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Note

The use of pyridinium chlorochromate for preparation of hexopyranosiduloses without epimerisation

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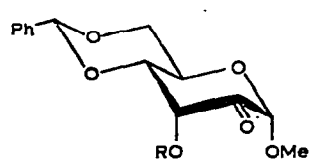
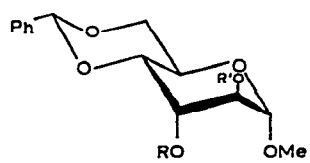
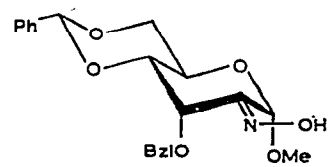
In seeking substantial quantities of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-2-ulose (**1**), methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-altropyranoside (**2**), readily prepared by the reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside with sodium benzyloxide, was considered as a precursor. However, it seemed likely that oxidation of **2** with chromium trioxide–pyridine or methyl sulphoxide-based reagents might result in epimerisation of the product at C-3, to give the more stable α-D-*arabino* arrangement, in which the benzyloxy substituent is equatorial[1]. Ruthenium tetraoxide, which has been used for a similar oxidation without epimerisation[2], is expensive to use in stoichiometric amounts on a large scale, and, in our experience, the catalytic method[3] has proved capricious.



1 R = Bzl
5 R = Me



2 R = Bzl, R' = H
6 R = Me, R' = H
8 R = H, R' = Me



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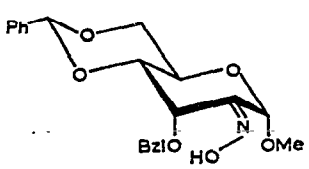

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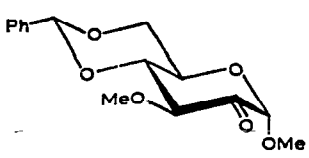

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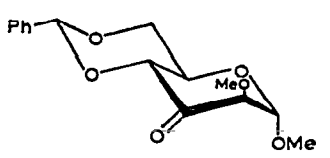

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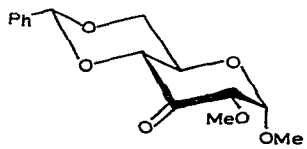
We have found that pyridinium chlorochromate[4], a readily available, economic, and experimentally convenient reagent, can be used for the preparation of **1** and

other potentially epimerisable hexopyranosiduloses in good yield and without any epimerisation occurring.

When the altropyranoside **2** was treated with pyridinium chlorochromate in refluxing dichloromethane, the 2-ulose **1** was isolated crystalline in 70% yield. That epimerisation at C-3 had not occurred was shown by conversion of **1** into a mixture of two oximes[5]. The major product was assigned the (*Z*)-configuration (**3**), on the basis of the appearance of the anomeric-proton resonance at low field (δ 5.78), whilst the minor (*E*)-isomer (**4**) showed a doublet at low field (δ 5.30) ascribed to H-3; the coupling constant (3.0 Hz) clearly indicated that H-3 was equatorial and that the benzyloxy group had remained axial.

Similarly, methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*ribo*-hexopyranosid-2-ulose (**5**) was prepared by oxidation of the altropyranoside[6] **6**. In this case, the lack of epimerisation was shown by treatment of **5** with triethylamine in ethanol which caused clean isomerisation to the known[7] α-D-*arabino* isomer **7**.

Oxidation of a 3-ulose also occurred without epimerisation. Treatment of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-altropyranoside (**8**) with pyridinium chlorochromate in refluxing dichloromethane gave the α-D-*arabino*-hexopyranosid-3-ulose[2] **9** (70%), which could be epimerised with triethylamine in ethanol[8] to the α-D-*ribo* isomer (**10**) having physical and spectroscopic properties as previously reported[8].



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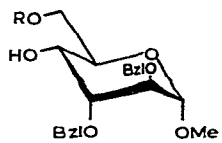
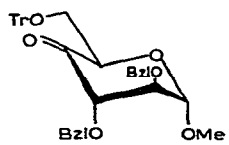


11 R = H

12 R = Tr



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In order to investigate the behaviour of a hexopyranosid-4-ulose, methyl 2,3-di-*O*-benzyl-α-D-altropyranoside[9] (**11**) was converted into its 6-*O*-trityl derivative (**12**) in the usual manner. Oxidation of **12** with pyridinium chlorochromate gave crystalline methyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-D-*arabino*-hexopyranosid-4-ulose (**13**) in 64% yield. The absence of epimerisation was shown by treatment of **13** with sodium borohydride; the precursor **12** was produced in 80% yield, by hydride attack from the sterically least-hindered side, together with a trace of another material.

Our results thus indicate that pyridinium chlorochromate is a useful and convenient oxidant in carbohydrate chemistry, particularly for the formation of ketoses where it is required to maintain α-substituents in the thermodynamically less-favourable orientation.

EXPERIMENTAL

General methods. — Solutions were evaporated under reduced pressure;

solvent extracts were dried with anhydrous sodium sulphate. Optical rotations were measured at room temperature with a Bendix–NPL 143D automatic polarimeter (path-length, 1 cm). N.m.r. spectra (100 MHz) were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a JEOL MH-100 spectrometer. Column chromatography was performed on Silica Gel G (Merck). Melting points are uncorrected.

Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-altropyranoside (**2**). — Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[10] (15 g) was dissolved in a solution prepared from sodium (3 g) in benzyl alcohol (40 ml). The mixture was heated under reflux for 15 min, and was then cooled, diluted with ether (200 ml), filtered, and evaporated, to yield a mobile liquid that was cooled to 0° and dissolved in pyridine (200 ml) and acetic anhydride (200 ml). The mixture was left to stand overnight, and then partitioned between water (500 ml) and dichloromethane (3 × 200 ml). The organic layer was dried and evaporated, and benzyl acetate removed under high vacuum. The resulting solid was treated with sodium methoxide [from methanol (200 ml) and sodium (0.5 g)], and the solution was stirred at room temperature for 20 min. After neutralisation with Amberlite IRC-50(H^+) resin, removal of solvent left a viscous syrup. This was partitioned between water (10 ml) and dichloromethane (200 ml). The dried organic layer was evaporated, to give a solid that was crystallised from chloroform to yield **2** (13.65 g, 65%), m.p. 137–138°, $[\alpha]_D$ +31.7° (*c* 1.3, chloroform); n.m.r. data: δ 5.54 (s, 1 H, PhC*H*), 4.64 (s, 1 H, H-1), and 3.40 (s, 3 H, OMe).

Anal. Calc. for $C_{21}H_{24}O_6$: C, 67.74; H, 6.45. Found: C, 67.39; H, 6.63.

Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-ribo-hexopyranosid-2-ulose (**1**). — Pyridinium chlorochromate (1.84 g, 4 equiv.) was added to a stirred solution of **2** (0.74 g) in dichloromethane (15 ml), and the mixture was heated under reflux for 5 h. Ether (50 ml) was added, the mixture was filtered, and the solid residue was washed thoroughly with dichloromethane (3 × 100 ml). The combined filtrate and washings were concentrated to a syrup that was chromatographed on silica gel with dichloromethane–ethyl acetate (3:1). After evaporation of solvent, the syrupy residue was crystallised from chloroform–ether, to give **1** (0.505 g, 67%), m.p. 79–80°, $[\alpha]_D$ +55° (*c* 0.86, chloroform); n.m.r. data: δ 7.34 (m, 10 H, 2 Ph), 5.54 (s, 1 H, PhC*H*), 4.60 (m, 3 H, $-CH_2-$ and H-1), 4.38 (m, 2 H), 4.20 (d, 1 H), 3.78 (m, 2 H), and 3.50 (s, 3 H, OMe).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.11; H, 5.96. Found: C, 68.13; H, 6.15.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-(Z)-hydroxyimino-α-D-ribo-hexopyranoside (**3**) *and the* (E)*-isomer* (**4**). — Hydroxylamine hydrochloride (0.077 g) was added to a solution of **1** (0.371 g) in pyridine (3 ml) and ethanol (8 ml). After being heated for 1.5 h at reflux, the mixture was diluted with water (30 ml) and extracted with chloroform (3 × 50 ml). The extracts were dried and evaporated to give a syrup which was chromatographed on silica gel. Elution with dichloromethane–ethyl acetate (6:1) gave, first, the (*Z*)-oxime (**3**) as a syrup (0.197 g, 51.5%), $[\alpha]_D$ +27.9° (*c* 0.60, chloroform); n.m.r. data: δ 5.78 (s, 1 H, H-1), 5.72 (s, 1 H, PhC*H*), and 3.48 (s, 3 H, OMe).

Anal. Calc. for $C_{21}H_{23}NO_6$: C, 65.45; H, 5.97; N, 3.64. Found: C, 65.48; H, 5.89; N, 3.76.

Further elution yielded the (*E*)-oxime (**4**) as a syrup (0.101 g, 26.5%), $[\alpha]_D$ +7.1° (*c* 0.55, chloroform); n.m.r. data: δ 5.48 (s, 1 H, PhC*H*), 5.30 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-1), and 3.44 (s, 3 H, OMe).

Anal. Calc. for $C_{21}H_{23}NO_6$: C, 65.45; H, 5.97; N, 3.64. Found: C, 65.53; H, 6.10; N, 3.42.

*Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-*D*-ribo-hexopyranosid-2-ulose* (**5**). — To a stirred solution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-altropyranoside (**6**, 0.64 g) in dichloromethane (10 ml) was added pyridinium chlorochromate (1.84 g). After being heated under reflux for 3 h, the reaction mixture was worked-up as described above for **1**. Crystallisation of the product from chloroform gave **5** (0.41 g, 64%), m.p. 92–93°, $[\alpha]_D$ +52° (*c* 0.385, chloroform); n.m.r. data: δ 5.54 (s, 1 H, PhC*H*), 4.68 (s, 1 H, H-1), 3.50 and 3.42 (2 s, 6 H, 2 OMe).

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.12. Found: C, 61.06; H, 6.26.

Epimerisation of compound **5**. — A solution of **5** (25 mg) in ethanol (5 ml) containing triethylamine (0.1 ml) was heated under reflux for 1.5 h. T.l.c. indicated formation of a new material. The cooled mixture was diluted with dichloromethane (30 ml), decolorised with charcoal, filtered through Kieselguhr, and evaporated. Crystallisation of the residue from ether–light petroleum (b.p. 60–80°) gave methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (12 mg), m.p. 133–135°; lit.[7] m.p. 136–137°.

*Methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-*D*-arabino-hexopyranosid-3-ulose* (**9**). — Compound **8** (0.64 g) was oxidised with pyridinium chlorochromate and the product isolated as described above for the preparation of **5**. Compound **9** was obtained as a clear syrup (0.435 g, 68.3%) having spectral properties identical with those of the compound described by Overend *et al.*[2].

*Methyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-*D*-altropyranoside* (**12**). — Trityl chloride (0.31 g) was added to a stirred solution of methyl 2,3-di-*O*-benzyl-α-D-altropyranoside[9] (0.70 g) in dry pyridine (10 ml). After 24 h at room temperature, the mixture was diluted with water (100 ml) and extracted with chloroform (3 × 50 ml). The syrup obtained after drying and evaporation of the combined extracts was chromatographed on silica gel with dichloromethane–hexane (1 : 1), to give **12** as a syrup (0.958 g, 83%), $[\alpha]_D$ +25° (*c* 0.20, chloroform); n.m.r. data: δ 4.74 (s, 1 H, H-1) and 3.48 (s, 3 H, OMe).

Anal. Calc. for $C_{40}H_{40}O_6$: C, 77.92; H, 6.49. Found: C, 78.17; H, 6.63.

*Methyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-*D*-arabino-hexopyranosid-4-ulose* (**13**). — Compound **12** (1.19 g) was oxidised with pyridinium chlorochromate (1.84 g, 4 equiv.), and the reaction mixture was worked-up as described above for **1**, except that dichloromethane was used for chromatography. The product was crystallised from ethanol–ether to yield **13** (0.756 g, 64%), m.p. 146–147°, $[\alpha]_D$ +35.4°; n.m.r. data: δ 5.0 (d, 1 H, $J_{2,3}$ 2.0 Hz, H-3) and 3.36 (s, 3 H, OMe).

Anal. Calc. for $C_{40}H_{38}O_6$: C, 78.18; H, 6.18. Found: C, 78.03; H, 6.37.

Borohydride reduction of **13**. — A solution of **13** (0.29 g) in methanol (10 ml) was treated with sodium borohydride (0.925 g). The reaction mixture was stirred for 2 h, diluted with water (20 ml), and extracted with chloroform (3 × 50 ml). Evaporation of the extracts and chromatography of the residue on silica gel with dichloromethane–hexane (1 : 1) yielded a single, major product that was identical (t.l.c., i.r., n.m.r.) with compound **12**. Only a trace of a second compound was detected by t.l.c.

ACKNOWLEDGMENT

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