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Note

A ready route to a functionalized anhydro derivative of 1,6-anhydro-β-D-glucopyranose (levoglucosan)*

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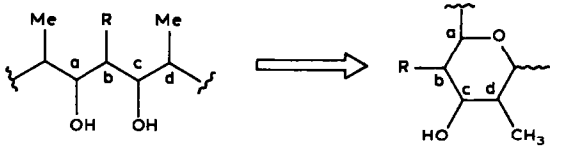
An area of interest in several laboratories[1], including our own[2], is the use of carbohydrate precursors for the preparation of polypropionate-derived natural products. Regardless of the conceptual approach employed in this pursuit, it is almost inevitable that one of the hydroxyl groups of the target (for example, **I**) would be made to coincide with the ring oxygen atom (namely, O-5) of a sugar precursor. This, in turn, implies that methyl groups would be located at C-2 and C-4, as in **IIa**. The preparation of the appropriate doubly-branched "chiron"[1b] as a pure diastereomer is highly desirable and is not trivial[3–5]. For our interests, this objective was made more demanding by the fact that, in some of the polypropionate targets[6], the corresponding C-4 residue, R, may be either CH_3 (**Ia**), or CO_2Me (**Ib**). In view of these requirements, a hydroxymethyl group at C-4, as present in the synthon **IIb**, seems logical, as deoxygenation would give **Ia**, while oxidation would give **Ib**.



I
a R = CH_3
b R = CO_2Me

II
a R = CH_3
b R = CH_2OH

A further complication in our approach is that the C-4 residue is required to be axially oriented in the $^4C_1$(D) conformation[2a]. According to the pioneering work of Černý and Staněk[7], this objective may be met efficiently by taking advantage of

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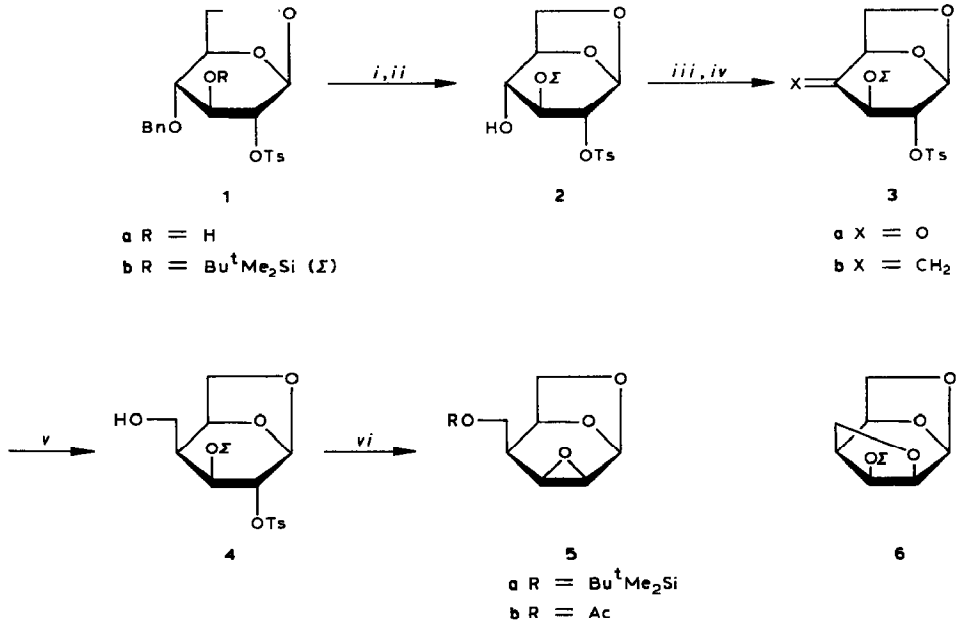

(i) Bu^tMe_2SiCl, imidazole (97%); *(ii)* H_2, Pd/C, EtOH; *(iii)* pyridinium chlorochromate (88%); *(iv)* Ph_3PCH_3Br—BuLi—THF (75%); *(v)* B_2H_6, H_2O_2—NaOH 0° (78%); *(vi)* NaH—THF (95%).

the facial differentiation offered by the 1,6-anhydrohexopyranose skeleton. In the course of our studies based on this approach, we have prepared a valuable dianhydro derivative, **5**, and we describe this result in this manuscript.

Additions to trigonal C-4 centers of 1,6-anhydropyranoses occur predominantly from the α-face and on this basis we decided to hydroborate the corresponding exocyclic methylene precursor, 1,6-anhydro-3-*O*-*tert*-butyldimethylsilyl-4-deoxy-4-*C*-methylene-2-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranose (**3b**). This material was prepared, as outlined in the Scheme, beginning with 1,6-anhydro-4-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**1a**). The silylated derivative **1b** of the latter was hydrogenolyzed, and the resulting alcohol **2** was oxidized to give 1,6-anhydro-3-*O*-*tert*-butyldimethylsilyl-2-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranos-4-ulose (**3a**). Standard reaction with methylene triphenylphosphorane afforded the desired alkene, **3b**, in 75% yield.

In keeping with expectations, hydroboration occurred with complete stereoselectivity to give the desired hydroxymethyl compound, 1,6-anhydro-3-*O*-*tert*-butyldimethylsilyl-4-deoxy-4-*C*-(hydroxymethyl)-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (**4**). Our next objective was to protect the primary alcohol of **4**; however, when **4** was treated with sodium hydride, an immediate reaction occurred and a compound was isolated in virtually quantitative yield whose elemental analysis was consistent with either of the dianhydro structures **5a** or **6**. In order to

differentiate these, the silyl group was removed and the product converted into the acetate **5b** by standard procedures*. This transformation caused *two* protons to be shifted to lower field (from 3.61 and 4.10, and to 4.16 and 4.35 p.p.m., respectively) in the 300 MHz ^{1}H-n.m.r. spectrum. This observation is consistent only with structure **5**.

The extreme case of this silyl migration from the secondary to the primary hydroxyl group of **4** is fortunate. Interestingly, the separation between H-4*exo* and H-4*endo* (1.11 p.p.m.) in **5a** was much greater than that of the pair of C-6 protons.

EXPERIMENTAL

General. — Melting points were determined in capillary tubes, using a Büchi Model 510 apparatus and are uncorrected. Solutions were evaporated *in vacuo*. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). Optical rotations were determined at the sodium D line using a Perkin–Elmer 241 polarimeter. The progress of all reactions was monitored by t.l.c., performed on silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator (Merck, 5539), with detection by u.v. (254 nm), by charring with H_2SO_4, spray, or by charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aq. H_2SO_4 (500 mL)[9]. Flash chromatography[10] was effected on silica gel (Merck 70–230 mesh ASTM or 230–400 mesh ASTM) ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si), unless otherwise stated, with an IBM NR-80 or a Bruker WM-250 spectrometer. Coupling constants were measured directly from the spectra, or calculated from the peak listing. I.r. spectra for films or solutions were determined by using a Perkin–Elmer 298 spectrometer.

*1,6-Anhydro-4-*O*-benzyl-3-*O*-tert-butyldimethylsilyl-2-*O*-p-tolylsulfonyl-β-*D*-glucopyranose* (**1b**). — To a solution of 1,6-anhydro-4-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose[8] (**1a**, 0.4 g, 0.98 mmol) and imidazole (0.1 g, 1.48 mmol) in dimethylformamide (15 mL) was added *tert*-butylchlorodimethylsilane (0.29 g, 1.97 mmol) under an argon atmosphere. After 12 h at 50°, the mixture was diluted with Et_2O and washed with solutions of $NaHCO_3$ and NaCl. After drying (Na_2SO_4), the solution was evaporated and the residue was purified by flash chromatography on silica gel to give 0.5 g (97%) of compound **1b**; R_F 0.35 (1:4 EtOAc–hexane); $[\alpha]_D^{23}$ −30.2° (*c* 0.41, $CHCl_3$); ^{1}H-n.m.r. (80 MHz): δ 0.10 (s, 6 H, $SiMe_2$), 0.8 (s, 9 H, Bu^t), 2.42 (s, 3 H, SO_2PhMe), 3.22–4.20 (m, 6 H, H-2,3,4,5,6*endo*,6*exo*), 4.62 (s, 2 H, OCH_2Ph), 5.3 (s, 1 H, H-1), and 7.25–7.90 (m, 9 H, OCH_2Ph, OSO_2PhMe).

Anal. Calc. for $C_{26}H_{36}O_7SSi$: C, 59.96; H, 6.91. Found: C, 59.91; H, 6.80.

*1,6-Anhydro-3-*O*-tert-butyldimethylsilyl-2-*O*-p-tolylsulfonyl-β-*D*-glucopyranose* (**2**). — A solution of **1b** (0.3 g, 0.69 mmol) in EtOH (10 mL) was hydro-

*This differentiation to establish structure **5** was suggested by a referee.

genolyzed over 10% Pd–C (0.085 g). After 7 h at 50°, the catalyst was removed by filtration and the filtrate was evaporated. Flash chromatography afforded 0.24 g (96%) of the alcohol **2** as an oil, R_F 0.16 (1:4 EtOAc–hexane); $[\alpha]_D^{23}$ −41.6° (*c* 0.1, $CHCl_3$); ^{1}H-n.m.r. (80 MHz): δ 0.08 (s, 6 H, $SiMe_2$), 0.92 (s, 9 H, Bu^t), 2.45 (s, 3 H, SO_2PhMe), 3.45–4.72 (m, 6 H, H-2,3,4,5,6*endo*,6*exo*), 5.35 (s, 1 H, H-1), 7.42, and 7.84 (AB, 2 d, *J* 7 Hz, SO_2PhMe).

Anal. Calc. for $C_{19}H_{30}O_7SSi$: C, 52.99; H, 6.97. Found: C, 52.83; H, 7.99.

*1,6-Anhydro-3-*O-tert-*butyldimethylsilyl-2-*O-p-*tolylsulfonyl-β-*D-xylo-*hexopyranos-4-ulose* (**3a**). — To a solution of alcohol **2** (0.3 g, 0.69 mmol) and 0.3 g of powdered molecular sieves (4Å) in dry CH_2Cl_2 at room temperature was added 0.45 g of pyridinium chlorochromate (2.1 mmol). After 2 h, the solution was diluted with Et_2O, filtered over Florisil, and evaporated. Flash chromatography afforded 0.26 g (88%) of ketone **3a**; R_F 0.66 (3:7 EtOAc–hexane); $[\alpha]_D^{23}$ +35.8° (*c* 1.1, $CHCl_3$); ν_{max} 1740 cm^{-1}; ^{1}H-n.m.r. (80 MHz): δ 0.25 (s, 3 H, SiMe), 0.05 (s, 3 H, SiMe), 0.82 (s, 9 H, Bu^t), 2.42 (s, 3 H, SO_2PhMe), 3.70 (dd, 1 H, *J* 6 and 4 Hz, H-6*exo*), 3.98 (d, 1 H, *J* 6 Hz, H-6*endo*), 4.2–4.74 (m, 3 H, H-2,3,5), 5.64 (s, 1 H, H-1), 7.30, and 7.80 (AB, 2 d, *J* 7 Hz, SO_2PhMe).

*1,6-Anhydro-3-*O-tert-*butyldimethylsilyl-4-deoxy-*C-*methylene-2-*O-p-*tolylsulfonyl-β-*D-xylo-*hexopyranose* (**3b**). — To a solution of 0.5 g (1.4 mmol) of methyltriphenylphosphonium bromide in dry tetrahydrofuran (20 mL) was added 0.6 mL of butyllithium (2.3M in hexane) at room temperature under an argon atmosphere. After 1 h, a solution of ketone **3a** (0.2 g, 0.46 mmol) in dry tetrahydrofuran (5 mL) was added to the reaction flask dropwise at 0°. After stirring for 3 h at room temperature, the solution was diluted with saturated aq. NH_4Cl and processed conventionally. Flash chromatography gave 0.15 g (75%) of **3b**; R_F 0.54 (1:4 EtOAc–hexane); $[\alpha]_D^{23}$ +68° (*c* 1.3, $CHCl_3$); ^{1}H-n.m.r. (80 MHz): δ 0.03 (s, 6 H, $SiMe_2$), 0.82 (s, 9 H, Bu^t), 2.43 (s, 3 H, SO_2PhMe), 3.72 (dd, 1 H, *J* 6 and 4 Hz, H-6*exo*), 4.02 (d, 1 H, *J* 6 Hz, H-6*endo*), 4.22 (m, 2 H, H-2,3), 4.8 (d, 1 H, *J* 4 Hz, H-5), 5.12 (br s, 2 H, H-4,4′), 5.26 (br s, 1 H, H-1), 7.35, and 7.80 (AB, 2 d, *J* 7 Hz, SO_2PhMe).

Anal. Calc. for $C_{20}H_{30}O_6SSi$: C, 56.30; H, 7.03. Found: C, 56.28; H, 6.99.

*1,6-Anhydro-3-*O-tert-*butyldimethylsilyl-4-deoxy-4-*C-*(hydroxymethyl)-2-*O-p-*tolylsulfonyl-β-*D-*galactopyranose* (**4**). — To a solution of diborane (0.7 mL, M in tetrahydrofuran), which had been cooled to 0°, was added a solution of **3b** (0.1 g, 0.23 mmol) in dry tetrahydrofuran (3 mL) dropwise during 20 min under an argon atmosphere. After 5 h, 1.0 mL of 3M aq. NaOH was added slowly at 0°, followed by 1.0 mL of 30% H_2O_2. After 1 h at room temperature, the aqueous phase was saturated with NaCl. The tetrahydrofuran phase was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated. The excess of water was removed azeotropically with PhMe, after which flash chromatography afforded the title compound **4** (0.081 g, 78%) as an amorphous white solid; R_F 0.42 (3:7 EtOAc–hexane); m.p. 112°, $[\alpha]_D^{23}$ −43.5° (*c* 0.6, $CHCl_3$); ^{1}H-n.m.r. (250 MHz): δ 0.02 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.86

(s, 9 H, Bu^t), 1.58 (s, 1 H, OH), 2.34 (m, 1 H, H-4), 2.48 (s, 3 H, SO_2PhMe), 3.61 (dd, *J* 6.5 and 6 Hz, H-6*exo*), 3.65–3.72 (m, 2 H, H-3,4'), 4.10 (m, 1 H, H-4'), 4.14 (t, 1 H, *J* 1.5 Hz, H-2), 4.25 (d, 1 H, *J* 6.5 Hz, H-6*endo*), 4.53 (t, 1 H, *J* 6 Hz, H-5), 5.15 (s, 1 H, *J* 1.5 Hz, H-1), 7.33, and 7.72 (AB, 2 d, *J* 7.5 Hz, SO_2PhMe).

Anal. Calc. for $C_{20}H_{32}O_7SSi$: C, 54.02; H, 7.19. Found: C, 54.00; H, 7.08.

*1,6:2,3-Dianhydro-4-*C*-*tert*-*butyldimethylsiloxymethyl)-4-deoxy-β-*D*-talopyranose* (**5a**). — To a suspension of 0.023 g (0.56 mmol) of 60% NaH dispersion (prewashed with dry hexane) in dry tetrahydrofuran (3 mL) was added 0.05 g of **4** (0.11 mmol) in 1 mL of tetrahydrofuran. After 4 h, the solution was diluted with Et_2O and procesed conventionally. Flash chromatography gave 0.029 g (95%) of **5**; R_F 0.74 (3:7 EtOAc–hexane); $[\alpha]_D^{23}$ −165° (*c* 0.15, $CHCl_3$); ^{1}H-n.m.r. (250 MHz): δ 0.06 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), 0.88 (s, 9 H, Bu^t), 2.56 (m, 1 H, H-4), 3.13 (t, 1 H, *J* 3 Hz, H-3), 3.42 (t, 1 H, *J* 3 Hz, H-2), 3.55 (t, 1 H, *J* 6.5 Hz, H-6*exo*), 3.67 (t, 1 H, *J* 9 Hz, H-4*exo*), 3.85 (d, 1 H, *J* 6.5 Hz, H-6*endo*), 3.93 (dd, 1 H, *J* 9 and 5 Hz, H-4*endo*), 4.50 (t, 1 H, *J* 6.5 Hz, H-5), and 5.70 (d, 1 H, *J* 3 Hz, H-1).

Anal. Calc. for $C_{13}H_{24}O_4Si$: C, 57.31; H, 8.81. Found: C, 57.28; H, 8.79.

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