THE SYNTHESIS AND DEGRADATION OF BENZYL 4,6-*O*-BENZYLIDENE-2,3-DIDEOXY-3-*C*-ETHYL-2-*C*-HYDROXYMETHYL-α-D-GLUCOPYRANOSIDE AND -MANNOPYRANOSIDE*

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ABSTRACT

The use of carbohydrates for establishing, by synthesis, the absolute configuration of branched aliphatic alcohols is demonstrated by the synthesis and degradation of carbohydrate derivatives that contain two branch points. Benzyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (**23**) and -mannopyranoside (**24**) were formed from benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) by a reaction sequence that involved ring-opening with ethylmagnesium chloride, oxidation, epimerisation, methylenation, and hydroboronation. The *gluco* isomer **23** was converted into (+)-(*R*)-2,3-bisacetoxymethylpentyl acetate (**1**) by sequential hydrogenolysis, borohydride reduction, periodate oxidation, borohydride reduction, and acetylation. The synthesis of **1** provides confirmatory evidence for the absolute configuration of the alkaloid pilocarpine (**2**). Unidentified products, and not the expected free-sugars, were obtained by acidic hydrolysis of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (**8**) and -mannopyranoside (**9**). Convenient syntheses of benzyl α-D-glucopyranoside derivatives are described.

INTRODUCTION

In recent publications, the utility of carbohydrates as sources of asymmetric centres for the synthesis of non-carbohydrate, asymmetric molecules has been clearly demonstrated. Thus (*S*)-piperidin-3-ol[1] and (*R*)- and (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acids[2] have been synthesised from D-mannitol, and biotin derivatives have been prepared from D-glucose[3]. In this paper, we report a configurational assignment, by synthesis, of (+)-(*R*)-2,3-bisacetoxymethylpentyl acetate (**1**). This synthesis demonstrates that carbohydrates containing two branch points may be synthesised and then degraded to simple branched alcohols, and also provides confirmation of the absolute configuration of the Jaborandi alkaloid pilocarpine[4] (**2**).

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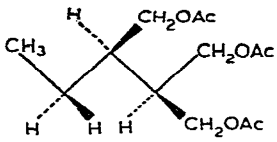
*Dedicated to Professor M. Stacey, C.B.E., F.R.S., in honour of his 65th birthday.



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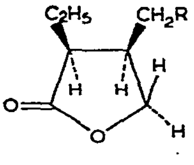

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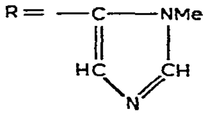
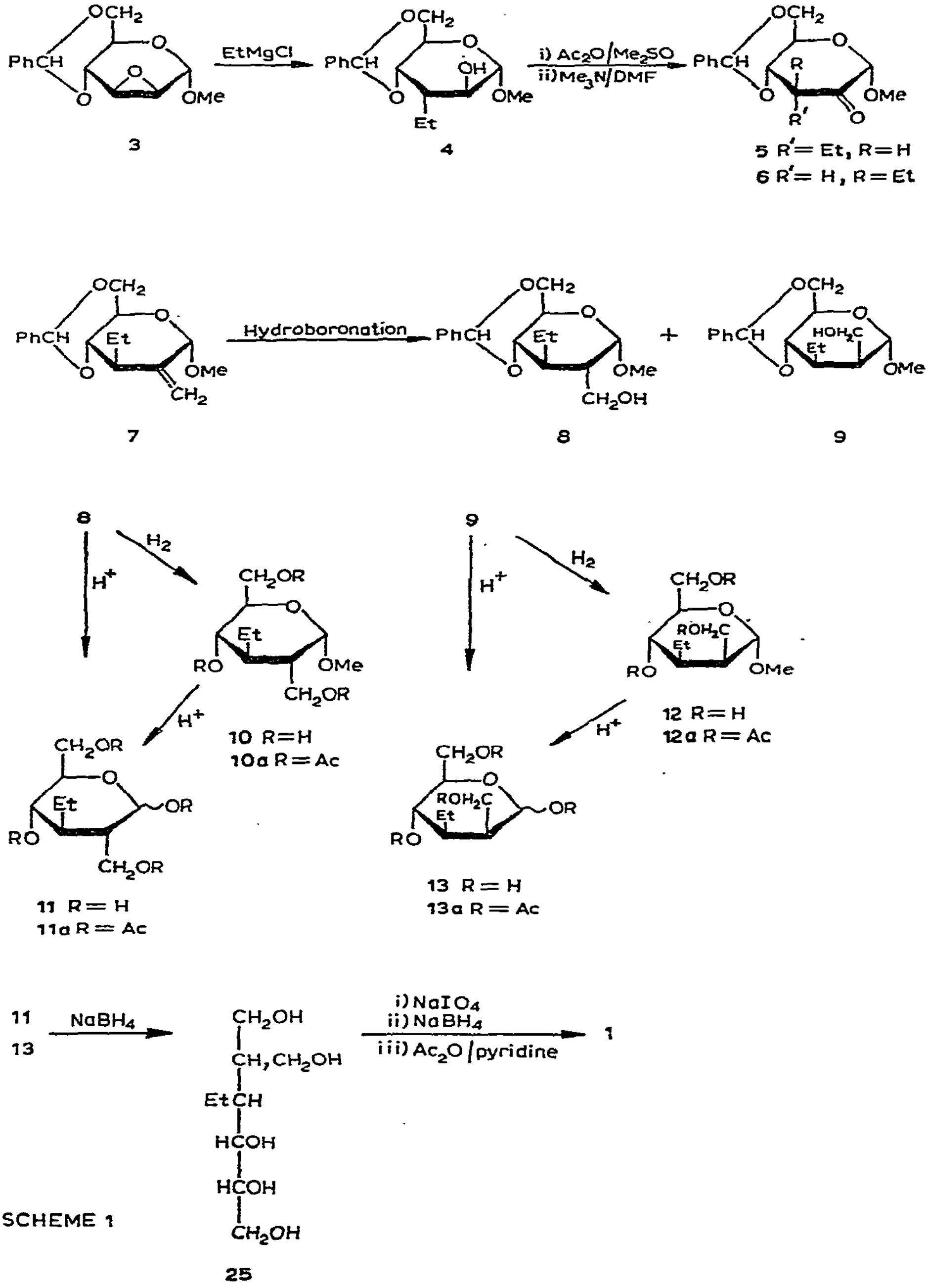


DISCUSSION

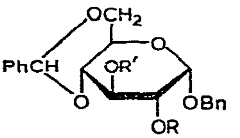
The synthetic sequence that was envisaged for the stereopecific synthesis of (*R*)-2,3-bisacetoxymethylpentyl acetate (**1**) is illustrated in Scheme 1. The formation of the 3-*C*-ethyl-altroside **4** has been reported previously[5], as have the oxidation of **4** to **5** and the isomerisation[6] of **5** to **6**. Treatment of the hexopyranosid-2-ulose **6** with methylenetriphenylphosphorane gave the 2-*C*-methylene derivative **7**, which was converted by conventional hydroboronation[7] into a mixture of 2-*C*-hydroxymethyl sugars (**8** and **9**) that were separated by chromatography over silica gel. The first compound obtained was crystalline and had n.m.r. parameters (*inter alia* $J_{1,2}$ 3.5 Hz) consistent with the structure methyl 4,6-*O*-benzylidene-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (**8**), and the second, non-crystalline product had n.m.r. parameters (*inter alia* $J_{1,2}$ <1 Hz) consistent with the mannopyranoside structure **9**. However, it was not possible to hydrolyse **8** or **9** directly to the free sugars (**11** and **13**), nor was it possible to effect clean, glycosidic hydrolysis of the debenzylidenated derivatives **10** and **12**. It was shown by t.l.c. that, in hot 4M hydrochloric acid, both **8** and **10** initially gave a product having a higher R_F value than that of **10**. [If, at this stage, the reaction product was acetylated, no n.m.r. signals for anomeric protons consistent with **11a** were evident.] Prolonged hydrolysis with 4M hydrochloric acid or with Amberlite IR-120(H$^+$) resin led to decomposition and/or polymerisation of the product. Similar hydrolysis experiments were also unsuccessful with a mixture of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-hydroxymethyl-α-D-*arabino*- and -*ribo*-hexopyranosides, which were prepared from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[8] by a sequence involving oxidation with acetic anhydride in methyl sulphoxide, treatment with methylenetriphenylphosphorane, and hydroboronation (see Experimental). Although hydrolysis of the glycoside was clearly demonstrated, the product was a complex mixture and was possibly polymeric (n.m.r. evidence). No n.m.r. evidence for the formation of peracetylated hexopyranoses was found on examination of the crude, acetylated hydrolysate. At present, we can offer no evidence concerning the nature of the hydrolysis products of the 2-deoxy-2-*C*-hydroxymethylglycosides.

To overcome the difficulties associated with the glycosidic hydrolysis step, the series of transformations **3**→**8**+**9** was repeated by using benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) in place of **3**, so that cleavage of the glycosidic bond could be accomplished by hydrogenolysis rather than hydrolysis. Accordingly, it was necessary to develop a synthetic sequence that would give **17** in appreciable quantities. The route D-glucose → benzyl α-D-glucopyranoside → benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**14**) → benzyl 4,6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-α-D-glucopyranoside (**15**) →**17** was attractive, even though no satisfactory synthesis of benzyl α-D-glucopyranoside or of **14** had been reported. It was

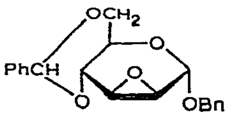


SCHEME 1

found that crystalline benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**14**) could be obtained in 20% yield from D-glucose by direct benzylidination of the syrup that was precipitated by ether from a D-glucose–benzyl alcohol–toluene-*p*-sulphonic acid reaction mixture. Selective toluene-*p*-sulphonylation of **14** proceeded readily, and the resulting, crystalline 2-toluene-*p*-sulphonate (**15**) was converted smoothly into the anhydromannoside **17** with boiling, methanolic sodium methoxide. For comparison purposes, **14** was also converted into its ditoluene-*p*-sulphonate (**16**) which, on treatment with sodium methoxide in methanol, afforded crystalline benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-aliopyranoside (**18**). The n.m.r. spectra of **17** and **18** were consistent with the proposed structures and essentially similar to those of the corresponding methyl α-D-mannopyranoside and -allopyranoside derivatives.



14 R = R' = H
15 R = Ts, R' = H
16 R = R' = Ts



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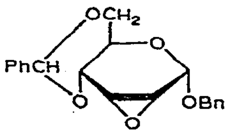

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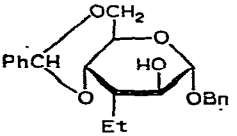

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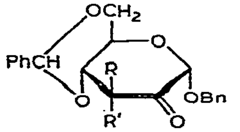
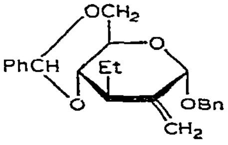


20 R = H, R' = Et
21 R = Et, R' = H

Benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) reacted smoothly with ethylmagnesium chloride in ether to afford the 3-*C*-ethyl-altropyranoside derivative **19** in 54% yield. Oxidation of **19** with acetic anhydride–methyl sulphoxide gave the *ribo*-hexopyranosid-2-ulose derivative **20** which, by analogy with the corresponding methyl glycoside[6] **5**, was epimerised to benzyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino*-hexopyranosid-2-ulose (**21**). Treatment of **21** with methylenetriphenylphosphorane afforded the 2-*C*-methylene derivative **22** which, on hydroboronation, gave a mixture of the crystalline 2-*C*-hydroxymethyl derivatives **23** and **24**, which were separated easily by chromatography over silica gel. No significant stereoselectivity was observed in the hydroboronation of **22**, **7**, or methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-methylene-α-D-*erythro*-hexopyranoside.



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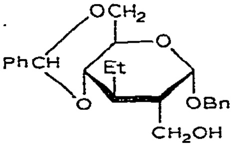

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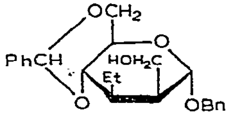

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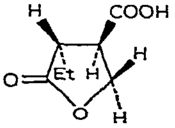

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Although the conversion of the *gluco* and *manno* derivatives **23** and **24** into the free sugars **11** and **13**, respectively, was accomplished smoothly by catalytic hydrogenolysis over palladium in methanol, some comment about these reactions is pertinent. It could be inferred from t.l.c. studies that catalytic hydrogenolysis of the benzylidene group in **23** and **24** proceeded more readily than hydrogenolysis of the benzyl aglycon group. T.l.c. also indicated that the free sugars **11** and **13**, once formed, were converted, in the cold, essentially neutral, hydrogenolysis mixture, into methyl glycosides. Glycosidation was accelerated when the methanolic solutions were concentrated at 50°. The products formed from **23** were identified, after acetylation, as an anomeric mixture of 2-*C*-acetoxymethyl-1,4,6-tri-*O*-acetyl-2,3-dideoxy-3-*C*-ethyl-D-glucopyranose [anomeric signals in the n.m.r. spectrum at 6.21 ($J_{1,2}$ 3.5 Hz) and 5.75 p.p.m. ($J_{1,2}$ 8.5 Hz)] and methyl tri-*O*-acetyl-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-D-glucosides. Two OMe signals were observed in the n.m.r. spectrum, one of which corresponded to the signal from the methyl α-D-glucopyranoside derivative **10a**. Similar results were obtained with the products from the hydrogenolysis of **24**. In this case, however, only one anomer of the acetylated glycoside **12** was obtained.

The ease with which **11** and **13** underwent glycoside formation, even under essentially neutral conditions, was confirmed in a series of exploratory, chromatographic experiments, when it was also observed that glycosides were formed from **11** and **13** in aqueous, acidic, methanolic solutions. Therefore, to avoid difficulties associated with the susceptibility of **11** to form glycosides, the transformation of **11** into (+)-(*R*)-2,3-bisacetoxymethylpentyl acetate (**1**) was accomplished in the following manner. Hydrogenolysis of **23** was carried out over palladium-on-charcoal in ethanol, and the resulting solution was added directly to an excess of aqueous sodium borohydride. The hexitol derivative (**25**) was purified by chromatography over silica gel, oxidised with sodium periodate, and further reduced with sodium borohydride. The resulting triol was acetylated and purified by chromatography over silica gel to give (+)-(*R*)-2,3-bisacetoxymethylpentyl acetate (**1**). Compound **1**, which had $[\alpha]_D$ *ca.* +3° (methanol) had a plain, positive o.r.d. curve.

(+)-(*R*)-2,3-Bisacetoxymethylpentyl acetate (**1**) was also obtained by reduction of (+)-isopilopic acid[9] (**26**) with lithium aluminium hydride, followed by acetylation. Since it is well established that the configurations at C-4 in (+)-isopilopic acid and pilocarpine[4,10,11] are the same but that the configuration at C-3 differs in the two compounds, the finding that (+)-2,3-bisacetoxymethylpentyl acetate has the (*R*)-configuration confirms the configurational assignment of pilocarpine as *3*(*S*),*4*(*R*)-3-ethyl-3,4-dihydro-4-[(1-methylimidazol-5-yl)methyl]-(3*H*)-furan-2-one[11].

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography (t.l.c.) was performed on microscope slides coated with Silica Gel G (Merck), and column chromatography was performed with Silica Gel (Merck) of particle size 0.05–0.2 mm. The chromatoplates were developed with 50% sulphuric acid and/or iodine vapour.

N.m.r. spectra were measured with a Jeol-JNM-4H-100 n.m.r. spectrometer at 100 MHz, with deuteriochloroform as solvent and tetramethylsilane as internal standard. Only distinctive n.m.r. data are reported. Solvents were dried over magnesium sulphate unless stated otherwise, and light petroleum refers to the fraction b.p. 60–80°. O.r.d. measurements were made on a FICA Spectropole 1B spectropolarimeter.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-3-C-ethyl-2-C-methylene-α-D-*arabino*-hexopyranoside* (7). — A solution of butyl-lithium in hexane (15%, 18 ml) was added to a suspension of methyltriphenylphosphonium bromide (6 g) in ether[12]; only by this procedure were satisfactory Wittig reagents produced. A solution of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino*-hexopyranosid-2-ulose[6] (5 g) in ether was then added, and the mixture was stirred at room temperature for 1 h. The suspension was poured into water and extracted with ether, and the ether extract was dried and concentrated. The product was separated from a little unreacted **6** by chromatography over silica gel in light petroleum–acetone (20:1) to yield **7** (3.7 g, 74%), m.p. 47° (from aqueous ethanol), $[\alpha]_D^{20}$ +16.4° (*c* 1.5, chloroform) (Found: C, 70.1; H, 7.6. $C_{17}H_{22}O_4$ calc.: C, 70.3; H, 7.6%). N.m.r. data (δ): benzylic H, 5.49; $=CH_2$, 5.03 and 5.16 ($J_{H,H}$ 1.5 Hz); H-1, 4.76; OMe, 3.40 p.p.m.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-C-ethyl-2-C-hydroxymethyl-α-D-glucopyranoside (**8**) *and -α-D-mannopyranoside* (**9**). — Diborane, generated by reaction of sodium borohydride (0.8 g) and boron trifluoride etherate (8 ml) in Diglyme[7] was passed into a solution of **7** (2 g) in tetrahydrofuran. A solution of 3M sodium hydroxide (3 ml) was added, followed by hydrogen peroxide (3 ml), and the mixture was warmed at 50° for 1 h. The solution was poured into water and extracted with ether, and the ether extract was dried and concentrated. The residue was resolved chromatographically over silica gel in benzene–ether (4:1) to afford (*a*) methyl 4,6-O-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (**8**) (0.8 g, 38%), m.p. 103° (from light petroleum), $[\alpha]_D$ +5° (*c* 2, chloroform) (Found: C, 66.4; H, 7.7. $C_{17}H_{24}O_5$ calc.: C, 66.3; H, 7.8%). N.m.r. data (δ): benzylic H, 5.54; H-1, 4.72 p.p.m. ($J_{1,2}$ 3.5 Hz); and (*b*) methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-mannopyranoside (**9**) (0.8 g, 38%), $[\alpha]_D$ +20° (*c* 1, chloroform). N.m.r. data (δ): benzylic H, 5.51; H-1, 4.87 p.p.m. ($J_{1,2}$ <1 Hz).

Benzyl 4,6-O-benzylidene-α-D-glucopyranoside (**14**). — A solution of D-glucose (800 g) and toluene-*p*-sulphonic acid (40 g) in benzyl alcohol (1500 ml) was heated at 80–100° for 5 h and then poured, after cooling, into an excess of ether. The ether solution was stirred for 15 min and stored overnight at room temperature. The supernatant was then decanted from a syrupy residue which contained, *inter alia*, benzyl α-D-glucopyranoside. A mixture of this residue and zinc chloride (500 g) in benzaldehyde (1500 ml) was stirred vigorously at room temperature for 3 h and poured into a mixture of water (3 l) and light petroleum (3 l). The solution was stirred for 30 min, and the solid product was collected by filtration, dissolved in the minimal volume of hot ethanol (containing ammonia), and poured into excess of water. The precipitate was filtered off and recrystallised from ethanol to afford benzyl

4,6-*O*-benzylidene-α-D-glucopyranoside (**14**) (320 g, 20%), m.p. 152°, $[\alpha]_D^{20}$ +51° (*c* 3, chloroform) (Found: C, 67.1; H, 6.1. $C_{20}H_{22}O_6$ calc.: C, 67.0; H, 6.2%); n.m.r. data (δ): benzylic H, 5.58; H-1, 4.97 ($J_{1,2}$ 3.5 Hz); $PhCH_2O$, 4.59 and 4.84 p.p.m. ($J_{H,H}$ 12 Hz). The glucopyranoside **14** afforded a crystalline diacetate, m.p. 103–105° (from ethanol), $[\alpha]_D^{20}$ +52.6° (*c* 3, chloroform) (Found: C, 65.0; H, 5.9. $C_{24}H_{26}O_8$ calc.: C, 65.1; H, 5.9%); n.m.r. data (δ): benzylic H, 5.49; H-1, 5.13 ($J_{1,2}$ 3.5 Hz); H-2, 4.90 ($J_{2,3}$ 10.2 Hz); H-3, 5.16 ($J_{3,4}$ 10 Hz); $PhCH_2O$, 4.53 and 4.77 p.p.m. ($J_{H,H}$ 12.2 Hz).

*Benzyl 4,6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-α-D-glucopyranoside* (**15**). — An ice-cold solution of toluene-*p*-sulphonyl chloride (7.7 g) in pyridine was added dropwise to an ice-cold solution of **14** (10 g) in pyridine. The mixture was stored at room temperature for 3 h, and then poured into water and extracted with chloroform. [The course of the reaction was monitored by t.l.c. (benzene–ether, 19:1), and the conditions described gave satisfactory yields of monotoluene-*p*-sulphonate (R_F 0.5) and minimal yields of the ditoluene-*p*-sulphonate (R_F 0.66)]. Conventional work-up afforded the product which was recrystallised from ethanol to yield **15** (9.3 g, 65%), m.p. 138–140°, $[\alpha]_D^{20}$ +35° (*c* 2, acetone) (Found: C, 63.0; H, 5.4. $C_{27}H_{28}O_8S$ calc.: C, 63.1; H, 5.7%).

*Benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside* (**17**). — A solution of **15** (15 g) in methanol, to which sodium methoxide (1.2 g of sodium) had been added, was boiled under reflux for 6 h. After this time, no **15** remained (t.l.c.; ether–light petroleum, 1:1). The solution was neutralised (CO_2), diluted with water, and extracted with chloroform. The extract was dried and concentrated, and the residue was recrystallised from ethanol to yield **17** (6.6 g, 66%), m.p. 118°, $[\alpha]_D^{20}$ +45.4° (*c* 2, chloroform) (Found: C, 70.3; H, 5.8. $C_{20}H_{20}O_5$ calc.: C, 70.6; H, 5.9%); n.m.r. data (δ): benzylic H, 5.52; H-1, 5.07 ($J_{1,2}$ <0.5 Hz); H-3 and H-4, 3.18 and 3.46 p.p.m ($J_{3,4}$ 3 Hz). The spectrum of **17** was similar to that of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[13].

*Benzyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-altropyranoside* (**19**). — A solution of benzyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) (23 g) in ether was added to a solution of ethylmagnesium chloride (10-fold excess) in ether, and the mixture was boiled under reflux for 10 h; no **17** then remained (t.l.c.; ether–light petroleum, 1:1). The mixture was worked up in the usual way, and the product was chromatographed over silica in ether–light petroleum (1:2). The major product (13 g, 54%), which had R_F 0.4 (ether–light petroleum, 1:1) and spectroscopic data consistent with the title product, afforded a crystalline acetate, m.p. 85° (from ethanol), $[\alpha]_D^{20}$ +104° (*c* 2.4, chloroform) (Found: C, 69.2; H, 6.8. $C_{23}H_{28}O_6$ calc.: C, 69.0; H, 7.1%). N.m.r. data (δ): benzylic H, 5.56; H-2, 5.10 ($J_{2,3}$ <1.5 Hz); H-1, 4.72 p.p.m. ($J_{1,2}$ ~1 Hz).

*Benzyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino-*hexopyranosid-2-ulose* (**21**). — A solution of **19** (13 g) and acetic anhydride in methyl sulphoxide was stored at room temperature for 24 h, and then poured into water and extracted with ether. The extract was dried and concentrated to afford a residue, which, by analogy with similar oxidations of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-altropyranoside, was presumed to be benzyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*ribo*-hexopyranosid-2-ulose (**20**). A solution of **20** and triethylamine in *N*,*N*-dimethylformamide was stored at room temperature overnight, and then poured into water and extracted with ether. The extract was dried and concentrated, and the residue was recrystallised from light petroleum to afford **21** (9 g, 70%), m.p. 124°, $[\alpha]_D$ +81° (*c* 2, chloroform) (Found: C, 71.9; H, 6.3. $C_{22}H_{24}O_5$ calc.: C, 71.7; H, 6.6%). N.m.r. data (δ): benzylic H, 5.51; H-1, 4.70; H-3, 2.96; benzylic H, 4.62 and 4.84 ($J_{H,H}$ 12.2 Hz); $\underline{CH_3}$–CH_2–, 0.96; CH_3–$\underline{CH_2}$–, 1.75 p.p.m.

*Benzyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-methylene-α-*D-arabino-*hexopyranoside* (**22**). — A solution of **21** (9 g) in ether was added to a solution of methyltriphenylphosphonium bromide (24 g) to which ethereal butyl-lithium (25 ml, 15%) had been added. The mixture was stored at room temperature for 4 h, poured into water, and extracted with ether, and the ether extract was dried and concentrated. T.l.c. (light petroleum–ether, 9:1) indicated that *ca.* 40% of **21** remained in the residue. The residue was re-treated with the same quantity of the methyltriphenylphosphonium bromide–butyl-lithium reagent and the mixture worked up as before. The product was chromatographed over silica gel in light petroleum–ether (9:1) to afford **22** (4.6 g, 51%), m.p. 95° (from light petroleum), $[\alpha]_D$ +61° (*c* 2, chloroform) (Found: C, 75.4; H, 6.8. $C_{23}H_{26}O_4$ calc.: C, 75.4, H, 7.1%); n.m.r. data (δ): benzylic H, 5.50; H-1, 5.07; $=CH_2$, 5.03, 5.13 ($J_{H,H}$ 1.8 Hz); $Ph\underline{CH_2}O$–, 4.55, 4.78 p.p.m. ($J_{H,H}$ 12.2 Hz).

*Benzyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-*D*-glucopyranoside* (**23**) *and -mannopyranoside* (**24**). — Diborane, generated by reaction of sodium borohydride (1.6 g) and boron trifluoride etherate (16 ml) in Diglyme, was passed through a trap of sodium borohydride into a solution of **22** (4.6 g) in tetrahydrofuran (previously dried by distillation from lithium aluminium hydride). 3M Sodium hydroxide (16 ml) was added, followed by hydrogen peroxide (6 ml), and the mixture was warmed at 50° for 1 h. The solution was poured into water and extracted with chloroform, and the extract was dried and concentrated. The residue was resolved chromatographically over silica gel in benzene–ether (5:1) to afford (*a*) benzyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (**23**) (2.1 g, 45%), m.p. 133° (from light petroleum), $[\alpha]_D^{20}$ +100° (*c* 1.7, chloroform) (Found: C, 72.2; H, 7.0. $C_{23}H_{28}O_5$ calc.: C, 71.9; H, 7.3%); n.m.r. data (δ): benzylic H, 5.56; H-1, 4.92 ($J_{1,2}$ 3.6 Hz); $PhCH_2O$–, 4.53 and 4.72 ($J_{H,H}$ 12.3 Hz); $\underline{CH_3}CH_2$–, 0.9 p.p.m.; (*b*) benzyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-mannopyranoside (**24**) (1.6 g, 34%), m.p. 135° (from light petroleum), $[\alpha]_D^{20}$ +33.5° (*c* 2.3, chloroform) (Found: C, 72.1; H, 7.1, $C_{23}H_{28}O_5$ calc.: C, 71.9; H, 7.3%); n.m.r. data (δ): benzylic H, 5.49; H-1, 5.07 ($J_{1,2}$ <1 Hz); $PhCH_2O$–, 4.48 and 4.72 p.p.m. ($J_{H,H}$ 12.4 Hz).

Hydrogenolysis of the glucopyranoside derivative **23**. — (*a*) A solution of **23** (0.2 g) in methanol (40 ml) was hydrogenolysed over 10% palladium-on-charcoal, and the reaction was monitored by t.l.c. (benzene–ethanol, 4:1). The hydrogenolysis of the benzylidene group took place more rapidly than the hydrogenolysis of the aglycon group, and the presence of benzyl 2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (R_F 0.6) was evident at intermediate stages of the hydrogenolysis. The final product was shown to contain methyl 2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-α-D-glucopyranoside (R_F 0.49) in addition to 2,3-dideoxy-3-*C*-ethyl-2-*C*-hydroxymethyl-D-glucopyranose (R_F 0.27). The solution was filtered and concentrated (bath 40°), and the product was acetylated with acetic anhydride in pyridine at room temperature for 24 h. The solution was concentrated, and the residue was chromatographed over silica gel in light petroleum–acetone (9:1) to afford a mixture of methyl glycosides [n.m.r. data (δ): OMe 3.37, 3.48 p.p.m.; the signal at 3.37 corresponded to the signal observed in **10a** obtained from **8** by hydrogenolysis and acetylation] and a chromatographically homogeneous syrup (0.1 g), $[\alpha]_D^{20}$ +27° (*c* 1, chloroform), which had an n.m.r. spectrum consistent with an anomeric mixture of 2-*C*-acetoxymethyl-1,4,6-tri-*O*-acetyl-2,3-dideoxy-3-*C*-ethyl-D-glucopyranose. N.m.r. data (δ): H-1 (α), 6.21 ($J_{1,2}$ 3 Hz); H-1 (β), 5.75 p.p.m. ($J_{1,2}$ 8.5 Hz).

(*b*) A solution of **23** (1 g) in ethanol (100 ml) was hydrogenolysed over 10% palladium-on-charcoal. The solution was filtered and added dropwise to a solution of sodium borohydride (0.5 g) in water (200 ml). The solution was stored at room temperature for 1 h, excess of borohydride was then destroyed by dropwise addition of acetic acid, and inorganic matter was removed by passing the solution successively through columns of Amberlite IR-120(H^+) and Amberlite IRA-400 (OH^-) resins. The solution was concentrated and the residue chromatographed over silica gel in benzene–ethanol (4:1) to give, *inter alia*, a chromatographically homogeneous syrup (300 mg, R_F 0.15) which consumed 2 mol. of sodium periodate and which had spectral properties consistent with 2-deoxy-2-*C*-ethyl-1,1-bishydroxymethyl-D-arabinitol (**25**).

(R)-*2,3-Bisacetoxymethylpentyl acetate* (**1**). — (*a*) A solution of **25** (0.3 g) in water (20 ml), to which sodium metaperiodate (0.4 g) had been added, was stored at room temperature for 1 h. Saturated, aqueous barium chloride was then added, and the solution was filtered and added to aqueous sodium borohydride. After 24 h, excess of borohydride was destroyed with acetic acid, and inorganic matter was removed by passing the solution successively through columns of Amberlite IR-120 (H^+) and Amberlite IRA-400 (OH^-) resins. The solution was concentrated and acetylated, and the product was purified by chromatography over silica gel (benzene–ether, 7:3) to give **1** (60 mg) which was chromatographically and spectroscopically indistinguishable from samples prepared from pilopic and isopilopic acid, had a plain, positive o.r.d. curve, and had $[\alpha]_D$ *ca.* +3° (methanol).

(*b*) A solution of (+)-isopilopic acid[11] (1 g) in ether was added dropwise to a solution of lithium aluminium hydride in ether. Excess of lithium aluminium hydride and alkoxides were destroyed by addition of ethyl acetate and water, and the solution was dried, filtered, and concentrated. The product was acetylated and purified by chromatography over silica gel in light petroleum–ether to give **1** (300 mg) which had $[\alpha]_D$ *ca.* +3° (methanol) and had a plain, positive o.r.d. curve.

Hydrogenolysis of the mannopyranoside derivative (**24**). — A solution of **24**

(0.4 g) in methanol was hydrogenolysed over palladium-on-charcoal. The solution was filtered and concentrated, and the residue was acetylated at room temperature overnight with acetic anhydride in pyridine. From the product mixture was isolated, by chromatography over silica gel, a mixture of methyl mannopyranoside acetates [n.m.r. data (δ): OMe 3.30, 3.35, 3.4 p.p.m.) and 2-*C*-acetoxymethyl-1,4,6-tri-*O*-acetyl-2,3-dideoxy-3-*C*-ethyl-D-mannopyranose, $[\alpha]_D^{20}$ +6° (c 1, chloroform); n.m.r. data (δ): H-1, 6.20 ($J_{1,2}$ <1 Hz); H-4, 4.92 p.p.m. ($J_{3,4} = J_{4,5} = 10$ Hz).

Benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (**18**). — A solution of **14** (10 g) and toluene-*p*-sulphonyl chloride (20 g) in pyridine was stored at room temperature for 6 h, and then poured into water and extracted with chloroform. The extract was washed with dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. [A portion of the residue was purified by chromatography over silica gel in benzene–ether (19:1) to give **16** (R_F 0.66), $[\alpha]_D^{20}$ +40.5° (c 3.2, chloroform), which did not crystallise.] The main portion of the residue was dissolved in methanolic sodium methoxide, and the solution was boiled under reflux for 3 h, after which time no **16** remained (t.l.c., ether–light petroleum, 1:1). The solution was diluted with water and extracted with chloroform, and the extract was dried and concentrated. The product was recrystallised from ethanol to yield **18** (5.9 g, 60%), m.p. 185°, $[\alpha]_D^{20}$ +274° (c 0.8, chloroform) (Found: C, 70.4; H, 5.9. $C_{20}H_{20}O_5$ calc.: C, 70.6; H, 5.9%); n.m.r. data (δ): benzylic H, 5.03; H-1, 5.01 ($J_{1,2}$ ~3 Hz); $PhCH_2$–O, 4.61 p.p.m. The n.m.r. spectrum of **18** was similar to that of methyl 4,6-*O*-benzylidene-α-D-allopyranoside[13].

*Preparation and attempted hydrolysis of methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-hydroxymethyl-α-*D-arabino- *and* -ribo-*hexopyranosides*. — A solution of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[8] (14 g) and acetic anhydride (42 ml) in methyl sulphoxide (250 ml) was stored overnight at room temperature and then poured into water and extracted with ether. The ether solution was dried and concentrated, and the product was recrystallised from light petroleum to yield methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose (6 g, 42%), m.p. 114°, $[\alpha]_D^{20}$ +112° (c 1.7, chloroform) (Found: C, 63.9; H, 6.2. $C_{14}H_{16}O_5$ calc.: C, 63.6; H, 6.1%); n.m.r. data (δ): benzylic H, 5.49; H-1, 4.56; H-3 and H-3′, 2.9 p.p.m.

A solution of the hexopyranosid-2-ulose derivative (3 g) in ether was added to a solution of methyltriphenylphosphonium bromide in ether to which butyl-lithium had been added. The suspension was stirred at room temperature for 1 h, and then poured into water and extracted with ether. The extract was dried and concentrated, and the product was purified by chromatography over silica gel in ether–light petroleum (1:1) to afford methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-methylene-α-D-*erythro*-hexopyranoside (25 g, 83%), m.p. 112° (from light petroleum), $[\alpha]_D^{20}$ +77.5° (c 3.1, chloroform) (Found: C, 69.0; H, 6.9. $C_{15}H_{18}O_4$ calc.: C, 68.6; H, 6.9%); n.m.r. data (δ): benzylic H, 5.51; CH_2, 5.02 (broad, two-proton signal); H-1, 4.85; H-3 and H-3′, 2.7 p.p.m.

The olefin (2 g) was hydroboronated, as described for the *arabino*-pyranoside derivative (7). The product (1.4 g), purified by chromatography in ether–light petroleum (1:1), had an extended m.p. and had an n.m.r. spectrum consistent with its being a mixture of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-hydroxymethyl-α-D-*arabino*- and -*ribo*-hexopyranosides in the ratio 2:1. N.m.r. data (δ): (*a*) *arabino*-isomer; benzylic H, 5.53; H-1, 4.70 ($J_{1,2}$ 3.5 Hz); (*b*) *ribo*-isomer; benzylic H, 5.50; H-1, 4.65 p.p.m. ($J_{1,2}$ <1 Hz).

When the above mixture was hydrolysed with 4M hydrochloric acid, rapid darkening of the solution occurred. When the solution was neutralised, concentrated, and acetylated, no evidence of peracetylated 2,3-dideoxy-2-*C*-hydroxymethyl-D-*arabino*(*ribo*)-hexopyranose could be obtained by n.m.r. methods. Similar results were obtained when the hexopyranoside mixture was hydrolysed with 4M hydrochloric acid after initial hydrogenolysis over palladium-on-charcoal. Hydrolysis of crude methyl 2,3-dideoxy-2-*C*-hydroxymethyl-α-D-*arabino*(*ribo*)-hexopyranoside in boiling water containing Amberlite IR-120(H$^+$) resin gave a polymerised product or a complex mixture of products (as indicated by n.m.r.), and not the expected free-sugar.

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