Synthesis of a Nonasaccharide Containing Terminal *N*-Acetyl-β-D-lactosaminyl Residues, Part of the 'Complex-Type' Carbohydrate Moiety of Glycoproteins

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Silver trifluoromethanesulphonate-promoted condensation of 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl bromide with benzyl *O*-(3,6-di-*O*-benzyl-α-D-mannopyranosyl)-(1 → 3)-*O*-[3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1 → 6)]-2,4-di-*O*-benzyl-α-D-mannopyranoside gave a protected nonasaccharide derivative in 19% yield. The free oligosaccharide was obtained after exchanging the 2-phthalimido-groups for 2-acetamido-groups and deblocking.

THE *N*-glycosidically linked carbohydrate chains in glycoproteins are of two major types; the 'high-mannose (oligomannosidic) type' and the 'complex (*N*-acetyl-D-lactosaminic) type'.[1] The complex type chains have been found with two, three, or four *N*-acetyl-D-lactosaminyl residues which are usually substituted with *N*-acetylneuraminic acid (sialic acid) on the D-galactosyl groups. The asialo-form of the *N*-glycosidically linked carbohydrate portion (1) of fetuin is a representative example.[1,2]

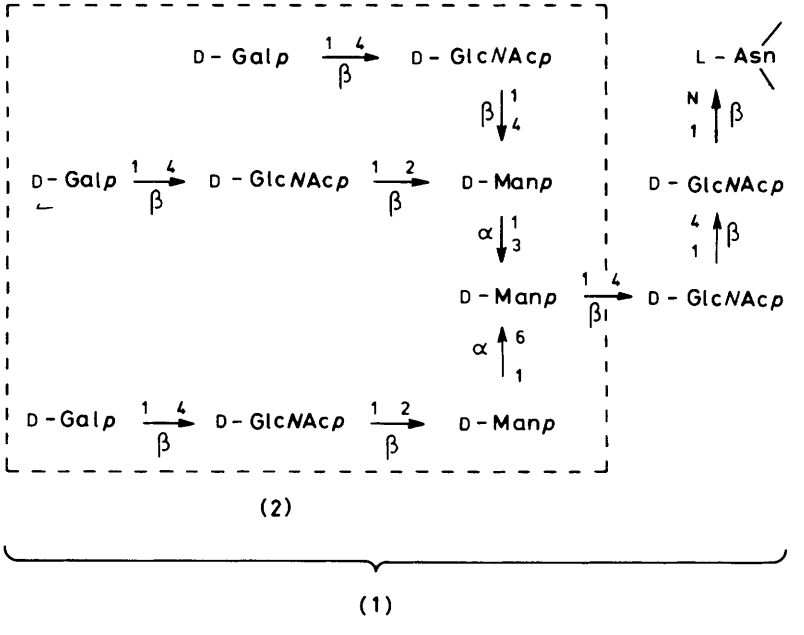
This type of structure has been suggested to be involved in different biologically important phenomena,[1] *e.g.* in interactions with carbohydrate-binding proteins.[1,3-6] The synthesis of oligosaccharides which form part of these structures is therefore a matter of interest. Consequently, hepta-,[7,8] hexa-,[9] penta-,[7,8,10,11] and tri-saccharides [8,10-17] derived from these carbohydrate portions have been prepared.

We now report the synthesis of the nonasaccharide (2) [indicated by the dotted line in structure (1)]. Compound (2) should be of value in specificity studies of certain carbohydrate-binding proteins, *e.g.* the D-galactose-binding protein of mammalian hepatocytes.[4]

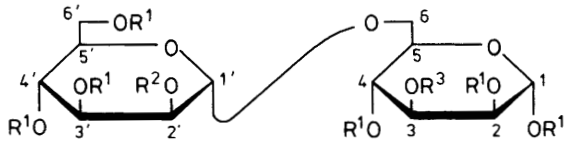
RESULTS AND DISCUSSION

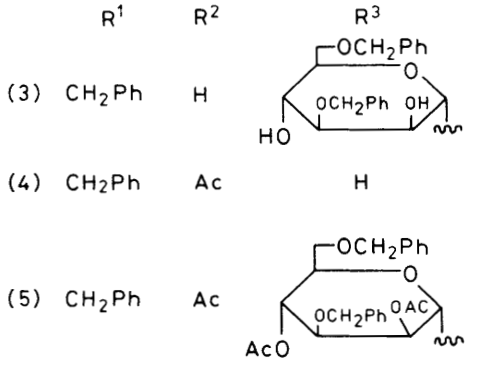
For the preparation of the nonasaccharide (2) a block synthesis was used. Thus, the trisaccharide derivative benzyl *O*-(3,6-di-*O*-benzyl-α-D-mannopyranosyl)-(1 → 3)-*O*-[3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1 → 6)]-2,4-di-*O*-benzyl-α-D-mannopyranoside (3) with three free hydroxy-groups in the required positions was condensed with 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl bromide (A). This bromide is known to give high yields of β-glycosides in silver trifluoromethanesulphonate-promoted condensations.[7,8,10,13]

The preparation of compound (3) required two glycosylations. Thus, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride [12] (1.1 mol equiv.) was condensed with benzyl 2,4-di-*O*-benzyl-α-D-mannopyranoside [12] using silver trifluoromethanesulphonate–*s*-collidine as promoter.[18] After chromatography on silica gel, the disaccharide derivative (4) was obtained in 42% yield. An aliquot of com-



pound (4) was subjected to catalytic hydrogenation (Pd–C catalyst), sodium borohydride reduction, and methylation analysis.[19] This analysis afforded 1,2,3,4,5-penta-*O*-methyl-D-mannitol and 2,3,4,6-tetra-*O*-methyl-D-mannose, indicating that the (1 → 6)-linked disaccharide had been obtained. This assignment was in agreement with the ^{13}C n.m.r. spectrum of compound (4) where no signal was discernible at δ *ca.* 62 p.p.m., indicating the absence of primary hydroxy-groups.

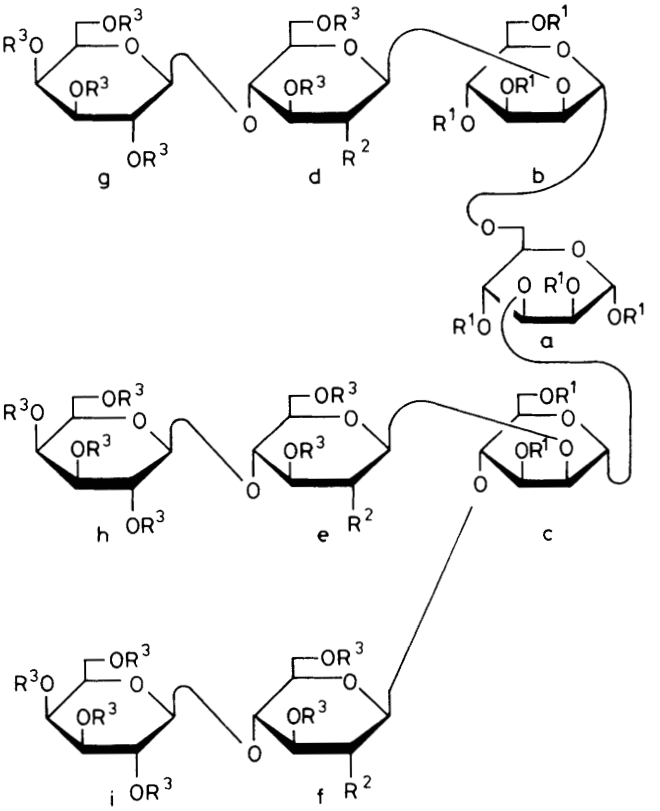




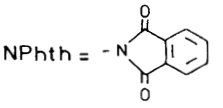
Benzyl 3,6-di-*O*-benzyl-α-D-mannopyranoside [8] was hydrolysed with aqueous acetic acid–hydrochloric acid to give, after chromatography on silica gel, 3,6-di-*O*-benzyl-D-mannose in 47% yield. This compound was acetylated yielding 1,2,4-tri-*O*-acetyl-3,6-di-*O*-benzyl-α,β-D-mannopyranose. This was then treated with hydrogen bromide yielding 2,4-di-*O*-acetyl-3,6-di-*O*-benzyl-α,β-D-mannopyranosyl bromide. The crude mannopyranosyl bromide was condensed with compound (4) as above yielding, after chromatography, the trisaccharide derivative (5) in 47% yield. This compound was de-*O*-acetylated to give the trisaccharide derivative (3). The ^{13}C n.m.r. spectrum of compound (3) showed, *inter alia*, three signals in the anomeric region: δ 101.7 {^1J[C(1)–H(1)] 171 Hz}, 99.7 {^1J[C(1)–H(1)] 169 Hz}, and 96.1 {^1J[C(1)–H(1)] 170 Hz}. From these coupling constants [20] it is obvious that both glycosylation reactions described above have given α-D-mannosidic linkages. Furthermore, a sample of compound (3) was de-*O*-benzylated giving 3,6-di-*O*-(α-D-mannopyranosyl)-D-mannose, indistinguishable from an authentic sample by ^{1}H and ^{13}C n.m.r. spectroscopy and g.l.c.–m.s. of its permethylated alditol.[12]

The bromide (A) [7,8] (*vide supra*) was condensed with the trisaccharide derivative (3) using silver trifluoromethanesulphonate–*s*-collidine as promoter.[8,18,21] After silica-gel chromatography the nonasaccharide derivative (6) was obtained in 19% yield. This yield corresponds to 58% condensation yield per hydroxy-group in the trisaccharide derivative (3). Compound (6) was treated with hydrazine hydrate [21] in ethanol and acetylated yielding the *N*-acetyl derivative (7) in 44% yield. This yield corresponds to 76% conversion from phthalimido- to acetamido-group in each amino-sugar unit. The structures of compounds (6) and (7) were evident from their modes of synthesis and from their ^{13}C n.m.r. spectra which were in good agreement with those from related penta- [8,10] and hepta-saccharide [8] derivatives. Finally, compound (7) was deprotected by treatment with sodium methoxide in methanol and catalytic hydrogenation over palladium–charcoal to give, after gel filtration and freeze-drying, the nonasaccharide derivative (2), $[\alpha]_D^{22}$ +8°, as an amorphous powder in 85% yield. Compound (2) was homogeneous on h.p.l.c. Methylation analysis [19] of the alditol of compound (2) gave 2,3,4,6-tetra-*O*-methyl-D-galactose, 2-deoxy-3,6-di-*O*-methyl-2-*N*-methylacetamido-D-glucose, 3,4,6-tri-*O*-methyl-D-mannose, 3,6-di-*O*-methyl-D-mannose, and 1,2,4,5-tetra-*O*-methyl-D-mannitol. The ^{1}H and ^{13}C n.m.r. spectra obtained from compound (2) were in good agreement with the postulated structure and similar to those obtained from related natural [22] and synthetic compounds.[7,8,10,12,13]

Biological experiments performed with this nonasaccharide derivative (2) will be reported elsewhere.



	R^1	R^2	R^3
(2)	H	NHAc	H
(6)	CH_2Ph	NPhth	Ac
(7)	CH_2Ph	NHAc	Ac



EXPERIMENTAL

The general methods were the same as described earlier.[8] H.p.l.c. of compound (2) was performed with a Waters solvent delivery system 6000 — RCM 100 unit attached to a Dextropak column which was irrigated with water. In the n.m.r. data, superscripts α and β refer to the signals for the α- and β-anomer, respectively.

Benzyl 6-O-(2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2,4-di-O-benzyl-α-D-mannopyranoside (4).—Silver trifluoromethanesulphonate (480 mg), *s*-collidine (95 mg), and ground molecular sieves (type 3Å; *ca.* 0.5 g) were added to a solution of benzyl 2,4-di-*O*-benzyl-α-D-mannopyranoside [12] (700 mg) in dichloromethane (10 cm^3) and the mixture was cooled to −25 °C under nitrogen. A solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride [made [12] from 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannose (1.0 g)] in dichloromethane (10 cm) was added dropwise with stirring. After 45 min the reaction mixture was filtered and the solution washed successively with dilute aqueous sodium thiosulphate, dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water and was then finally concentrated. The product was purified on silica gel with toluene–ethyl acetate (4 : 1) as eluant to yield the pure *disaccharide derivative* (4) as a syrup (600 mg, 42%); $[\alpha]_D^{21}$ +42° (*c* 1.0, $CHCl_3$); R_F 0.64 (solvent as above); δ_C (25.05 MHz; $CDCl_3$) 20.9 [C(:O)CH_3], 66.3—78.4 (CH_2Ph, C-6, and ring C), 95.5 (C-1), 97.7 (C-1′), 125.1—138.4 (aromatic), and 169.9 p.p.m. (C=O) (Found: C, 72.6; H, 6.65. $C_{56}H_{60}O_{12}$ requires C, 72.7; H, 6.54%).

3,6-Di-O-benzyl-D-mannose.—Benzyl 3,6-di-*O*-benzyl-α-D-mannopyranoside [8] (4.16 g) was dissolved in a mixture of 90% aqueous acetic acid and 6M hydrochloric acid (60 cm^3; 5 : 1) The mixture was heated for 10 min at 100 °C, then cooled, diluted with water, and extracted with ethyl acetate. The product was purified on silica gel with toluene–ethyl acetate (1 : 5) as eluant to yield the *mannose derivative* as a syrup (1.51 g, 47%); $[\alpha]_D^{21}$ −6° (*c* 1.0, $CHCl_3$); R_F 0.46 (solvent as above); δ_H (99.60 MHz; $CDCl_3$) 3.2—4.6 (10 H, m, 2 × CH_2Ph, 4 × ring H, and 6-H_2), 4.75 (0.3 H, s, 1-H^β), 5.20 (0.7 H, s, 1-H^α), and 7.2—7.4 (10 H, m, aromatic); δ_C (25.05 MHz; $CDCl_3$) 66.7 (C^β-2), 67.3 (C^α-2), 68.0 (C^α-4), 68.3 (C^β-4), 69.9 (C^β-6), 70.3 (C^α-6), 70.7 (C^α-5), 71.1 (C^β-5), 71.6 and 73.4 (CH_2Ph), 79.1 (C^α-3), 80.9 (C^β-3), 94.0 (C^α-1), 94.2 (C^β-1), and 127.7—137.8 p.p.m. (aromatic).

1,2,4-Tri-O-acetyl-3,6-di-O-benzyl-α,β-D-mannopyranose.—The dibenzyl-D-mannose (0.75 g) was acetylated with acetic anhydride–pyridine (1 : 1) (10 cm^3) for 1 h at 100 °C. After concentration the product was purified on silica gel with toluene–ethyl acetate (3 : 1) as eluant to yield the *triacetate* as a syrup (0.90 g, 88%), $[\alpha]_D^{21}$ ±0° (*c* 1.0, $CHCl_3$); R_F 0.47 (solvent as above); δ_H (99.60 MHz; $CDCl_3$) 1.92, 2.10, and 2.14 (3 × OAc, α-form), 1.91, 2.03, and 2.19 (3 × OAc, β-form), 3.6—5.6 (10 H, m, 2 × CH_2Ph, 4 × ring H, and 6-H_2), 5.75 (0.3 H, d, $J_{1,2}$ *ca.* 1.5 Hz, 1-H^β), 6.10 (0.7 H, d, $J_{1,2}$ *ca.* 1.5 Hz, 1-H^α), and 7.2—7.4 (10 H, m, aromatic); δ_C (25.05 MHz; $CDCl_3$) 20.8 and 20.9 [3 C, C(:O)-CH_3,] 66.8 (C^β-2), 67.1 (C^α-6), 67.7 (C^β-6), 67.9 (C^α-2), 69.3 (C^β-4), 71.1 (C^β-4), 71.4 and 73.5 (CH_2Ph), 72.2 (C^α-5), 74.2 (C^α-3), 74.7 (C^β-5), 76.3 (C^β-3), 91.1 (0.7 C, C^α-1), 91.2 (0.3 C, C^β-1), 127.6—137.7 (aromatic), and 168.1—169.9 p.p.m. (C=O).

2,4-Di-O-acetyl-3,6-di-O-benzyl-α,β-D-mannopyranosyl Bromide.—The previous compound (645 mg) was stirred in dichloromethane (30 cm^3), saturated with hydrogen bromide for 15 min at room temperature. The solution was evaporated to dryness yielding the crude *bromide* as a syrup which was used without purification in the subsequent step. The bromide showed R_F 0.63 in toluene–ethyl acetate (3 : 1); δ_H (25.05 MHz; $CDCl_3$) *inter alia*, 6.35 (0.8 H, $J_{1,2}$ *ca.* 1.0 Hz), indicating that mainly the α-bromide had been obtained.

Benzyl O-(2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1 → 6)-O-[2,4-di-O-acetyl-3,6-di-O-benzyl-α-D-mannopyranosyl-(1 → 3)]-2,4-di-O-benzyl-α-D-mannopyranoside (5).—The disaccharide (4) (600 mg) and the mannopyranosyl bromide (670 mg) were condensed using silver trifluoromethanesulphonate (330 mg) and *s*-collidine (40 mg) as promoter, as described for the corresponding preparation of compound (4). The product was purified on silica gel with toluene–ethyl acetate (3 : 1) as eluant to yield the *trisaccharide derivative* (5) as a syrup (410 mg, 47%); $[\alpha]_D^{21}$ +37° (*c* 1.0, $CHCl_3$); R_F 0.65 (solvent as above); δ_C (25.05 MHz; $CDCl_3$) 20.8 [C(:O)CH_3], 66.4—79.5 (CH_2Ph, C-6, and ring C), 95.9 (C^a-1), 98.0 (C^b-1), 99.8 (C^c-1), 126.4—138.5 (aromatic), and 169.7—170.2 p.p.m. (C=O) (Found: C, 70.9; H, 6.6. $C_{80}H_{86}O_{19}$ requires C, 71.1; H, 6.41%).

Benzyl O-(3,6-Di-O-benzyl-α-D-mannopyranosyl)-(1 → 3)-O-[3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1 → 6)]-2,4-di-O-benzyl-α-D-mannopyranoside (3).—Sodium (10 mg) was added to a solution of compound (5) (550 mg) in dry methanol (25 cm^3); the mixture was left at room temperature overnight, neutralized with acetic acid, and evaporated to dryness. The product was purified on silica gel with toluene–ethyl acetate (3 : 2) as eluant to yield the *trisaccharide derivative* (3) as a syrup (350 mg, 70%); $[\alpha]_D^{21}$ +46° (*c* 1.0, $CHCl_3$); R_F 0.33 (solvent as above); δ_C (25.05 MHz; $CDCl_3$) 65.8—79.4 (CH_2Ph, C-6, and ring C), 96.1 {^1J[C(1)–H(1)] 170 Hz, C^a-1}, 99.7 {^1J[C(1)–H(1)] 169 Hz, C^b-1}, 101.7 {^1J[C(1)–H(1)] 171 Hz, C^c-1}, and 126.6—138.4 p.p.m. (aromatic).

Nonasaccharide Derivative (6).—Silver trifluoromethanesulphonate (1.1 g), *s*-collidine (450 mg), and ground molecular sieves (type 3Å; *ca.* 0.5 g) were added to a solution of the trisaccharide derivative (3) (725 mg) in dichloromethane (10 cm^3) and the mixture was cooled to −40 °C under nitrogen. A solution of the bromide (A) (see Results and Discussion) (2.3 g) in dichloromethane (20 cm^3) was added in three portions (1 : 1 : 0.3) after 0, 1, and 16 h reaction time. The mixture was allowed to attain room temperature over the total reaction time of 18 h. The mixture was filtered and the filtrate was washed successively with dilute aqueous sodium thiosulphate, dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water, and then finally concentrated. The product was purified on a silica-gel column with toluene–ethyl acetate (1 : 1) as eluant and then on another silica-gel column with toluene–ethyl acetate (6 : 7) as eluant to yield the *nonasaccharide derivative* (6) as an amorphous powder (374 mg, 19%); $[\alpha]_D^{21}$ +11° (*c* 1.0, $CHCl_3$). Compound (6) was chromatographically homogeneous [R_F 0.18; toluene–ethyl acetate (6 : 7)] but in its ^{13}C n.m.r. spectrum (see below) some minor peaks indicated the presence of an unidentified impurity ' (imp.) ' (<5%); δ_C (50.0 MHz; $CDCl_3$; 50 °C) 20.4—20.7 [C(:O)CH_3], 54.9 and 55.8 (3 C, C^d-2, C^e-2, and C^f-2), 60.9—77.7 (CH_2Ph, C-6, and ring C), 92.5 (imp.), 96.2 (C^a-1), 96.7 (2 C, C^e-1 and C^d-1), 97.1 (C^b-1), 98.3 (C^f-1),

99.2 (C^e-1), 99.7 (imp.), 100.9, 101.1, and 101.3 (3 C, C^g-1, C^h-1, and C^i-1), 123.3—139.0 (aromatic), and 167.7—170.1 p.p.m. (C=O) (Found: C, 60.1; H, 5.55; N, 1.15. $C_{170}H_{185}N_3O_{67}$ requires C, 61.1; H, 5.58; N, 1.26%).

Nonasaccharide Derivative (7).—Compound (6) (355 mg) was dissolved in 90% aqueous ethanol (40 cm^3), hydrazine hydrate (4 cm^3) was added, and the solution was refluxed overnight. After cooling, the solution was evaporated to dryness. The product was then acetylated with acetic anhydride–pyridine (1 : 1) (10 cm^3) at 100 °C for 1 h. After concentration the product was purified on silica gel with chloroform–acetone (3 : 2) as eluant to yield the pure *nonasaccharide derivative* (7) as a syrup (143 mg, 44%); $[\alpha]_D^{21}$ +3° (*c* 1.0, $CHCl_3$); R_F 0.45 (solvent as above); δ_C (25.05 MHz; $CDCl_3$; 45 °C) 20.5—23.1 [C(:O)CH_3], 53.8 and 54.6 (3 C, C^d-2, C^e-2, and C^f-2), 60.9—78.3 (CH_2Ph, C-6, and ring C), 97.5 (C^a-1), 99.0 and 99.2 (2 C, C^d-1 and C^e-1), 100.0 (2 C, C^b-1 and C^c-1), 100.8 (C^f-1), 101.3 (3 C, C^g-1, C^h-1, and C^i-1), 126.0—128.7 (aromatic), and 168.0—170.5 p.p.m. (C=O).

O-{2,4-*Di*-O-[O-β-D-*galactopyranosyl*-(1 → 4)-2-*acetamido*-2-*deoxy*-β-D-*glucopyranosyl*]-α-D-*mannopyranosyl*-(1 → 3)}-O-{[O-β-D-*galactopyranosyl*-(1 → 4)-2-*acetamido*-2-*deoxy*-O-β-D-*glucopyranosyl*-(1 → 2)]-α-D-*mannopyranosyl*-(1 → 6)}-α,β-D-*mannopyranose* (2).—Sodium (10 mg) was added to a solution of compound (7) (93 mg) in dry methanol (15 cm^3). The mixture was left at room temperature overnight, neutralized with acetic acid, and evaporated to dryness. The product was dissolved in 90% aqueous acetic acid (25 cm^3) and hydrogenated at 400 kPa over 10% palladium–charcoal (100 mg) overnight. After filtration and concentration the product was de-salted by gel filtration on a Sephadex G-25 column (2.5 × 90 cm) irrigated with water. After freeze-drying the *nonasaccharide derivative* (2) was obtained as an amorphous powder (41 mg, 85%); $[\alpha]_D^{22}$ +8° (*c* 0.8, H_2O). On h.p.l.c. compound (2) showed R_t 2.88 (retention time relative to sucrose); δ_H (200 MHz; D_2O), 2.06br. (9 H, s, 3 × Ac), 4.48 (3 H, d, $J_{1,2}$ 7.5 Hz, 1-H^g, 1-H^h, and 1-H^i), 4.58br. (3 H, m, 1-H^d, 1-H^e, and 1-H^f), 4.92br. (1.4 H, s, 1^a-H^β and 1-H^b), and 5.15br. (1.6 H, s, 1$^\alpha$-H^a and 1-H^c); δ_C (25.05 MHz; D_2O) 23.4 and 23.6 [3 C, C(:O)CH_3], 56.1 and 56.4 (3 C, C^d-2, C^e-2, and C^f-2), 61.2—62.8 (8 C, C-6 of residues b—i), 66.9—79.8 C^a-6 and ring C), 95.0 (0.3 C, C^a-1$^\beta$), 95.4 (0.7 C, C^a-1$^\alpha$), 98.1 (C^b-1), 100.3 (C^c-1), 100.7 (2 C, C^d-1 and C^e-1), 102.8 (C^f-1), 104.2 (3 C, C^g-1, C^h-1, and C^i-1), and 175.8 and 176.0 p.p.m. (C=O).

We thank Professors Per J. Garegg and Bengt Lindberg for their interest, and the Swedish Natural Science Research Council for financial support.

[1/1814 *Received*, 23*rd November*, 1981]

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