Note

The synthesis and reactions of unsaturated sugars. Part III[1]. The action of hydrogen bromide–acetic acid on methyl 4-*O*-benzyl-2,3-dideoxy-6-*O*-trityl-α-D-*erythro*-hex-2-enoside

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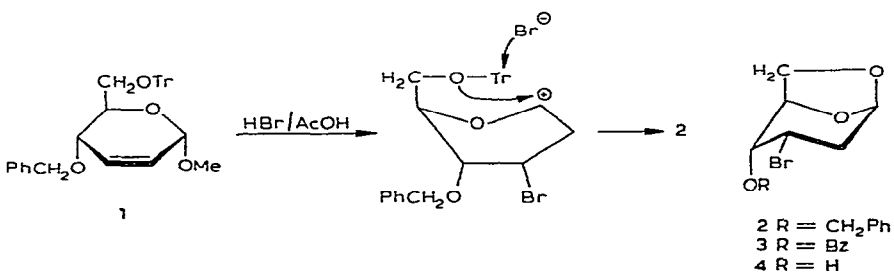
Although the addition reactions of glycals have been studied extensively[2,3] and are now well understood, the related 2,3-dideoxyhex(pent)-2-enosides have not been afforded the same treatment. Horton *et al.*[4] have shown that methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside undergoes *trans* addition when treated with bromine or acetyl hypobromite. We now report another example of *trans* addition to the double bond of a hex-2-enopyranose system.

Treatment of methyl 4-*O*-benzyl-2,3-dideoxy-6-*O*-trityl-α-D-*erythro*-hex-2-enoside[1] (**1**) with hydrogen bromide–glacial acetic acid (at 10°) resulted in a rapid reaction accompanied by the customary precipitation of trityl bromide. A mixture of eight detritylated carbohydrate components was formed, from which a somewhat unstable, crystalline solid was isolated by preparative-layer chromatography. This compound is now considered to be 1,6-anhydro-4-*O*-benzyl-3-bromo-2,3-dideoxy-β-D-*ribo*-hexopyranose (**2**) on the basis of its elemental analysis, high negative optical rotation, and n.m.r. data, and not the *arabino*-hexopyranose as was initially believed[5]. Although the n.m.r. spectrum of this compound was not suitable for first-order analysis, due to the similar chemical shifts for H-3 and H-5 and the complexity of the H_a-2 and H_e-2 resonances, the spectrum did indicate a methylene group at C-2, oxygenated functions at C-4, and, by inference, bromine at C-3. Moreover, spin-decoupling experiments indicated that $J_{1,2a} \simeq J_{1,2e} \simeq 1.0$–1.5 Hz, while $J_{2a,3}$ was large enough (6.0–9.0 Hz) to be consistent with a *trans*-diaxial relationship between H_a-3 and H_a-2.



1

2 R = CH_2Ph
3 R = Bz
4 R = H

Scheme A

The reaction of **2** with neutral potassium permanganate resulted in slow but extensive oxidation of the C-4 benzyl ether substituent to give the 4-benzoate **3**, which also had a high negative optical rotation.

Removal of the benzyl group from **2** by catalytic hydrogenolysis gave 1,6-anhydro-3-bromo-2,3-dideoxy-β-D-*ribo*-hexopyranose (**4**) as an unstable, crystalline solid of high negative optical rotation. Since **4** was obtained by debenzoylation (methanolic sodium methoxide) of **3**, and also gave **3** on benzoylation, **2**, **3**, and **4** must all have the same basic structural skeleton. Since no epoxide formation was observed on alkaline treatment of **3** or **4**, a *trans* relationship between the C-4 and C-3 substituents, and thus the presence of the *arabino* configuration, had to be considered unlikely. Although the n.m.r. analysis of **4** gave no more information than that already obtained for **2**, the 100-MHz spectrum of the benzoate **3** was amenable to a more-detailed analysis. Thus, with the help of double-resonance experiments, all the coupling constants, except $J_{2a,2e}$ (hidden in a deceptively simple signal which nevertheless requires computerised treatment), were calculated. The most important feature was $J_{2a,3}$ 8.0 Hz, confirming the *ribo* configuration (*trans*-diaxial relationship between H-3 and H_a-2) assigned to compounds **2**, **3**, and **4**, and thus the presence of the 1,6-anhydro-3-bromo-2,3-dideoxy-β-D-*ribo*-hexopyranose structural skeleton.

Within the major course of the reaction giving rise to **2** from the alkene **1**, at least three separate stages are likely to be involved: (*i*) loss of the anomeric group, (*ii*) addition, and (*iii*) anhydro-ring closure. The difficulty lies in deciding in which order these take place, since the mixture from which **2** is isolated is complex enough to accommodate a number of possible mechanisms. Due to the high acid-lability of the allylic anomeric substituent[6] and the relative stability of the 2,3-unsaturated glycosyl carbonium ion, we favour a mechanism (Scheme A) in which the anhydro-ring closure occurs last.

Although unusual, the above type of anhydro-ring closure is not unprecedented. Thus, detritylation of 1,2,3-tri-*O*-acetyl-5-*O*-trityl-D-ribose with hydrogen bromide–acetic acid gives rise to a 1,5-anhydro sugar[7].

The oxidation of a benzyl ether group in the presence of neutral potassium permanganate has not previously been observed in carbohydrates, although a similar oxidation with chromium trioxide–pyridine has been reported[8].

EXPERIMENTAL

Melting points were determined with an Electrothermal apparatus and are uncorrected. The specific rotations were measured on a Bellinger and Stanley (Model A) polarimeter with a 0.5-dm tube. The n.m.r. spectra were recorded, with spin decoupling, on Varian A-60 and HA-100 spectrometers, for deuteriochloroform solutions with tetramethylsilane as the internal standard. Thin-layer chromatography (t.l.c.) and preparative-layer chromatography (p.l.c.) were performed as previously described[1] with ethyl acetate–light petroleum (b.p. 40–60°) (1:1).

*1,6-Anhydro-4-*O*-benzyl-3-bromo-2,3-dideoxy-β-*D*-*ribo*-hexopyranose* (**2**). — To a cool (10°) solution of methyl 4-*O*-benzyl-2,3-dideoxy-6-*O*-trityl-α-D-*erythro*-hex-2-

enopyranoside[1] (1.0 g) in glacial acetic acid (10 ml) was added a 45% (w/v) solution (0.5 ml) of hydrogen bromide in glacial acetic acid. Trityl bromide, which immediately separated, was filtered off and washed with cool (10°) glacial acetic acid (2 × 10 ml). The combined washings and the filtrate were diluted with ether (100 ml), and the resulting solution was washed thoroughly with saturated aqueous sodium hydrogen carbonate until neutral and then with water (3 × 50 ml). The dried (Na_2SO_4) ethereal solution was evaporated under diminished pressure at 40° to 5 ml, and the major component (R_F 0.39) was isolated by p.l.c. and recrystallised from ether–light petroleum (b.p. 40–60°) to yield **2** (0.3 g, 50%), m.p. 82° (dec.), $[\alpha]_D^{22}$ −102° (*c* 2.0, chloroform) (Found: C, 52.38; H, 4.96; Br, 26.70. $C_{13}H_{15}BrO_3$ calc.: C, 52.17; H, 5.04; Br, 26.71%); 100-MHz n.m.r. data: τ 2.6 (5-proton multiplet, Ph), 4.55 (1-proton triplet, small coupling, H-1), 5.12 (2-proton singlet, benzylic CH_2), 5.6 (2-proton multiplet, H-3 superimposed on H-5), 6.31 (2-proton triplet, H-6,6'), 6.5 (1-proton quartet, H-4), 7.72 (2-proton multiplet, H_a-2, H_e-2).

*1,6-Anhydro-3-bromo-2,3-dideoxy-β-*D-ribo-*hexopyranose* (**4**). — A suspension of 5% palladium-on-charcoal (2.0 g) in ethanol (50 ml) was treated with hydrogen at room temperature until no further uptake of gas was observed. A solution of 1,6-anhydro-4-*O*-benzyl-3-bromo-2,3-dideoxy-*β*-D-*ribo*-hexopyranose (1.0 g) in ethanol (50 ml) was then added, and the resulting mixture was treated with hydrogen at room temperature until the steady uptake of gas ceased. The catalyst was filtered off, and the filtrate was evaporated under diminished pressure to give a white, crystalline solid. The product was recrystallised from a small volume of ether to yield **4** as long needles (0.66 g, 94.5%), m.p. 75° (dec.), $[\alpha]_D^{23}$ −121.9° (*c* 1.2, chloroform) (Found: C, 34.29; H, 4.21; Br, 38.50. $C_6H_9BrO_3$ calc.: C, 34.47; H, 4.33; Br, 38.23%); 60-MHz n.m.r. data: τ 4.71 (1-proton triplet, small coupling, H-1), 5.61 (2-proton multiplet, H-3 superimposed on H-5), 6.31 (3-proton multiplet, H-4, H-6,6'), 7.05 (broad, 1-proton singlet, OH), 7.8 (2-proton quintet, H_a-2, H_e-2).

*1,6-Anhydro-4-*O*-benzoyl-3-bromo-2,3-dideoxy-β-*D-ribo-*hexopyranose* (**3**). — To a solution of compound **2** (1.0 g) in acetone (25 ml) was added, dropwise and with stirring, in an atmosphere of carbon dioxide, and at room temperature, a 1% solution (25 ml) of potassium permanganate in 10% aqueous acetone. After 24 h, the treatment was repeated. The resulting reaction mixture was filtered and evaporated under diminished pressure. The syrupy product was isolated by p.l.c. on two chromatoplates; yield 0.6 g (57.3%), $[\alpha]_D^{22}$ −199.6° (*c* 4.1, chloroform) (Found: C, 50.01; H, 4.20; Br, 25.4. $C_{13}H_{13}BrO_4$ calc.: C, 49.90; H, 4.16; Br, 25.5%); 100-MHz n.m.r. data: τ 1.85 (2-proton multiplet, Ph *o*-H), 2.5 (3-proton multiplet, Ph *m*- and *p*-H), 4.45 (1-proton triplet, $J_{1,2e}$ 0.7 Hz, $J_{1,2a}$ 1 Hz, H-1), 4.7 (1-proton quartet, $J_{3,4}$ 4 Hz, $J_{4,5}$ 3 Hz, H-4), 5.15 (1-proton quartet, H-5), 5.4 (1-proton octet, $J_{3,2a}$ 8.0 Hz, $J_{3,2e}$ 1.5 Hz, H-3), 6.1 (2-proton octet, $J_{5,6}$ 5.5 Hz, $J_{5,6'}$ 1.0 Hz, $J_{6,6'}$ 9.0 Hz, H-6,6'), 7.6 (2-proton multiplet, $J_{2a,2e}$ estimated at 12–14 Hz, H_a-2, H_e-2).

*Alkaline hydrolysis of 1,6-anhydro-4-*O*-benzoyl-3-bromo-2,3-dideoxy-β-*D-ribo-*hexopyranose* (**3**). — To a solution of compound **3** (0.25 g) in anhydrous methanol (10 ml) was added 2.7M methanolic sodium methoxide (3.0 ml), and the reaction was

allowed to proceed at 30° for 1 h. The reaction mixture was then diluted with chloroform (50 ml), and the resulting solution was washed successively with M sulphuric acid (2 × 25 ml), saturated aqueous sodium hydrogen carbonate (2 × 25 ml), and water (2 × 25 ml). The dry (Na_2SO_4) chloroform solution was evaporated under diminished pressure, and the solid residue was crystallised from ether to give **4** as small needles (0.1 g, 57.5%), m.p. 75° (dec.) alone or in admixture with authentic **4**.

*Benzoylation of 1,6-anhydro-3-bromo-2,3-dideoxy-β-*D-ribo-*hexopyranose* (**4**). — To a cold (0°) solution of compound **4** (0.5 g) in anhydrous pyridine (20 ml) was added benzoyl chloride (0.4 g). The solution was stored at 0° overnight and was then processed in the usual manner to give a pale-yellow syrup. P.l.c. on one chromatoplate then gave **3** (0.5 g, 66.8%), which had the same n.m.r. spectrum and optical rotation as authentic **3**.

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REFERENCES

1 Part II: S. Dimitrijevich and N. F. Taylor, *Carbohyd. Res.*, 11 (1969) 531.
2 R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, 42 (1964) 532.
3 R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, 43 (1965) 1460.
4 E. Albano, D. Horton, and J. H. Lauterbach, *Chem. Commun.*, (1968) 357; *Carbohyd. Res.*, 9 (1969) 149.
5 R. J. Ferrier, *Advan. Carbohyd. Chem.*, 24 (1969) 236 (ref. 93a).
6 E. Albano, D. Horton, and T. Tsuchiya, *Carbohyd. Res.*, 2 (1966) 349.
7 H. Bredereck, H. Kothnig, and E. Berger, *Ber.*, 73 (1940) 2956.
8 S. J. Angyal and K. Jones, *Carbohyd. Res.*, 12 (1970) 147.