 Hz, H-6b), 4.71 (dd, $J_{1',2'}$=3.0, $J_{2',3'}$=10.5 Hz, H-2'), 4.90 (m, H-4'), 5.11 (d, $J_{1',2'}$=3.0 Hz, H-1'), 5.12 (dd, $J_{1,2}$=7.8, $J_{2,3}$=9.2 Hz, H-2), 5.19 (dd, $J_{3,4}$=9.1, $J_{4,5}$=10.2 Hz, H-4), 5.29 (dd, $J_{2',3'}$=10.5, $J_{3',4'}$=9.4 Hz, H-3'), 5.61 (d, $J_{1,2}$=7.8 Hz, H-1).

Ethyl 2,4,6-Tri-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-1-thio-β-D-glucopyranoside (6). Boron trifluoride etherate (185 μL, 1.47 mmol) was added to a stirred solution of **5** (0.45 g, 0.73 mmol), molecular sieves (1 g) and ethanethiol (136 μL, 1.83 mmol) in dichloromethane (2 mL). After 30 min, another 100 μL of boron trifluoride etherate was added. The solids were filtered off and thoroughly washed with dichloromethane. The filtrate was further diluted with dichloromethane, washed with aqueous sodium bicarbonate, dried (magnesium sulfate), concentrated and purified on a silica gel column (toluene/ethyl acetate 1/1) to give **6** (0.36 g, 0.59 mmol, 80%). Crystallization from diethyl ether gave colorless crystals with mp. 141-2 °C, $[\alpha]_D$=+28°. NMR data: ^{13}C, δ 14.8 (**C**H$_3$-CH$_2$), 20.6-21.1 (**C**H$_3$COO), 24.0 (-**C**H$_2$-S), 59.0 (C-5'), 62.3 (C-6), 69.0 (C-3',4'), 69.5 (C-4), 70.8 (C-2), 71.4 (C-2'), 76.1 (C-5), 79.8 (C-3), 83.7 (C-1), 96.6 (C-1'), 169-170 (CH$_3$**C**OO); ^{1}H, δ 1.25 (t, J_{CH_3,CH_2}=7.5 Hz, C**H**$_3$-CH$_2$-S), 1.95-2.15 (s, C**H**$_3$-COO), 2.71 (q, $J_{CH_2-CH_3}$=7.5 Hz, S-C**H**$_2$-CH$_3$), 3.58 (m, H-5), 3.69 (m, H-5'a,5'b), 3.85 (dd, $J_{2,3}$=9.2, $J_{3,4}$=9.2 Hz, H-3), 4.10 (dd, $J_{5,6a}$=2.7, $J_{6a,6b}$=12.4 Hz, H-6a), 4.19 (dd, $J_{5,6b}$=4.9, $J_{6a,6b}$=12.4 Hz, H-6b), 4.36 (d, $J_{1,2}$=9.9 Hz, H-1), 4.72 (dd, $J_{1',2'}$=3.5, $J_{2',3'}$=10.3 Hz, H-2'), 4.93 (m,H-4'), 5.04 (dd, $J_{1,2}$=9.9, $J_{2,3}$=9.2 Hz, H-2), 5.13 (d, $J_{1',2'}$=3.5 Hz, H-1'), 5.17 (dd, $J_{3,4}$=9.2, $J_{4,5}$=9.9 Hz, H-4), 5.32 (dd, $J_{2',3'}$=10.3, $J_{3',4'}$=9.3 Hz, H-3').

Anal. Calcd for $C_{25}H_{36}O_{15}S$: C, 49.3; H, 6.0. Found: C, 49.3; H, 5.8.

***N*-(9-Fluorenylmethyloxycarbonyl)-3-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-β-D-glucopyranosyl]-L-serine phenacylester (7).** Bromine (38 μL, 0.75 mmol) was added to a stirred solution of **6** (0.35 g, 0.57 mmol) in dichloromethane (1.5 mL) containing molecular sieves (1 g). Cyclohexene was added after 30 min to destroy excess bromine. *N*-(9-Fluorenylmethyloxycarbonyl)-L-serine phenacyl ester[17] (0.507 g, 1.14 mmol) in dichloromethane (1 mL) was added and the solution was cooled to -50 °C. A solution of silver triflate (0.39 g, 1.50 mmol) in toluene (1.5 mL) was added. After 20 min pyridine (0.5 mL) was added and the reaction mixture was allowed to attain room temperature. The solids were filtered off and were thoroughly washed with dichloromethane. The filtrate was further diluted with dichloromethane, washed with 0.5 M aqueous sodium thiosulfate, 0.1 M aqueous hydrochloric acid, and aqueous sodium bicarbonate, dried with magnesium sulfate and concentrated. Column chromatography (toluene/ ethyl acetate 6/4) of the residue gave pure **7** (0.31 g, 0.31 mmol, 54 %). Crystallization from ether gave white needles with mp 151-2 °C, $[\alpha]_D$ +29°. NMR data: ^{13}C, δ 20-21.5 (**C**H_3CO), 47.2 (**C**HAr_2), 54.4 (α-**C**H), 58.9 (C-5'), 62.0 (C-6), 67.0, 67.1, 67.2 (β-CH_2, FMOC-CH_2, O**C**H_2CO), 69.0, 69.1, 69.6 (C-4,3',4'), 71.1, 71.3, 72.0 (C-2,5,2'), 78.0 (C-3), 96.4 (C-1'), 101.0 (C-1); ^1H, δ 5.13 (d, $J_{1',2'}$=3.6 Hz, H-1'), 5.63 (d, $J_{1,2}$=8.1 Hz, H-1).

Anal. Calcd for $C_{49}H_{53}O_{21}N$: C, 59.3; H, 5.4. Found: C, 58.8; H, 5.3.

***N*-(9-Fluorenylmethyloxycarbonyl)-3-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-β-D-glucopyranosyl]-L-serine (8).** Activated zinc[18] (1.5 g, 22.9 mmol) and **7** (172 mg, 174 mmol) were vigorously stirred for 30 min in 80 % aqueous acetic acid (10 mL). The solids were filtered off and the filtrate concentrated and purified by column chromatography (ethyl acetate/ acetic acid 9/1) to give **8** as an amorphous solid (137 mg, 0.157 mmol, 90%), $[\alpha]_D$ +47°. NMR data (CD_3OD): ^1H, δ 3.65 (dd, H-5'a), 3.68 (ddd, $J_{4,5}$=9.6, $J_{5,6a}$=2.4,

$J_{5,6b}$=4.7 Hz, H-5), 3.72 (dd, $J_{4',5'b}$=6.0, $J_{5'a,5'b}$=11.0 Hz, H-5'b), 3.89 (dd, J=4.2, J=10.7 Hz, β-CH_2a), 4.00 (t, $J_{2,3}$=9.4, $J_{3,4}$=9.4 Hz, H-3), 4.06 (dd, $J_{5,6a}$=2.5, $J_{6a,6b}$=12.3 Hz, H-6a), 4.09 (dd, J =5.4, 10.7 Hz, β-CH_2b), 4.21 (dd, $J_{5,6b}$=4.7, $J_{6a,6b}$=12.3 Hz, H-6b), 4.23 (t, J=6.7 Hz, FMOC-CH), 4.37 (m, FMOC-CH_2a), 4.43 (dd, J=6.7, 10.6 Hz, FMOC-CH_2b), 4.52 (d, $J_{1,2}$=8.0 Hz, H-1), 4.76 (dd, $J_{1',2'}$=3.5, $J_{2',3'}$=10.3 Hz, H-2'), 4.92 (m, H-2), 4.94 (dd, $J_{3',4'}$=10.7, $J_{4',5'b}$=6.1 Hz, H-4'), 5.09 (t, $J_{3,4}$=9.4, $J_{4,5}$=9.6 Hz, H-4), 5.17 (d, $J_{1',2'}$=3.5 Hz, H-1'), 5.28 (dd, $J_{2',3'}$=10.3, $J_{3',4'}$=10.7 Hz, H-3'); ^{13}C, d 48.4 ($CHAr_2$) 55.4 (α-CH), 59.9 (C-5'), 63.1 (C-6), 67.9, 69.9, 70.2, 70.4, 71.3, 72.2, 72.9, 73.2 (C-2, 4, 5, C-2', 3', 4', β-CH_2, FMOC-CH_2), 78.4 (C-3), 97.4 (C-1'), 101.7 (C-1).

ACKNOWLEDGEMENTS

We thank Mr. Gunnar Grönberg, BioCarb Technology AB, for recording of NMR spectra. Support was obtained from the Swedish National Board for Technical Development.

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