Carbohydrate Research, 136 (1985) 207–213
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

A SYNTHESIS OF 8-METHOXYCARBONYLOCT-1-YL *O*-α-D-GALACTOPYRANOSYL-(1→3)-*O*-β-D-GALACTOPYRANOSYL-(1→4)-2-ACETAMIDO-2-DEOXY-β-D-GLUCOPYRANOSIDE

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(Received April 30th, 1984; accepted for publication, September 3rd, 1984)

ABSTRACT

Halide-assisted glycosylation, using a non-participating 2-substituent (benzyl) in the glycosyl halide, was used to obtain the α-D-galactosyl linkage and silver triflate promotion with a participating 2-substituent (benzoyl) was used to obtain the β-D-galactosyl linkage in a facile synthesis of the title trisaccharide derivative. The synthesis also incorporates the use of stable thioglycoside intermediates, easily converted into the appropriate galactosyl bromides, as well as regioselective, reductive and acid-catalysed openings of cyclic acetals and orthoesters, respectively, to obtain the required intermediates.

INTRODUCTION

The title compound was required for immunological studies on Ehrlich ascites tumour cells[1,2]. The free trisaccharide had previously been synthesised[3] using a different route to that described here. The present synthesis involves regioselective reductive ring-opening of 4,6-benzylidene acetals[4], regioselective acid-catalysed opening of a five-membered cyclic orthoester[5], and thioglycosides as stable synthetic intermediates, easily convertible into glycosyl bromides.

RESULTS AND DISCUSSION

8-Methoxycarbonyloct-1-yl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[6] was benzylated under conditions which avoid the formation of *N*-benzyl compounds[7], to yield the 3-benzyl ether **1**. Reductive cleavage of the 4,6-benzylidene acetal group in **1**, using borane–trimethylamine and aluminium chloride[4], afforded 63% of **2**. The disaccharide bromide **9** was obtained as follows. Acetonation of methyl 1-thio-β-D-galactopyranoside afforded a mixture of the 3,4- and 4,6-acetals, the former preponderating. Benzoylation of the mixture followed by chromatography yielded **3** and **4**. The ^{13}C-n.m.r. spectrum of **3** [δ 26.4, 27.8 (methyl carbons), and 110.8 (acetal carbon, five-membered cyclic isopropylidene

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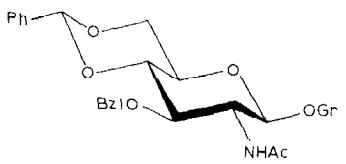

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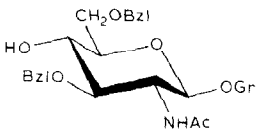

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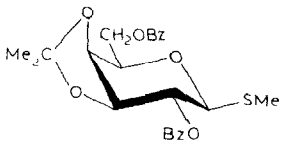

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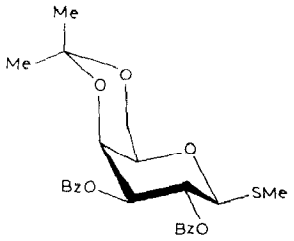

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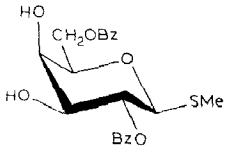

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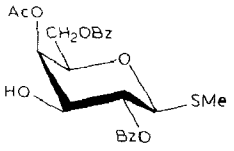

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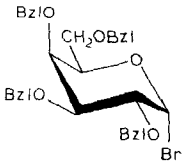

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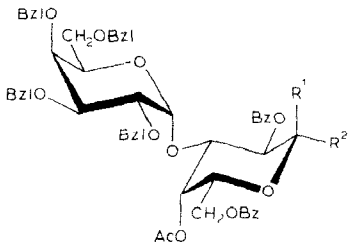
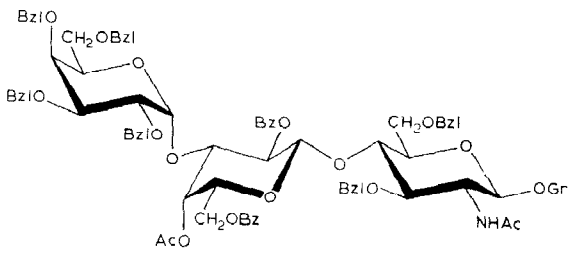


8 R^1 = H, R^2 = SMe

9 R^1 = Br, R^2 = H



10

acetal)] and **4** [δ 18.6, 29.1 (methyl carbons), and 98.9 (acetal carbon, 6-membered cyclic isopropylidene acetal)][8] established the identity of each compound. Acid-catalysed hydrolysis of the major acetal **3** to yield **5** was followed by conversion of the product into the 3,4-linked cyclic methyl orthoester derivative, which, without isolation, was treated under acid conditions to afford **6** regioselectively[5]. The overall yield of **6** from methyl 1-thio-β-D-galactopyranoside was 61%. Halide-assisted glycosylation[9] of **6** with tetra-*O*-benzyl-D-galactopyranosyl bromide then gave 72% of **8**. This product was converted by treatment with bromine[10] into the glycosyl bromide **9** which was used in silver triflate-mediated condensation[11] with **2**, to yield 73% of the protected trisaccharide **10**. Catalytic hydrogenation of **10** followed by treatment with sodium methoxide in methanol afforded 75% of the title compound.

EXPERIMENTAL

The general methods were the same as those reported elsewhere[12]

8-Methoxycarbonyloct-1-yl 2-acetamido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside (**1**). — Benzyl bromide (0.7 mL), barium oxide (2.0 g), and barium hydroxide octahydrate (0.6 g) were added at room temperature to a stirred solution of 8-methoxycarbonyloct-1-yl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[6] (1.4 g) in dry *N,N*-dimethylformamide (10 mL). After 3 h, the mixture was diluted with *N,N*-dimethylformamide (10 mL) and filtered, insoluble material was washed with the same solvent (10 mL) and dichloromethane (10 mL), and the combined filtrate and washings were concentrated. Column chromatography (toluene–ethyl acetate, 3:1) of the residue on silica gel yielded **1** (1.3 g, 79%), which crystallised from ethanol; m.p. 187–188°, $[\alpha]_D$ −2° (*c* 1, chloroform). ^{13}C-N.m.r. data (25 MHz, $CDCl_3$, Me_4Si): δ 23.4 (CH_3CONH), 24.8, 25.7, 29.0, 29.4 [$(CH_2)_6$, overlap], 34.0 (CH_2CO), 51.4 (OMe), 57.9 (C-2), 65.9, 68.8, 70.0, 74.4, 76.6, 82.7 (C-3,4,5,6, $PhCH_2$, CH_2O, methoxyoctyl residue), 100.4, 101.1 (C-1 and PhCH), 126.0, 127.7, 128.2, 128.3, 128.9, 137.4, 138.5 (aromatic C, overlap), 170.3, and 174.0 (carbonyl C).

Anal. Calc. for $C_{32}H_{43}NO_8$: C, 67.5; H, 7.61; N, 2.46. Found: C, 67.1; H, 7.60; N, 2.13.

8-Methoxycarbonyloct-1-yl 2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**2**). — Anhydrous aluminium chloride (700 mg) was added at room temperature with stirring to a solution of **1** (600 mg) and borane–trimethylamine (400 mg) in tetrahydrofuran–1,2-dimethoxyethane (1:1, 10 mL). After being stirred overnight, the mixture was poured with stirring into ice-cold 2M sulfuric acid. Dichloromethane was added and the two phases were separated. The organic phase was washed with aqueous sodium hydrogensulfate, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (toluene–ethyl acetate, 3:2) on silica gel yielded **2** (380 mg, 63%) which crystallised from ethyl acetate–hexane; m.p. 108–109°, $[\alpha]_D$ −8° (*c* 1, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 23.4 (CH_3CONH), 24.9, 25.8, 29.0, 29.1, 29.5 [$(CH_2)_6$, overlap], 34.0 (CH_2CO), 51.4 (OMe), 56.2

(C-2), 69.5, 70.5, 72.5, 73.5, 73.9, 74.5, 81.1 (C-3,4,5,6, 2 Ph*C*H_2, CH_2O methoxyoctyl), 100.3 (C-1), 127.6, 128.0, 128.4, 138.0, 138.7 (aromatic C), 170.7, and 174.0 (carbonyl C).

Anal. Calc. for $C_{32}H_{45}NO_8$: C, 67.2, H, 7.93; N, 2.45. Found: C, 66.9; H, 7.96; N, 2.30.

*Methyl 2,6-di-O-benzoyl-3,4-O-isopropylidene-1-thio-β-*D*-galactopyranoside* (**3**) *and methyl 2,3-di-O-benzoyl-4,6-O-isopropylidene-1-thio-β-*D*-galactopyranoside* (**4**). — Methyl 1-thio-β-D-galactopyranoside[13,14] (4.0 g) and toluene-*p*-sulfonic acid monohydrate (150 mg) were stirred with acetone (250 mL) at room temperature for 3 h. T.l.c. (chloroform–methanol, 5:1) then revealed two major products, but the separation was poor. The mixture was neutralised with pyridine, unreacted material (~200 mg) was removed, the filtrate was concentrated, and the residue was treated with benzoyl chloride (7 mL) and pyridine (25 mL) for 2 h at room temperature. The usual work-up and column chromatography (toluene–ethyl acetate, 19:1) on silica gel gave **3** (faster-moving product, 6.3 g, 72%) which, after crystallisation from methanol, had m.p. 90–91°, $[\alpha]_D$ +62° (*c* 0.85, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 11.8 (SMe), 26.4, 27.8 [$(CH_3)_2C$], 63.9 (C-6), 71.6, 73.8, 74.6, 77.2 (C-2,3,4,5), 82.7 (C-1), 110.8 [$(CH_3)_2C$], 128.4, 129.7, 129.9, 133.2 (aromatic C, overlap), 165.4, and 166.3 (carbonyl C).

Anal. Calc. for $C_{24}H_{26}O_7S$: C, 62.9; H, 5.72; S, 7.00. Found: C, 62.0; H, 5.63; S, 7.00.

The slower-moving product **4** (1.7 g, 19%) crystallised from ethanol; m.p. 129–130°, $[\alpha]_D$ +97° (*c* 0.8, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 10.3 (SMe), 18.6, 29.1 [$(CH_3)_2C$], 62.8 (C-6), 66.6, 66.9, 69.7, 73.8 (C-2,3,4,5), 82.0 (C-1), 98.9 [$(CH_3)_2C$], 128.3, 129.3, 129.7, 133.1, 133.2 (aromatic C, overlap), 165.4, and 166.0 (carbonyl C).

Anal. Calc. for $C_{24}H_{26}O_7S$: C, 62.9; H, 5.72; S, 7.00. Found: C, 62.7; H, 5.71; S, 6.95.

*Methyl 2,6-di-O-benzoyl-1-thio-β-*D*-galactopyranoside* (**5**). — Compound **3** (5.6 g) was stirred and dissolved in aqueous 90% trifluoroacetic acid (10 mL) for 15 min. The solution was concentrated, and toluene was thrice distilled from the residue which was then crystallised from ethyl acetate–hexane to give **5** (4.6 g, 90%), m.p. 128°, $[\alpha]_D$ +9° (*c* 0.7, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 11.6 (SMe), 63.6 (C-6), 69.2, 71.2, 73.3, 76.5 (C-2,3,4,5), 83.3 (C-1), 128.4, 129.2, 129.7, 130.0, 133.3 (aromatic C, overlap), and 166.6 (2 carbonyl C).

Anal. Calc. for $C_{21}H_{22}O_7S$: C, 60.3; H, 5.30; S, 7.65. Found: C, 60.2; H, 5.29; S, 7.48.

*Methyl 4-O-acetyl-2,6-di-O-benzoyl-1-thio-β-*D*-galactopyranoside* (**6**). — A mixture of **5** (3.5 g), toluene-*p*-sulfonic acid monohydrate (100 mg), and trimethyl orthoacetate (2.1 mL) was stirred and dissolved in acetonitrile (35 mL) for 5 min. After concentration, the residue was dissolved in acetonitrile (20 mL), and the solution was treated with aqueous 90% trifluoroacetic acid (1 mL) for 5 min and then concentrated. A solution of the residue in dichloromethane was washed with

aqueous sodium hydrogencarbonate, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (toluene–ethyl acetate, 4:1) of the residue on silica gel gave **6** (3.6 g, 94%), $[\alpha]_D$ −8° (*c* 0.7, chloroform). N.m.r. data ($CDCl_3$): ^{13}C, δ 11.8 (SMe), 20.8 (CH_3CO), 62.4 (C-6), 70.2, 71.0, 71.9, 74.9 (C-2,3,4,5), 83.6 (C-1), 128.0, 128.5, 129.3, 129.7, 129.9, 133.3 (aromatic C, overlap), 166.1, 166.3 (2 Ph*C*O), and 171.1 (CH_3CO); ^1H (100 MHz), δ 2.3 (s, 6 H, SMe, OAc).

*Methyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galacto-pyranosyl)-1-thio-β-*D*-galactopyranoside* (**8**). — Methyl 1-thio-β-D-galacto-pyranoside[13,14] (4.0 g) was benzylated with sodium hydride and benzyl bromide in *N,N*-dimethylformamide to yield, after column chromatography on silica gel, methyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (8.0 g, 74%), $[\alpha]_D$ +2° (*c* 1.4, chloroform). A solution of this product (2.5 g) in dichloromethane (30 mL) was treated with bromine (0.25 mL) at 0° for 10 min. The mixture was concentrated and the glycosyl bromide was used directly without purification. A mixture of **6** (1.7 g), the above bromide, tetraethylammonium bromide (1.0 g), crushed molecular sieves (4 Å), dichloromethane (20 mL), and *N,N*-dimethylformamide (0.2 mL) was stirred at room temperature for 48 h, diluted with dichloromethane, and filtered. The solution was washed with aqueous sodium hydrogencarbonate, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (toluene–ethyl acetate, 20:1) of the residue on silica gel gave **8** (2.6 g, 72%), $[\alpha]_D$ +70° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^{13}C, δ 11.5 (SMe), 20.5 (CH_3CO), 62.2, 65.2 (C-6,6′), 68.6, 69.5, 70.0, 72.6, 73.2, 73.3, 73.4, 74.4, 74.8, 75.7, 78.8 (C-2,3,4,5, C-2′,3′,4′,5′, 4 PhCH_2, one overlap), 83.6 (C-1), 93.4 (C-1′), 127.5, 127.6, 128.1, 128.4, 128.9, 129.4, 129.7, 129.8, 133.2, 138.3, 138.4, 138.6 (aromatic C, overlap), 165.0, 165.9 (2 Ph*C*O), and 170.2 (CH_3CO); ^1H (100 MHz), δ 1.9 (s, 3 H, OAc), 2.2 (s, 3 H, SMe), and 5.2 (d, 1 H, $J_{1,2}$ 3 Hz, H-1′).

8-Methoxycarbonyloct-1-yl O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-(1→3)-*O*-(4-*O*-acetyl-2,6-di-*O*-benzoyl-β-*D*-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**10**). — A solution of **8** (600 mg) in dichloromethane (10 mL) was treated with bromine (50 μL) at −10° for 10 min. The mixture was concentrated and the crude glycosyl bromide **9** was used directly without purification. Silver trifluoromethanesulfonate (380 mg) in toluene–nitromethane (1:1, 10 mL) was added to a stirred mixture of **9**, **2** (300 mg), and crushed molecular sieves (4 Å) in the same solvent mixture (10 mL) at −20°. After being stirred at room temperature for 30 min, the mixture was neutralised with triethylamine, diluted with dichloromethane, filtered, and concentrated. Column chromatography (toluene–ethyl acetate, 3:1) of the residue on silica gel gave **10** (580 mg, 73%), $[\alpha]_D$ +30° (*c* 1.2, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): δ 20.4 (CH_3CO), 23.2 (CH_3CONH), 24.9, 25.8, 29.0, 29.3 [$(CH_2)_6$, overlap], 34.0 (CH_2CO), 51.3 (OMe), 53.0 (C-2), 61.7, 64.9, 69.3, 69.8, 71.2, 71.6, 72.7, 73.1, 73.3, 73.5, 74.5, 74.8, 75.5, 77.8, and 78.7 (C-3,4,5,6, C-2′,3′,4′,5′,6′, C-2″,3″,4″,5″,6″, 6 PhCH_2, CH_2O, methoxyoctyl residue, overlap), 93.9 (C-1″), 99.6, 100.4 (C-1,1′), 127.3, 127.6, 127.9, 128.1, 128.3, 129.2, 129.7, 133.2, 133.4, 138.0,

138.4, 138.6 (aromatic C, overlap) 165.4, 165.8 (2 PhCO), 170.0, 170.1 (2 CH_3CO), and 174.1 (CH_2COOMe).

8-Methoxycarbonyloct-1-yl O-α-D-galactopyranosyl-(1→3)-O-β-D-galactopyranosyl-(1→4)-2-acetamido-2-deoxy-β-D-glucopyranoside. — A solution of **10** (170 mg) in aqueous 90% acetic acid (3 mL) was hydrogenated over 10% Pd/C (0.1 g) in a Parr apparatus overnight. Column chromatography (chloroform–methanol, 9:1) of the product on silica gel afforded a pure product (87 mg, 80%) which was deacylated with sodium methoxide in methanol. After neutralisation with Dowex 50 (H^+) resin, filtration, and concentration, the product was purified by elution from a column of Sephadex G-15 with water to yield the title compound (60 mg, 75%), $[\alpha]_D$ +49° (*c* 0.6, water). N.m.r. data (D_2O, external Me_4Si): ^{13}C, δ 23.6 (CH_3CONH), 25.7, 26.4, 29.6, 29.9 [$(CH_2)_6$, overlap], 35.0 (CH_2CO), 53.3 OMe), 56.4 (C-2), 61.4, 61.6, 61.8 (C-6,6′,6″), 66.2, 69.5, 70.5, 70.9, 71.6, 72.1, 73.8, 76.0, 76.3, 78.6, 80.2 (C-3,4,5, C-2′,3′,4′,5′, C-2″,3″,4″,5″, CH_2O, methoxyoctyl residue), 96.8 (C-1″), 102.3, 104.1 (C-1,1′), 175.3, and 178.5 (carbonyl C); ^1H (400 MHz, D_2O, internal sodium 2,2,3,3-tetradeuterio-3-trimethylsilylpropionate), δ 5.16 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1″), and 4.54 (2 d, 2 H, both $J_{1,2}$ 7.8 Hz, H-1,1′).

Methylation analysis of the title compound (comprising methylation, hydrolysis, reduction of the products to alditols, and acetylation) followed by g.l.c.–m.s. analysis of the resulting mixture of methyl alditol acetates[15] gave the expected result.

ACKNOWLEDGMENTS

We thank Professor I. J. Goldstein (University of Michigan, Medical School) for suggesting this work, Professor B. Lindberg for his interest, and the National Swedish Board for Technical Development and The Swedish Natural Science Research Council for financial support.

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