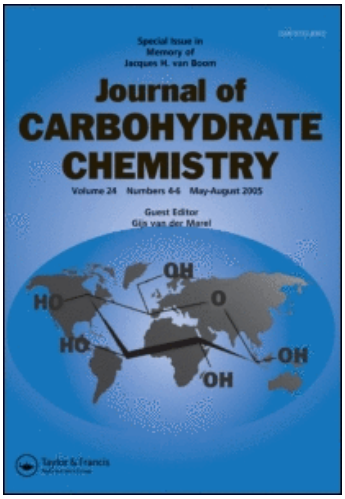

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A CONVENIENT SYNTHESIS OF 2,3-DI-*O*-ACETYL-1,6-ANHYDRO-β-D-GLUCOPYRANOSE*

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ABSTRACT

1,2,3-Tri-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-α- and -β-D-glucopyranose (4α,β) were derived from 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranose (1) in two steps. Compound 1, 1,2,3-tri-*O*-acetyl-β-D-glucopyranose (2), and 4α,β were subjected to the cyclization reaction using Lewis acids ($SnCl_4$ and BF_3-etherate), to give corresponding 1,6-anhydro derivatives.

INTRODUCTION

D. Shapiro et al. have reported that 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (levoglucosan 2,3-diacetate, 6) was an excellent aglycon for the unambiguous synthesis of oligosaccharides involving glycosidation at 4-OH of glucose.[2] During the course of our studies[3] on the unique glycosphingolipids isolated from spermatozoa of a fresh-water bivalve, *Hyriopsis schlegelii*,[4] compound 6 was required for our synthetic strategy. Compound 6 was synthesized from phenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside and phenyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside in three steps respectively by P. A. Seib[5] and D. Shapiro et al.[6] Although 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-

*Synthetic Studies on Oligosaccharide of a Glycolipid from the Spermatozoa of Bivalves, Part V. For Part IV, see ref. 1.

glucopyranose (levoglucosan triacetate, 7) has been formed from 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[7,8,9] and its 6-*O*-trityl ether[8,10,11] on treatment with Lewis acids, levoglucosan 2,3-diacetate (6) has not been obtained by the Lewis acid mediated method.

We report here convenient Lewis acid catalyzed syntheses of levoglucosan 2,3-diacetate (6) starting from readily available 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranose[12] (1).

RESULTS AND DISCUSSION

1,2,3-Tri-*O*-acetyl-β-D-glucopyranose (2) or equivalent 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranose (1) and 1,2,3-tri-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-α- and -β-D-glucopyranose (4α,β) were chosen as the substrates for the Lewis acid catalyzed cyclization reaction.

Compound 4α and 4β were prepared in the following manner. The reductive cleavage of the benzylidene group in 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranose (1) using $NaBH_3CN$-HCl[13] gave the 6-*O*-benzyl ether compounds 3α,β in 79.6% yield with almost complete anomerization. On the other hand, compound 3β was obtained in 59.7% yield by using $NaBH_3CN$-TMSCl[14] in acetonitrile. Compound 3α and 3β were chloroacetylated with chloroacetyl chloride-pyridine in dichloromethane at 0°C to give 1,2,3-tri-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-α- and -β-D-glucopyranose (4α,β) in high yields.

Cyclization of compounds 4α and 4β proceeded smoothly when catalyzed by $SnCl_4$ at room temperature to yield 2,3-di-*O*-acetyl-1,6-anhydro-4-*O*-chloroacetyl-β-D-glucopyranose (5) in 86% and 87.9% yield, respectively.

1 R^1 = OAc, R^2 = H, R^3, R^4 = benzylidene
2 R^1 = OAc, R^2 = H, R^3 = R^4 = H
3α R^1 = H, R^2 = OAc, R^3 = H, R^4 = Bn
3β R^1 = OAc, R^2 = H, R^3 = H, R^4 = Bn
4α R^1 = H, R^2 = OAc, R^3 = ClAc, R^4 = Bn
4β R^1 = OAc, R^2 = H, R^3 = ClAc, R^4 = Bn

5 R = ClAc
6 R = H
7 R = Ac

Bn: benzyl, ClAc: chloroacetyl

Compound 5 was dechloroacetylated by the action of $H_2NNH_2 \cdot AcOH$[15] in methanol to give compound 6 in high yield.

Contrary to the case of the reaction of compounds 4α,β, in which 4-OH was chloroacetylated, when 4-OH was protected with acetal or not protected, one step cyclizations of compound 1 and 2 were undertaken catalyzed by $SnCl_4$ and/or BF_3-etherate at room temperature, to give levoglucosan 2,3-diacetate (6) in 36.3% and 23.6% yield, respectively. When compound 1 was treated with $SnCl_4$ at 50°C for 24h, levoglucosan triacetate (7) was obtained in 39.6% yield.

In conclusion, convenient syntheses of levoglucosan 2,3-diacetate (6) were achieved by one-step synthesis in 36% yield and four steps via 1,2,3-tri-O-acetyl-6-O-benzyl-4-O-chloroacetyl-α- and -β-D-glucopyranose (4α,β) in 59.7% yield from 1,2,3-tri-O-acetyl-4,6-O-benzylidene-β-D-glucopyranose (1), which was readily available from D-glucose in two steps.

EXPERIMENTAL

General Procedures. Melting points were determined with a Yanagimoto microapparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. ^1H-NMR spectra were recorded at 100MHz with a JEOL FX-100 spectrometer. TLC was conducted on precoated silica gel plates (Merck 60F-254), and the detection of compounds was achieved by quenching of UV fluorescence and with 10% H_2SO_4 solution. Column chromatography was carried out on silica gel (Merck Kieselgel 60). 1,2-Dichloroethane was distilled over P_2O_5. $SnCl_4$ and BF_3-etherate were distilled from CaH_2, prior to use.

Materials. 1,2,3-Tri-O-acetyl-4,6-O-benzylidene-β-D-glucopyranose (1) and 1,2,3-tri-O-acetyl-β-D-glucopyranose (2) were obtained by the procedure of L. Zervas.[12]

1,2,3-Tri-O-acetyl-6-O-benzyl-α- and -β-D-glucopyranose (3α,β). Method (A): To a mixture of benzylidene acetal 1 (2 g, 5.07 mmol) and $NaBH_3CN$ (2.4 g, 38.2 mmol) in dry tetrahydrofuran (60 mL) containing powdered molecular sieves 3Å (8 g), HCl in ether was added until the mixture became acidic. After 3h at room temperature, the mixture was filtered through a Celite pad, extracted with chloroform, washed with saturated $NaHCO_3$ soln, dried over Na_2SO_4, filtered, and concentrated *in vacuo*, to give a syrup. Chromatography of the residue on a column of silica gel with 3:1 = hexane-ethyl acetate gave a mixture of compounds 3α,β (1.6 g, 79.6%, α:β = 14:1), from which 3α (1 g) was crystallized using ethyl acetate-hexane.

Method (B): To a mixture of benzylidene acetal 1 (1.03 g, 2.61 mmol) and $NaBH_3CN$ (0.98 g, 15.6 mmol) in dry acetonitrile (40 mL) containing powdered molecular sieves 3Å (4 g) was added TMSCl (2 mL, 15.8 mmol) in acetonitrile (2 mL). After stirring for 80h at room temperature, the reaction mixture was worked up according to method (A), giving compound 3β (617 mg, 59.7%) and 3α (60 mg); 3α: $[\alpha]_D^{20}$ +52.3°(*c* 1.6 chloroform); mp 72-74°C; TLC (3:2 hexane-ethyl acetate), Rf 0.33; ^{1}H-NMR data ($CDCl_3$): δ 7.26 (s, 5H, phenyl), 6.25 (d, 1H, $J_{1,2}$ = 3.9Hz, H-1), 5.30 (dd, 1H, $J_{2,3}$ = 10.1, $J_{3,4}$ = 8.6Hz, H-3), 4.99 (dd, 1H, H-2), 4.55 (s, 2H, benzyl methylene), 4.16-3.30 (m, 4H, H-4, H-5, H-6a, and H-6b), 3.19 (broad d, 1H, $J_{4,OH}$ = 4.1Hz, OH), 2.12, 2.06, and 1.97 (each s, 9H, 3xOAc): 3β: $[\alpha]_D^{20}$ -31.4°(c 0.5 chloroform); TLC (3:2 hexane-ethyl acetate), Rf 0.37; ^{1}H-NMR data ($CDCl_3$): δ 7.33 (s, 5H, phenyl), 5.68 (d with virtual coupling,[16] 1H, $J_{1,2}$ = 8.0Hz, H-1), 5.20-4.93 (m, 2H, H-2 and H-3), 4.60 and 4.50 (each d, 2H, J_{gem} = 12.1Hz, benzyl methylene), 3.95-3.50 (m, 4H, H-4, H-5, H-6a, and H-6b), 2.95 (broad s, 1H, OH), 2.09 (s, 6H, 2xOAc), and 2.02 (s, 3H, OAc).

Anal. Calcd for $C_{19}H_{24}O_9$ (396.39): C, 57.57; H, 6.10. 3α Found: C, 57.12; H, 5.78. 3β Found: C, 57.34; H, 6.42.

1,2,3-Tri-O-acetyl-6-O-benzyl-4-O-chloroacetyl-α- and -β-D-glucopyranose (4α,β). Dichloromethane (12 mL), pyridine (0.68 mL, 8.4 mmol), and chloroacetyl chloride (0.42 mL, 5.3 mmol) were successively added to the compound 3α (1.1 g, 2.78 mmol) under reduced pressure at 0°C. The mixture was stirred for 3h, then extracted with chloroform. The extract was washed with N HCl soln and saturated $NaHCO_3$ soln, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting syrup was chromatographed on a column of silica gel with 3:1 = hexane-ethyl acetate to give compound 4α (1.26 g, 95.8%). Compound 4β was obtained, as described for the preparation of 4α, in 91% yield; 4α: $[\alpha]_D^{20}$ +107.4°(*c* 1.1 chloroform); TLC (5:1 benzene-acetone), Rf 0.74; ^{1}H-NMR data ($CDCl_3$): δ 7.32 (s, 5H, phenyl), 6.33 (d, 1H, $J_{1,2}$ = 3.9Hz, H-1), 5.48 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.1 Hz, H-3), 5.27 (t, 1H, $J_{4,5}$ = 9.0Hz, H-4), 5.09 (dd, 1H, H-2), 4.57 and 4.41 (each d, 2H, J_{gem} = 11.6Hz, benzyl methylene), 4.10 (m, 1H, H-5), 3.81 (d, 2H, $ClCH_2$-), 3.57 (m, 2H, H-6a and H-6b), 2.18 (s, 3H, OAc) and 2.01 (s, 6H, 2xOAc). 4β: $[\alpha]_D^{20}$ +26.5°(c 1.1 chloroform); mp 91-92°; TLC (5:1 benzene-acetone), Rf 0.74; ^{1}H-NMR data ($CDCl_3$): δ 7.32 (s, 5H, phenyl), 5.73 (d with virtual coupling, 1H, $J_{1,2}$ = 7.9Hz, H-1), 5.45-5.02 (m, 3H, H-2, H-3, and H-4), 4.58 and 4.40 (each d, 2H, J_{gem} = 12.0Hz, benzyl methylene), 3.82 and 3.78 (each d, 2H, J_{gem} = 14.5Hz, $ClCH_2$-), 3.80 (m, 1H, H-5), 3.59 (m, 2H, H-6a and H-6b), 2.11, 2.02, and 2.01 (each s, 9H, 3xOAc).

Anal. Calcd for $C_{21}H_{25}O_{10}Cl$ (472.88): C, 53.34; H, 5.33. 4α Found: C, 52.97; H, 4.97. 4β Found: C, 53.26; H, 5.57.

2,3-Di-O-acetyl-1,6-anhydro-4-O-chloroacetyl-β-D-glucopyranose (5). Method (A): To a stirred solution of compound 4β (270 mg, 0.57 mmol) in 1,2-dichloroethane (5 mL) at 0°C under an inert atmosphere was added $SnCl_4$ (0.2 mL, 1.7 mmol). The mixture was stirred at room temperature for 6h, then extracted with chloroform. The extract was washed with water, and then dried (Na_2SO_4). Evaporation of the solvent gave a syrup, which was chromatographed on a column of silica gel using 3:1 hexane-ethyl acetate as eluent yielding 5 (162 mg, 87.9%)

Method (B): α-Acetate 4α was also treated with $SnCl_4$ to yield 5 in 86% yield. $[\alpha]_D^{20}$ -53.4°(*c* 0.8 chloroform); TLC (5:1 benzene-acetone), Rf 0.54; ^{1}H-NMR data ($CDCl_3$): δ 5.46 (broad s, 1H, H-1), 4.86 (broad s, 1H, H-2), 4.70 (broad s, 1H, H-4), 4.61 (broad s, 2H, H-3 and H-5), 4.17 (s, 2H, $ClCH_2$-), 4.11 (d, 1H, $J_{6a,6b}$ = 7.9Hz, H-6a), 3.83 (dd, 1H, $J_{5,6b}$ = 5.9Hz, H-6b), 2.15 and 2.12 (each s, 6H, 2xOAc).

Anal. Calcd for $C_{12}H_{15}O_8Cl$ (322.70): C, 42.66; H, 4.69. Found: C, 42.28; H, 4.33.

2,3-Di-O-acetyl-1,6-anhydro-β-D-glucopyranose (6). Method (A): $H_2NNH_2 \cdot AcOH$ (20 mg) was added to the solution of compound 5 (103 mg, 0.32 mmol) in methanol (5 mL). After stirring for 1h at room temperature, the solution was extracted with chloroform. The organic layer was washed with water and then dried (Na_2SO_4). Evaporation of the solvent gave a syrup that was chromatographed on silica gel. Elution with 20:1 benzene-acetone provided compound 6 (71.7 mg, 91%).

Method (B): To a stirred solution of compound 1 (159.4 mg, 0.4 mmol) in 1,2-dichloroethane (4 mL) under an inert atmosphere was added $SnCl_4$ (0.3 mL, 2.56 mmol). The mixture was stirred at room temperature for 12h, then extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated, to leave a syrupy residue. The residue was chromatographed as mentioned for method (A), to give 6 in a yield of 36.3%.

Method (C): To a stirred solution of compound 2 (34.3 mg, 0.11 mmol) in 1,2-dichloroethane (1.5 mL) at 0°C under an inert atmosphere was added BF_3-etherate (31 μL, 0.28 mmol). The mixture was stirred at room temperature for 8h, then extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated, to give a syrupy residue. The residue was purified by chromatography as mentioned for method (A), to give 6 in 23.6% yield. $[\alpha]_D^{20}$ -44.5°(*c* 1.2 chloroform) {lit.[5] $[\alpha]_D^{27}$ -45°(*c* 4.9), lit.[6] $[\alpha]_D^{22}$ -44.6°(*c* 3.5)}; TLC (1:1 benzene-ethyl acetate), Rf 0.27 (lit.[6] Rf 0.28); ^{1}H-NMR data ($CDCl_3$): δ 5.44 (broad s, 1H, H-1), 4.80 (broad s, 1H, H-2), 4.60 (broad s, 2H, H-3 and H-5), 4.09 (d, 1H, $J_{6a,6b}$ = 7.9Hz, H-6a), 3.81 (dd,

1H, $J_{5,6b}$ = 5.8Hz, H-6b), 3.56 (broad d, 1H, $J_{4,OH}$ = 8.0Hz, H-4), 3.02 (broad d, 1H, OH), 2.15 and 2.12 (each s, 6H, 2xOAc).

Anal. Calcd for $C_{10}H_{14}O_7$ (246.22): C, 48.78; H, 5.73. Found: C, 48.70; H, 5.79.

2,3,4-Tri-O-acetyl-1,6-anhydro-β-D-glucopyranose (7). To a stirred solution of compound 1 (382 mg, 0.97 mmol) in 1,2-dichloroethane (4 mL), $SnCl_4$ (0.6 mL, 5.12 mmol) was added under an inert atmosphere. The mixture was stirred at 50°C for 24h, then extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. The residue was chromatographed using 3:1 hexane-ethyl acetate as the eluent to give 7 (95 mg, 39.6%), which was crystallized from ethanol: mp 110-112°C(lit.[11,17,18] 108-109°C, lit.[19] 107-109°C); $[\alpha]_D^{22}$ -60°(*c* 1.73 chloroform) (lit.[19] $[\alpha]_D^{22}$ -63°(*c* 0.46 chloroform)).

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