Practical Synthesis of β-D-Xyl-(1→2)-β-D-Man-(1→4)-α-D-Glc-OMe, a Trisaccharide Component of the *Hyriopsis schlegelii* Glycosphingolipid

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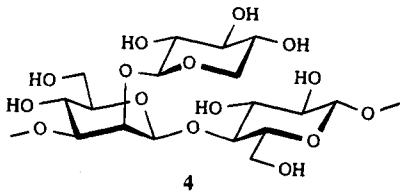
Received May 3, 1994 (Revised Manuscript Received August 19, 1994®)

By employing the readily accessible (preceding paper in this issue) 3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexosyl bromide (**1**) as an indirect, β-specific mannosyl donor, a practical three-step synthesis was elaborated for methyl xylosyl-β(1→2)-mannosyl-β(1→4)-glucoside (**11**), a trisaccharide component of *Hyriopsis schlegelii* ceramide oligosaccharides. Key steps were the silver aluminosilicate-induced, β-specific glycosidation of **1** with methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside and the silver triflate-promoted β-xylosylation with 2,3,4-tri-*O*-benzoyl-α-D-xylosyl bromide. The overall yield amounted to a satisfactory 47%.

Introduction

The benzyl-protected hexos-2-ulosyl bromide **1**, readily accessible from acetobromoglucose in a simple four-step sequence,[1] proved to be a highly reactive β-specific glycosyl donor for the efficient generation—through carbonyl reduction of the intermediate β-D-glycosid-2-uloses **2** → **3**—of β-D-mannosidic linkages (Scheme 1).[1] Aside from various β-D-mannosides, two disaccharides, i.e., β-D-Man*p*-(1→6)-D-Gal and β-D-Man*p*(1→4)-L-Rha*p*, have already been prepared by this "ulosyl bromide approach", which has the additional advantage that the disaccharides accumulate with a free 2-OH in the mannose portion and thus are ideally suited for the introduction of other glycosyl residues at O-2. These quite favorable features point toward the application of this methodology to the synthesis of biologically important 2-*O*-glycosyl-β-D-mannosides, such as, e.g., the β-(1→2)-linked mannooligosaccharides of the phosphomannan–protein complex of *Candida albicans*,[2] or the 2-*O*-xylosylated mannosyl-β(1→4)-glucose **4**, contained in a series of glycosphingolipids of *Hyriopsis schlegelii*.[3]



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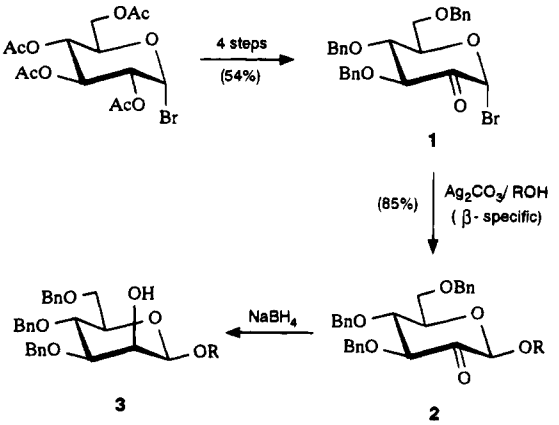
Xyl*p*-β(1→2)-Man*p*-β(1→4)-Glc*p* –

As part of our project on the synthesis β-D-mannose-[4] and *N*-acetyl-β-D-mannosamine-containing oligosaccharide[4,5] we here describe a practical synthesis of the trisaccharide **4** in the form of its terminal methyl glycoside.[6]

Scheme 1



Results and Discussion

The readily accessible[7] methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside (**5**) was deemed a suitable glucosyl acceptor and, hence, was brought to reaction with ulosyl bromide **1**. Under Koenigs–Knorr conditions (Ag_2CO_3, CH_2Cl_2, 25 °C), or when using silver silicate,[8] the glycosylation was exceedingly sluggish. More forcing conditions (Ag_2CO_3, 1,2-dichloroethane, 4 h, 50 °C) induced **1** to form substantial amounts of the 1,6-anhydro derivative **7**, as evidenced by the isolation of its reduction product, the crystalline 3,4-di-*O*-benzyl-1,6-anhydromannoside (**8**) (Scheme 2).

A most suitable, highly reactive promoter for the coupling of **1** with **5** proved to be the catalyst developed

® Abstract published in *Advance ACS Abstracts,* October 1, 1994.

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(6) Part of this work is contained in a review[4] and has been presented at the 207th American Chemical Society Meeting, San Diego, March 1994; Abstract CARB 100.

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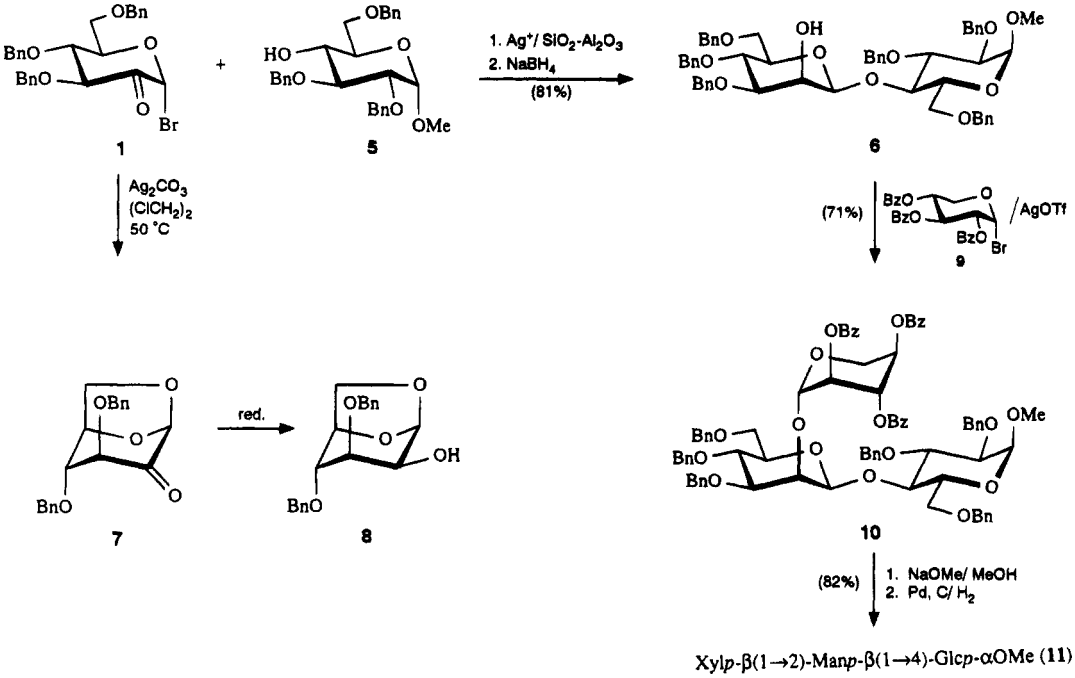
Scheme 2



Xylp-β(1→2)-Manp-β(1→4)-Glcp-αOMe (**11**)

by van Boeckel et al.,[9] comprising silver ion immobilized on a large surface $SiO_2-Al_2O_3$ carrier: the reaction in dichloromethane at room temperature was complete within 20 min, proceeded in exclusive β-fashion, and, when followed by $NaBH_4$ reduction, allowed the isolation of the mannosyl glucoside **6** in a satisfactory yield of 81% over the two steps.

Of the various xylosylation procedures that have been employed,[10-14] coupling of **6** with 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide (**9**) in dichloromethane/toluene at −40 °C with silver triflate as the promoter, as used by Garegg et al.,[14] was deemed the most useful. Indeed, these conditions smoothly generated the trisaccharide **10** (71%) without detectable formation of the α-anomer. Subsequent deprotection, first by treatment with sodium methoxide−methanol for de-*O*-benzoylation and then by catalytic hydrogenolysis of the benzyl groups, gave the target trisaccharide **11** (82%).

In conclusion, we have demonstrated the applicability of the benzylated ulosyl bromide **1** as a preparatively favorable, indirect β-D-mannosyl donor for the elaboration of fairly complex oligosaccharides, e.g., trisaccharide **11**, in essentially three steps (five functional changes) with an overall yield of 47%. This compares favorably with syntheses of analogs of **11** from other β-D-mannosyl donors, which not only involved more steps, but had a very modest (2.5:1[12]) or essentially no β-selectivity[11] in the glycosidation step.

Configurational Assignments and Conformation of Trisaccharide 11. Structural and configurational evidence for each of the new compounds described was secured by their 300 MHz ^1H NMR spectra, which were usually first order and warrant little comment beyond the information given in the experimental section. The only pecularity noticable is the $^1C_4$ conformation of the tribenzoyl-D-xylosyl portion in the blocked trisaccharide **10**, as evidenced by the small coupling constants $J_{1,2}$ = 2.1 Hz, $J_{2,3}$ = 3.4 Hz, and $J_{3,4}$ = 3.8 Hz. This has been observed in other acylated xylosyl saccharides[11,13] and reflects the pronounced tendency of simple tetra-*O*-acylated β-D-xylopyranones to prefer the $^1C_4$ over the $^4C_1$ chair in solution and in the crystal state.[15] After deblocking, however, i.e., in the free trisaccharide **11**, the β-D-xylopyranosyl residue adopts the usual $^4C_1$ conformation, as revealed by values for $J_{1,2}$ (7.6 Hz), $J_{2,3}$ (9.4 Hz), and $J_{3,4}$ (9.1 Hz), respectively. The extrication of these coupling constants from the ^1H NMR spectrum of **11** required ^1H-correlated 2D resolution at 500 MHz,[16] yet then allowed identification of all sugar protons and their assignment to the individual aldoses.

The overall shape of a trisaccharide of type **11** is determined by the orientation of the three pyranoid rings toward each other, i.e., by the torsional angles ϕ ($O_5-C_1-O_1-C_x$) and ψ ($C_1-O_1-C_x-C_{x-1}$) of the respective intersaccharidic linkages. A calculatory estimation of these angles was attempted using the PIMM88 force field program,[17] which has already been successfully applied to sucrose with relevant results.[18] The outcome is depicted in Figure 1 in ball and stick model representation, featuring ϕ and ψ values of −63 and −117°, respectively, for the xylosyl-β(1→2)-mannose linkage, versus −51 and +112° for the mannosyl-β(1→4) glucose link.

(9) van Boeckel, C. A. A.; Beetz, T.; Kock-van Dalen, A. C.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 596−598.
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(16) We are grateful to Dr. Klaus Pachler, E. Merck, Darmstadt, for kindly recording the 500 MHz ^1H NMR spectrum of the title trisaccharide **11**.
(17) Lindner, H. J. *PIMM-88−Closed Shell PI-SCF-LCAO-MO-Molecular Mechanics Program*; Technische Hochschule Darmstadt, 1988. Lindner, H. J. *Tetrahedron* **1974**, *30*, 1127−1132. Smith, A. E.; Lindner, H. J. *J. Comput. Aided Mol. Des.* **1991**, *5*, 235−262.
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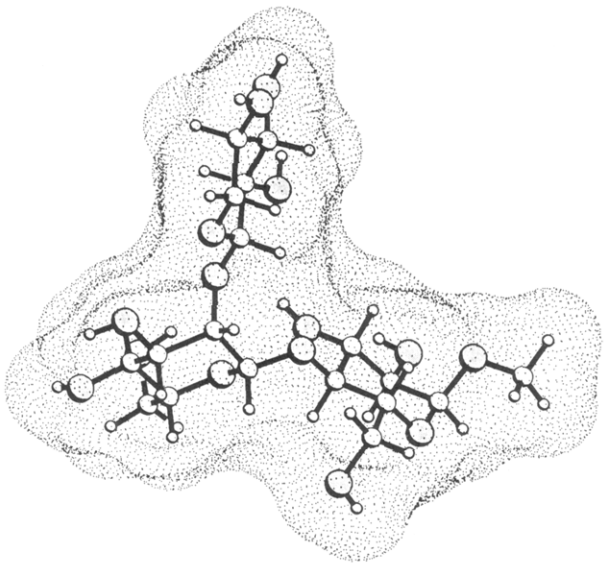

Figure 1. Ball and stick model representation of the lowest energy conformation of Xyl*p*-β(1→2)-Man*p*-β(1→4)-Glc*p*-αOMe (**11**), as calculated by the PIMM 88 force field program;[17] the intersaccharidic torsion angles ϕ and ψ are −63 and −117°, respectively, for the Xyl-β(1→2)Man linkage and −51 and +112° for the Manβ(1→4)Glc glycoside bond. The dots denote the contact surface relative to water (roughly equivalent to the solvent accessible surface); it was smoothly generated with the MOLCAD program.[19] The oxygen atoms are shaded.

In order to additionally get a notion on the overall shape of the trisaccharide **11** in space-filling terms, the contact surface relative to water (i.e., how water sees the molecule) was generated using the MOLCAD program[19] and depicted in dotted form (cf. Figure 1). It gives a clear conception of the xylosyl ring branching out of the linear mannosyl glucoside, which when extended to the natural ceramide-oligosaccharide—the glycosidic α-methoxy group to the right is replaced by β-ceramide, another linear mannosyl residue extends from the central mannosyl-3-*O* to the left—gives a notion of the quasiantennary shape of the biologically relevant molecule. More detailed molecular modelings of such oligosaccharides, particularly the generation and color visualization of their molecular lipophilicity potentials (MLP's), are currently being pursued.

Experimental Section

General. Melting points were determined with a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded at 300 and 500 MHz, ^{13}C NMR at 75.5 MHz; mass spectra (MS) were taken in EI and FAB modes. TLC on Kieselgel 60 F_{254} plastic sheets was used to monitor the reactions and to ascertain the purity of the products. Solvent systems employed: A, CCl_4/EtOAc (4:1); B, toluene/EtOAc (8:1). The spots were visualized by UV light or by spraying with 50% sulfuric acid and charring at 120 °C for 5 min. Column chromatography was performed using silica gel 60 (70−230 mesh).

Silver Aluminosilicate Catalyst.[9] A slurry of 20 g of silica−alumina SHPV catalyst (a porous aluminosilicate with a BET-surface 473 m^2/g; AKZO Chemie, Amsterdam) in 250 mL of N NaOH was stirred for 1 h at 100 °C. The material was then filtered, washed with water (5 × 50 mL), and stirred with a 0.2 M aqueous solution of $AgNO_3$ in the dark for 16 h at ambient temperature. Filtration and washing of the residue with water (2 × 30 mL) and acetone (200 mL), followed by *drying in vacuo for about 12 h at 90 °C*, gave the active material.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (6). A suspension of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[7] (**5**, 600 mg, 1.3 mmol), molecular sieves (4 Å, 1 g), and silver aluminosilicate catalyst (1.5 g, 4.8 mmol) in 4 mL of dry CH_2Cl_2 was stirred for 15 min at room temperature, and a solution of ulosyl bromide **1** (510 mg, 1.0 mmol) in 3 mL of CH_2Cl_2 was added dropwise during 20 min, whereafter the reaction was complete (TLC in solvent system A). The mixture was filtered over Celite, the filter cake was washed twice with CH_2Cl_2, the filtrate and washings were evaporated to dryness, and the resulting residue was purified by elution from a silica gel column with CCl_4/EtOAc (4:1), yielding 790 mg (87%) of the intermediate β-uloside as a colorless syrup.[20] A solution of this syrup in CH_2Cl_2−MeOH (1:1, 80 mL) was cooled (0 °C), $NaBH_4$ (350 mg) was added, and stirring was continued for 4 h. Dilution with CH_2Cl_2 (50 mL), successive washings with water (50 mL), 1% aqueous citric acid (2 × 50 mL), and water (2 × 50 mL) followed by drying of the organic layer (Na_2SO_4), and evaporation under reduced pressure gave a syrupy residue which was purified by elution from a silica gel column with cyclohexane−EtOAc (3:1): 730 mg (81%, based on **1**) of **6** as a colorless syrup; $[\alpha]^{20}_D$ +13.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *mannosyl-H* δ 2.49 (bs, 1H), 3.23 (m, 1H), 3.30 (dd, 1H, *J* = 2.9, 9.2 Hz), 3.64 (m, 1H), 3.76 (m, 1H), 3.84 (dd, 1H, *J* = 9.2, 9.5 Hz), 3.93 (m, 1H), 4.58 (bs, 1H); *glucosyl-H* δ 3.35 (*s*, 3H), 3.50 (*dd*, 1H, *J* = 3.6, 8.9 Hz), 3.59 (m, 2H), 3.76 (m, 1H), 3.90−4.0 (m, 2H), 4.59 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$), *mannosyl-C* δ 67.8, 69.9, 74.3, 75.5, 81.5, 99.8; *glycosyl-C* δ 55.2, 69.5, 69.9, 75.6, 79.5, 80.7, 98.1; MS (FD) *m/e* 897 (M^+). Anal. Calcd for $C_{55}H_{60}O_{11}$ (897.1): C, 73.64; H, 6.74. Found: C, 73.54; H, 6.82.

3,4-Di-*O*-benzyl-1,6-anhydro-β-D-mannopyranose (8). A suspension of Ag_2CO_3 (2 g) and molecular sieves (4 Å, 500 mg) in 1,2-dichloroethane (10 mL) was stirred for 45 min at ambient temperature with the strict exclusion of light and moisture. A solution of ulosyl bromide **1** (700 mg, 1.35 mmol) in 1,2-dichloroethane (3 mL) was then added, and the mixture was stirred for 8 h at 50 °C. Subsequent filtration over Celite and evaporation of the filtrate to dryness gave the syrupy anhydro-uloside **7** (^{1}H NMR), a syrup, which was not further characterized, but directly subjected to $NaBH_4$ reduction (150 mg) in CH_2Cl_2/EtOAc (1:1, 10 mL) for 2.5 h at 0 °C. Processing of the mixture as described for the isolation of **6** (cf. above) gave upon column filtration with CCl_4/EtOAc (4:1) and evaporation **8** as a crystalline residue: 150 mg (32%); mp 56−57 °C; $[\alpha]^{20}_D$ −61.4° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (d, 1H, *J* = 11.1 Hz), 3.48 (bs, 1H), 3.68 (dd, 1H, *J* = 6.0, 7.1 Hz), 3.71−3.78 (m, 2H), 4.05 (dd, 1H, *J* = 1.0, 7.1 Hz), 4.46−4.56 (m, 5H), 5.34 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 64.7, 66.4, 71.4, 73.7, 73.7, 75.5, 76.1, 101.1, 127.8−128.6, 137.1, 137.5; MS (FD) *m/e* = 343 [M^+ + 1]. Anal. Calcd for $C_{20}H_{22}O_5$ (342.4): C, 70.15; H, 6.47. Found: C, 70.47; H, 6.55.

Methyl 2-*O*-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)-4-*O*-(3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (10). A stirred mixture of **6** (380 mg, 0.42 mmol) and CH_2Cl_2 (15 mL) was put under N_2 and cooled to −40 °C. A solution of 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide (**9**,[21] 330 mg, 0.63 mmol) in 4 mL of CH_2Cl_2 was then added, followed by the dropwise addition of silver triflate (200 mg, 0.8 mmol) in toluene (2 mL). Stirring

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(20) On the basis of ^{1}H NMR, this syrup consists of an approximately 1:1 mixture of the blocked ulosyl glycoside and its monohydrate (H-1 of keto compound as a singlet at δ 4.89 versus 4.61 for the hydrate). Extensive drying over P_4O_{10} at 40 °C did not result in dehydration.

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at −40 °C was continued for 30 min, and the mixture was then filtered over Celite which was washed with CH_2Cl_2 (50 mL). The filtrate and washings were washed with 10% aqueous $Na_2S_2O_3$ (40 mL) and water (40 mL). Drying (Na_2SO_4) and evaporation to dryness in vacuo left a syrup which was purified by elution from a silica gel column (3 × 30 cm), with toluene/ethyl acetate (8:1). Evaporation of the eluants with $R_f = 0.2$ (in solvent B) gave 395 mg (71%) of **10** as a colorless syrup: $[\alpha]^{20}_D = -47$ (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$), *mannosyl-H* δ 3.25−3.31 (m, 3H), 3.53−3.73 (m, 2H), 4.90 (d, 1H, J = <1.0, 2.9 Hz), 4.42 (bs, 1H); *glucosyl-H* δ 3.33 (s, 3H), 3.42 (dd, 1H, J = 3.5, 9.3 Hz), 3.59 (m, 2H), 3.73 (m, 1H), 3.85 (dd, 1H, J = 9.4 Hz), 3.99 (d, 1H, J = 9.3, 9.4 Hz), 4.53 (d, 1H, J = 3.5 Hz); *xylosyl-H* δ 3.66 (m, 1H), 4.82 (m, 1H), 5.16 (m, 1H), 5.41 (d, 1H, J = 2.1 Hz), 5.49 (dd, 1H, J = 2.1, 3.4 Hz), 5.54 (dd, 1H, J = 3.4, 3.8 Hz); *others* 4.12 (m, 1H), 4.33−4.85 (m, 10 H), 7.10−7.57 and 7.96−8.07 (m, 45 H). Anal. Calcd for $C_{81}H_{80}O_{18}$ (1341.5): C, 72.52; H, 6.01. Found: C, 72.10; H, 5.97.

Methyl 2-*O*-β-D-Xylopyranosyl-4-*O*-β-D-mannopyranosyl-α-D-glucopyranoside (11). A suspension of 140 mg (0.1 mmol) of **10** in dry methanol (10 mL) containing 30 mg of sodium methoxide was stirred for 3 h at ambient temperature and was subsequently neutralized by briefly stirring with a strongly acidic ion exchange resin (e.g., Amberlite IR 120, H^+ form). Filtration, evaporation of the filtrate in vacuo, and elution of the residue from a silica gel column (2 × 10 cm) with $CHCl_3$/MeOH (15:1) gave a syrup (105 mg) which was directly subjected to hydrogenolysis over 10% Pd/C (30 mg) in methanol (15 mL) for 24 h. Filtration and removal of the solvent left a syrup which was dried in vacuo (finally 0.01 Torr): 43 mg (82%) of **11**; $[\alpha]^{20}_D$ +16.3° (c 0.35, water); ^1H NMR (500 MHz, D_2O) *glucosyl-H* δ 3.49 (s, 3H), 3.67 (dd, 1H, J = 3.9, 9.8 Hz), 3.72 (dd, 1H, J = 9.2, 9.3 Hz), 3.86 (m, 1H), 3.90 (dd, 1H, J = 9.8, 9.2 Hz), 3.93 (m, 2H), 4.88 (d, 1H, J = 3.9 Hz); *mannosyl-H* δ 3.50 (m, 1H), 3.65 (dd, 1H, J = 9.7, 9.8 Hz), 3.73 (dd, 1H, J = 3.3, 9.7 Hz), 3.83 (dd, 1H, J = 4.2, 12.3 Hz), 4.01 (dd, 1H, J = 2.5, 12.3 Hz), 4.31 (d, 1H, J = <1.0, 3.3 Hz), 4.89 (bs, 1H); *xylosyl-H* δ 3.33 (dd, 1H, J = 10.6, 11.5 Hz), 3.44 (dd, 1H, J = 7.6, 9.4 Hz), 3.52 (dd, 1H, J = 9.4, 9.1 Hz), 3.65 (m, 1H), 4.03 (d, 1H, J = 5.4, 11.5 Hz), 4.57 (d, 1H, J = 7.6 Hz); ^{13}C NMR (125.7 MHz, D_2O) *glucosyl-C* δ 57.9, 63.1, 73.0, 73.8, 74.5, 74.7, 101.9; *mannosyl-C* δ 63.4, 69.8, 79.3, 80.7, 81.7, 103.1; *xylosyl-C* δ 67.9, 72.1, 76.1, 78.2, 106.9.

Acknowledgment. The authors gratefully acknowledge the support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Special thanks are due to Dr. K. Pachler, E. Merck, Darmstadt, for kindly providing the 500 MHz data on trisaccharide **11**.