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Synthesis of some trideoxy-D-hexoses and derivatives thereof from D-glucono-1,5-lactone*†

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ABSTRACT

Enantiospecific syntheses of methyl 2,3,4-trideoxy-α-D- and -β-D-*glycero*-hexopyranoside (**10** and **11**), methyl α-D- and β-D-amicetopyranoside (**24** and **25**), (2*S*)-1,2-hexanediol (**36**), (2*S*)-1,2,6-hexanetriol (**37**), and some derivatives thereof from D-glucono-1,5-lactone are described.

INTRODUCTION

In continuing an investigation of the synthetic applications of D-gluconic acid derivatives[1], we now report the synthesis of some enantiomerically pure trideoxy-D-aldohexoses and derivatives thereof from methyl 2,3-dideoxy-5,6-*O*-isopropylidene-D-*erythro*-hexonate (**1**). We have previously described[2] the synthesis of this key intermediate from D-glucono-1,5-lactone. A modified and simplified synthesis of **1** is also presented.

RESULTS AND DISCUSSION

The formation of the olefin **2** by treatment of the chloro-ester **3** with potassium acetate in methanol has been described[2]. Catalytic hydrogenation of **2** in the presence of sodium acetate yielded the dideoxy ester **1** (65%). An improved yield (75.4%) of **1** was obtained when the crude product resulting from the treatment of **3** with sodium acetate was hydrogenated directly, without isolation of the intermediate olefin **2**. Compound **1** was further[2] characterised as the crystalline tosylate **4**.

The combined structural features of **1** and **2** suggest that these compounds could be useful synthetic intermediates. The synthesis of some deoxy sugar derivatives from **1** partially illustrates this point.

Treatment of **1** with triphenylphosphine–carbon tetrachloride–imidazole[2,3] gave 86% of the crystalline 4-chloro-ester **5**. The corresponding 4-bromo analogue **6** (79%) was obtained similarly using carbon tetrabromide. Attempted catalytic hydrogenation of **5** was unsuccessful. The relative reactivities of chlorine atoms in chlorodeoxy sugar

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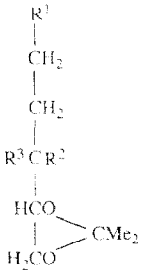

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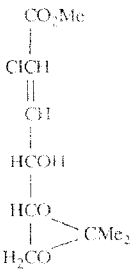

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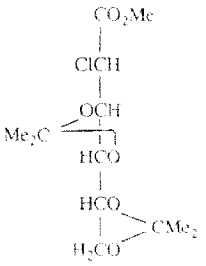

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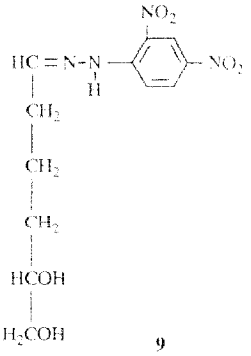
1	$R^1 = CO_2Me$, $R^2 = OH$, $R^3 = H$
4	$R^1 = CO_2Me$, $R^2 = OTs$, $R^3 = H$
5	$R^1 = CO_2Me$, $R^2 = H$, $R^3 = Cl$
6	$R^1 = CO_2Me$, $R^2 = H$, $R^3 = Br$
7	$R^1 = CO_2Me$, $R^2 = R^3 = H$
8	$R^1 = CHO$, $R^2 = R^3 = H$
16	$R^1 = CHO$, $R^2 = H$, $R^3 = Cl$
17	$R^1 = CHO$, $R^2 = H$, $R^3 = Br$
26	$R^1 = CHO$, $R^2 = OTs$, $R^3 = H$



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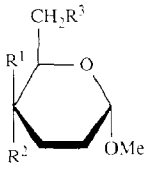
derivatives are not always predictable[4,5], and reductive dechlorination may be resisted even under very forcing conditions[6]. The successful[2] hydrogenolysis of chloro-ester **3** is due to the presence of the adjacent electron-withdrawing ester group. α-Halo-esters are generally[5] much more readily dehalogenated. Hydrogenolysis of the 4-bromo-ester **6** proceded smoothly to give the expected trideoxy-ester **7** ($[\alpha]_D$ +15°). The absolute enantiomeric purity of compound **7** ($[\alpha]_D$ +6.7°) prepared recently[7] by the addition of chiral radicals to electron-poor alkenes may be questioned, but the specificity of the route described here is without contention.

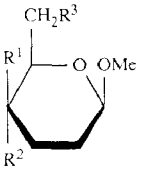
Reduction of **7** in toluene with di-isobutylaluminium hydride at −78° gave the pure aldehyde **8**, which was characterised, after hydrolysis with aqueous acetic acid, as the 2,4-dinitrophenylhydrazone **9**. Reaction of **8** with methanolic 1.5% hydrogen chloride, followed by flash-column chromatography, yielded pure methyl 2,3,4-trideoxy-α-D- and -β-D-*glycero*-hexopyranoside (**10** and **11**), which were characterised as the crystalline 3,5-dinitrobenzoates **12** and **13**, respectively.

Compounds **10** and **11** are disubstituted tetrahydropyrans [(2*S*,6*S*)- and (2*S*,6*R*)-2-hydroxymethyl-6-methoxytetrahydropyran, respectively] and represent the basic model structures for all of the methyl D-hexopyranosides. They are interesting model chiral intermediates for the study of chain-extension reactions of the hexopyranosides at C-6, and the resulting stereochemistry at the "off-template" centres for various natural product syntheses[8].

A recent[8] multi-step synthesis of **10** from D-glucose proceded *via* the dideoxygly-

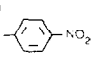
coside **14**. Compound **14** was obtained from the epoxide **15** in 51% overall yield by application in sequence of reduction with lithium aluminium hydride and Barton–McCombie deoxygenation[9]. The authors did not consider established[10,11] alternative routes to **14**, and did not comment on them. It is also noteworthy that they gave an incorrect empirical formula ($C_7H_{14}O_2$; mol. wt., 130.0994) for **10** ($C_7H_{14}O_3$; mol. wt., 146.1878), but nevertheless succeeded in locating a corresponding M^+ ion at 130.0996 in the mass spectrum. An earlier synthesis[12] of **10** had resulted during studies of the [4+2]-cycloaddition of 1-methoxy-1,3-butadiene to simple carbonyl compounds. The absolute configuration of **10** was assigned by chemical correlation studies[12,13].

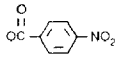




10 $R^1 = R^2 = H$, $R^3 = OH$

11 $R^1 = R^2 = H$, $R^3 = OH$

12 $R^1 = R^2 = H$, $R^3 =$ 

13 $R^1 = R^2 = H$, $R^3 =$ 

18 $R^1 = Cl$, $R^2 = H$, $R^3 = OH$

19 $R^1 = Cl$, $R^2 = H$, $R^3 = OH$

20 $R^1 = Br$, $R^2 = H$, $R^3 = OH$

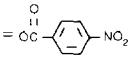
21 $R^1 = Br$, $R^2 = H$, $R^3 = OH$

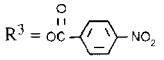
24 $R^1 = R^3 = H$, $R^2 = OH$

25 $R^1 = R^3 = H$, $R^2 = OH$

27 $R^1 = H$, $R^2 = OTs$, $R^3 = OH$

28 $R^1 = H$, $R^2 = OTs$, $R^3 = OH$

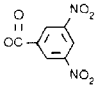
29 $R^1 = H$, $R^2 = OTs$, $R^3 =$ 

30 $R^1 = H$, $R^2 = OTs$, $R^3 =$ 

31 $R^1 = H$, $R^2 = R^3 = OTs$

32 $R^1 = H$, $R^2 = R^3 = OTs$

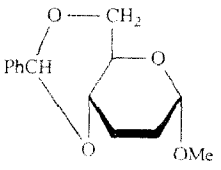
33 $R^1 = R^3 = H$, $R^2 =$ 

34 $R^1 = R^3 = H$, $R^2 =$ 

Our studies were subsequently directed toward an alternative synthesis of **10** and **11**. Reduction of the 4-halogeno-esters **5** and **6** with di-isobutylaluminium hydride at −78° yielded the crystalline 4-chloro-aldehyde **16** and the unstable 4-bromo-aldehyde **17**. Treatment of **16** and **17** with methanolic 1.5% hydrogen chloride at room temperature, followed by column chromatography, yielded the corresponding pure methyl glycosides **18**, **19**, **20**, and **21**, respectively. Attempted reductive hydrogenolysis of **18** and **19** over palladised charcoal, or with lithium aluminium hydride in boiling oxolane, was unsuccessful and the compounds were recovered unchanged. Catalytic hydrogenolysis of **20** and **21**, however, proceeded smoothly to yield **10** (89%) and **11** (62.5%), respectively.

The $[\alpha]_D$ values measured for **10** obtained by the two routes (+149° and +142°) are higher than that (+126°) reported recently[8]. Our values are closer in agreement with those reported[13] for **10** and its (2*R*,6*R*)-enantiomer (+137° and −141°, respectively), obtained from (±)-*trans*-6-hydroxymethyl-2-methoxy-5,6-dihydro-2*H*-pyran (**22**) by

chemical resolution followed by catalytic hydrogenation. Consideration of the close similarity of the two $[\alpha]_D$ values now measured for **10**, the specificity of the two chosen routes of synthesis, the absence of evidence for diastereomers in the ^{1}H-n.m.r. spectra of **10** and **11**, the exclusion of furanoid structures, and the relatively high negative $[\alpha]_D$ value of **11** suggests that our values represent the true upper values of the rotatory power of **10**.



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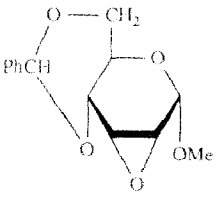

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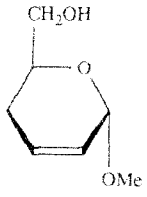
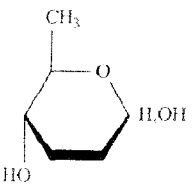


(±)**22**



23

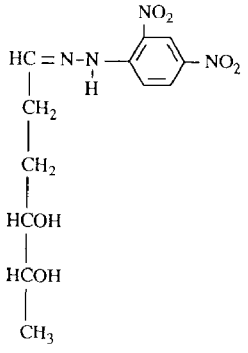
2,3,6-Trideoxy sugars are of interest in view of their occurrence in several antibiotics. D-Amicetose (**23**), derived from amicetin[14], has been synthesised severally from natural carbohydrate precursors[15-22] and other sources[23,24]. A synthesis of methyl α-D- and β-D-amicetoside (**24** and **25**) from the dideoxy-ester **1** was also developed during the current study.

The tosylate **4** was reduced by di-isobutylaluminium hydride at −78° to the unstable aldehyde **26**, which yielded a mixture of the stable methyl glycosides **27** and **28** on treatment with methanolic 1.5% hydrogen chloride. The mixture migrated as a single component in t.l.c., but the ^{1}H-n.m.r. spectrum indicated a ~4:1 mixture of **27** and **28**. The mixture could not be fractionated by column chromatography, and treatment with *p*-nitrobenzoyl chloride or *p*-toluenesulfonyl chloride in the usual manner yielded analytically pure mixtures of the crystalline-*p*-nitrobenzoates **29** and **30**, and the ditosylates **31** and **32**, which could not be separated by column chromatography or by fractional crystallisation.

Both **24** and **25** were obtained from the mixture of ditosylates **31** and **32** by reduction with lithium aluminium hydride. Thus, on treatment of the mixture with an excess of the reductant in ether for 20 h, **24** (49%) and **25** (20%) were obtained after column chromatography; the remainder of the material (8%) was a mixture of the two glycosides. The identity of **24** and **25** was confirmed by conversion into the crystalline 3,5-dinitrobenzoates **33** and **34**, respectively, and, after acid hydrolysis, into the 2,4-dinitrophenylhydrazone **35** of the free sugar **23**. Both ester **33** and hydrazone **35**

exhibited physical constants in accord with literature values. The glycoside **25** had not previously[17] been characterised.

We recently described[1] the synthesis of some deoxyalditols from D-glucono-1,5-lactone, and this series has now been extended to include the (2*S*)-diol **36** and the (2*S*)-triol **37**, which were obtained from the ester **1**. Both enantiomers of **36** have been described[25–27], but only racemic **37** seems to be recorded.



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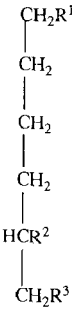
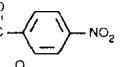
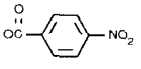
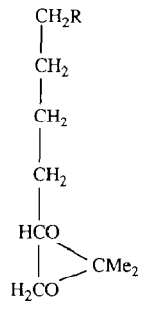


36 $R^1 = H, R^2 = R^3 = OH$

37 $R^1 = R^2 = R^3 = OH$

39 $R^1 = R^2 = R^3 =$ 

42 $R^1 = H, R^2 = R^3 =$ 



38 R = OH

40 R = OTs

41 R = H

Reduction of either **6** or **7** with lithium aluminium hydride in 1,2-dimethoxyethane yielded the alcohol **38**. Hydrolysis of **38** with aqueous 80% acetic acid then gave the required triol **37**, characterised as the crystalline tris(*p*-nitrobenzoate) **39**. *p*-Toluenesulfonylation of **38** yielded the syrupy monotosylate **40**, reductive detosylation of which with lithium aluminium hydride in oxolane[1] gave **41**. This was not isolated because of its volatility, but treated immediately with aqueous 33% acetic acid to give 70% of the diol **36**, characterised as the bis(*p*-nitrobenzoate) **42**.

The transformations described here further illustrate the potential of D-glucono-1,5-lactone as a cheap, but valuable, source of synthetically interesting intermediates. Their application in the synthesis of other deoxy and aminodeoxy sugars of biological interest is currently under investigation.

EXPERIMENTAL

Optical rotations were determined with a Perkin–Elmer Model 241 automatic polarimeter on 1% solutions in chloroform, unless stated otherwise, at 20°. T.l.c. was performed on Kieselgel 60 (Merck) with light petroleum–ethyl acetate (1:1) and detection by charring with 0.1 M $K_2Cr_2O_7$ in M sulfuric acid. Column chromatography and

flash-column chromatography were performed on Silica Gel 60 and 60 H with the solvent mixtures indicated. G.l.c. was conducted with a Hewlett–Packard HP 5890 gas chromatograph, using a capillary column (25 m) of HP-1, a temperature programme from 100 to 150° at 5°/min, followed by 5 min at 150° (isothermal), and nitrogen at 7.5 p.s.i. as the carrier gas. Di-isobutylaluminium hydride was purchased from Janssen Chimica as a M solution in hexane. ^{1}H-N.m.r. spectra were recorded with a Varian EM 2940 (90 MHz) spectrometer on solutions in $CDCl_3$ (internal Me_4Si).

*Methyl 2,3-dideoxy-5,6-O-isopropylidene-*D*-erythro-hexonate* (**1**). — A stirred mixture of **3** (ref. 2) (12.87 g, 41.7 mmol) and anhydrous sodium acetate (13 g) in methanol (130 mL) was heated overnight at reflux temperature. The mixture was cooled to room temperature, treated with palladised charcoal (10%, 300 mg), and then hydrogenated (1 atm) for 4 h. The inorganic material was removed by filtration and washed with methanol (2 × 10 mL), and the combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in dichloromethane (100 mL) was washed with water (100 mL) and the aqueous layer extracted with dichloromethane (50 mL). The combined dichloromethane solutions were then washed with saturated aqueous sodium hydrogen carbonate (50 mL) and water (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue (8.34 g) gave **1** (6.86 g, 75.4%), $[\alpha]_D$ +9.2° ; lit.[2] $[\alpha]_D$ +8.9°.

*Methyl 2,3-dideoxy-5,6-O-isopropylidene-4-O-*p*-tolylsulfonyl-*D*-erythro-hexonate* (**4**). — A stirred solution of **1** (8.15 g, 3.74 mmol) in pyridine (25 mL) at −18° was treated with tosyl chloride (8.56 g, 4.5 mmol) and then set aside at 5° for 2 days. The crude product (10.58 g), obtained after conventional work-up, was recrystallised from 2-propanol to give **7** (9.23 g, 66.5%), m.p. 62–64.5°, $[\alpha]_D$ −16.5°. ^{1}H-N.m.r. data: δ 7.83–7.37 (q_{AB}, 4 H, aromatic H), 4.70 (q, 1 H, H-4), 3.97 (m, 3 H, H-5,6,6'), 3.67 (s, 3 H, OMe), 2.45 (s, 3 H, tosyl Me), 2.40 (t, 2 H, H-2,2'), 1.96 (m, 2 H, H-3,3'), 1.33 and 1.30 (2 s, each 3 H, CMe_2).

Anal. Calc. for $C_{17}H_{24}O_7S$: C, 54.82; H, 6.50. Found: C, 54.65; H, 6.52.

*Methyl 4-chloro-5,6-O-isopropylidene-2,3,4-trideoxy-*D*-threo-hexonate* [(*4S*,*5R*)-*methyl 4-chloro-5,6-isopropylidenedioxyhexanoate*, **5**]. — Triphenylphosphine (8.34 g, 32.2 mmol) was added portionwise during 15 min to a stirred solution of **1** (3.0 g, 13.8 mmol) in dichloromethane (30 mL) containing carbon tetrachloride (6.9 mL) and imidazole (1.045 g, 15.4 mmol) maintained under nitrogen. The mixture was then stirred overnight at room temperature and added to a stirred mixture of light petroleum–ethyl acetate (3:1, 250 mL). After 1.5 h, the supernatant solution was decanted from the sticky residue, which was then washed with further quantities (4 × 50 mL) of the same solvent mixture. The combined supernatant solution and washings were filtered through a layer (7 × 4 cm) of silica gel and concentrated *in vacuo* to yield **5** (2.82 g, 86%) as an oil that crystallised on storage at −78°; m.p. 28.5–30° (from water), $[\alpha]_D$ +33°. ^{1}H-N.m.r. data: δ 4.10 (m, 4 H, H-4,5,6,6'), 3.68 (s, 3 H, OMe), 2.55 (m, 2 H, H-2,2'), 2.08 (m, 2 H, H-3,3'), 1.45 and 1.37 (2 s, each 3 H, CMe_2).

Anal. Calc. for $C_{10}H_{17}ClO_4$: C, 50.74; H, 7.24. Found: C, 50.79; H, 7.13.

*Methyl 4-bromo-5,6-O-isopropylidene-2,3,4-trideoxy-*D*-threo-hexonate* [(*4S*,*5R*)-

methyl 4-bromo-5,6-isopropylidenedioxyhexanoate, **6**]. — Treatment of **1** (4.58 g, 21.0 mmol), carbon tetrabromide (15.3 g, 46.2 mmol), and imidazole (1.71 g, 25.2 mmol) in dichloromethane (50 mL) with triphenylphosphine (12.7 g, 48.3 mmol), in the manner described above, yielded an oil (10.5 g) contaminated (^{1}H-n.m.r.) with bromoform. Flash-column chromatography (light petroleum–ethyl acetate, 3:1) of the material gave **6** (4.64 g, 79%), which crystallised on storage at −78°; m.p. 31.5–33.5° (from water), $[\alpha]_D$ +33°. ^{1}H-N.m.r. data: δ 4.12 (m 4 H, H-4, 5,6,6'), 3.70 (s, 3 H, OMe), 2.58 (m, 2 H, H-2,2'), 2.12 (m, 2 H, H-3,3'), 1.45 and 1.35 (2 s, each 3 H, CMe_2).

Anal. Calc. for $C_{10}H_{17}BrO_4$: C, 42.72; H, 6.09. Found: C, 42.81; H, 6.17.

(*5S*)-*Methyl 5,6-isopropylidenedioxyhexanoate* (**7**). — A solution of **6** (2.29) in methanol (25 mL) was treated with sodium acetate (2.3 g) and palladised charcoal (10%, 230 mg), and then hydrogenated (1 atm) for 4 h at room temperature. The inorganic material was removed by filtration and washed with methanol (10 mL), and the combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in dichloromethane (50 mL) was washed with saturated aqueous sodium hydrogen carbonate (10 mL) and water (20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give pure (t.l.c. and g.l.c.) **7** (1.62 g, 98%), $[\alpha]_D$ +15°; lit.[7] $[\alpha]_D$ +6.7°. ^{1}H-N.m.r. data: δ 4.08 (m, 2 H, H-6,6'), 3.68 (s, 3 H, OMe), 3.52 (m, 1 H, H-5), 2.35 (m, 2 H, H-2,2'), 1.65 (m, 4 H, H-3,3',4,4'), 1.40 and 1.35 (2 s, each 3 H, CMe_2).

(*5S*)-*5,6-Isopropylidenedioxyhexanal* (**8**). — A solution of di-isobutylaluminium hydride (3.8 mL) was added dropwise to a stirred, cooled (−78°) solution of **7** (0.643 g, 3.18 mmol) in light petroleum (15 mL) and dry toluene (15 mL) maintained under nitrogen. The mixture was then stirred for a further 3 h at the same temperature, treated with sodium sulfate decahydrate (1.0 g), allowed to attain room temperature, treated with anhydrous sodium sulfate (1.0 g), and filtered through a layer (0.5 cm) of anhydrous sodium sulfate. The inorganic material was washed with dichloromethane (2 × 10 mL), and the combined filtrate and washings were concentrated *in vacuo*. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue gave **8** (0.465 g, 85%), which was essentially pure (g.l.c.) Distillation *in vacuo* gave analytically pure **8** (0.373 g, 68%), b.p. 100°/0.25 mbar, $[\alpha]_D$ +16°. ^{1}H-N.m.r. data: δ 9.80 (t, 1 H, CHO), 4.03 (m, 2 H, H-6,6'), 3.48 (m, 1 H, H-5), 2.50 (m, 2 H, H-2,2'), 1.67 (m, 4 H, H-3,3',4,4'), 1.40 and 1.35 (2 s, each 3 H, CMe_2).

Anal. Calc. for $C_9H_{16}O_3$: C, 62.5; H, 9.1. Found: C, 62.8; H, 9.4.

Compound **8** (60 mg) in 2M hydrochloric acid (20 mL) was treated with 2,4-dinitrophenylhydrazine (95 mg), and the mixture was heated on a boiling water bath for 5 min and then set aside at room temperature. Column chromatography (1,2-dimethoxyethane–cyclohexane, 3:2) of the crystalline material (135 mg) yielded the hydrazone **9** (42 mg, 38%), m.p. 106–108° (from 1,2-dimethoxyethane–toluene), $[\alpha]_D$ −8° (*c* 0.4, pyridine).

Anal. Calc. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.46; H, 5.16; N, 17.82.

(*4S,5R*)-*4-Chloro-5,6-isopropylidenedioxyhexanal* (**16**). — A solution of compound **5** (0.5 g, 2.11 mmol) was treated with di-isobutylaluminium hydride (2.6 mL) and

processed as described above. Column chromatography (light petroleum–ethyl acetate, 3:1) of the resulting material gave **16** (0.37 g, 84.5%). A portion (95 mg) of the product was sublimed (90°/17 mbar) to give pure **16**, m.p. 28.5–32.5°, $[\alpha]_D$ +33.5°. ^{1}H-N.m.r. data: δ 9.85 (s, 1 H, CHO), 4.10 (m, 4 H, H-4,5,6,6'), 2.72 (t, 2 H, H-2,2'), 2.07 (m, 2 H, H-3,3'), 1.45 and 1.35 (2 s, each 3 H, CMe_2).

Anal. Calc. for $C_9H_{13}ClO_3$: C, 52.31; H, 7.2. Found C, 51.82; H, 7.15.

(4S,5R)-4-Bromo-5,6-isopropylidenedioxyhexanal (**17**). — A solution of compound **6** (1.008 g, 3.58 mmol) was treated with di-isobutylaluminium hydride (4.3 mL) and processed as described above. Column chromatography (light petroleum–ethyl acetate, 3:1) of the resulting material gave **17** (0.716 g, 80%) as an essentially pure (t.l.c.), but unstable oil, $[\alpha]_D$ +33.5°. ^{1}H-N.m.r. data: δ 9.87 (s, 1 H, CHO), 4.10 (m, 4 H, H-4,5,6,6'), 2.73 (m, 2 H, H-2,2'), 2.13 (m, 2 H, H-3,3'), 1.50 and 1.37 (2 s, each 3 H, CMe_2).

Methyl 4-chloro-2,3,4-trideoxy-α- (**18**) *and -β-*D-threo-*hexopyranoside* (**19**). — A solution of **16** (1.20 g, 5.08 mmol) in methanolic 1.5% hydrogen chloride (60 mL) was stirred overnight at room temperature, then neutralised with sodium hydrogen carbonate, and filtered. The inorganic material was washed with methanol (2 × 10 mL), and the combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in dichloromethane (50 mL) was washed with water (25 mL), the aqueous solution was extracted with dichloromethane (3 × 25 mL), and the combined dichloromethane extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash-column chromatography (light petroleum–ethyl acetate, 3:1) of the resulting crystalline material gave **18** (0.647 g, 62%), m.p. 101–102° (from isopropyl ether–light petroleum), $[\alpha]_D$ +123°. ^{1}H-N.m.r. data: δ 4.77 (bs, 1 H, H-1), 4.30 (bs, 1 H, H-4), 3.80 (m, 3 H, H-5,6,6'), 3.38 (s, 3 H, OMe), 2.20 (s, 1 H, OH), 1.9 (m, 4 H, H-2,2',3,3').

Anal. Calc. for $C_7H_{13}ClO_3$: C, 46.55; H, 7.25. Found: C, 46.56; H, 7.22.

Further elution gave **19** (0.157 g, 15%), m.p. 113.5–114.5° (from isopropyl ether–hexane), $[\alpha]_D$ −71°. ^{1}H-N.m.r. data: δ 4.47 (m, 1 H, H-1), 4.15 (bs, 1 H, H-4), 3.80 (m, 3 H, H-5,6,6'), 3.52 (s, 3 H, OCH_3), 2.01 (m, 5 H, H-2,2',3,3',OH).

Anal. Calc. for $C_7H_{13}ClO_3$: C, 46.55; H, 7.25. Found: C, 47.05; H, 7.25.

*Methyl 4-bromo-2,3,4-trideoxy-α-*D-threo-*hexopyranoside* (**20**) *and -β-*D-threo-*hexopyranoside* (**21**). — The aldehyde **17** (0.56 g, 2.22 mmol) was treated with methanolic 1.5% hydrogen chloride (60 mL) and processed as described above. Flash-column chromatography (light petroleum–ethyl acetate, 3:2) of the resulting material gave **20** (0.335 g, 67.3%), m.p. 125.5–127° (from isopropyl ether–light petroleum), $[\alpha]_D$ +113°. ^{1}H-N.m.r. data: δ 4.76 (bs, 1 H, H-1), 4.33 (bs, 1 H, H-4), 3.70 (m, 3 H, H-5,6,6'), 3.37 (s, 3 H, OMe), 2.03 (m, 5 H, H-2,2',3,3' and OH).

Anal. Calc. for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82. Found: C, 37.52; H, 5.82.

Further elution gave **21** (83.5 mg, 17%), m.p. 106.5–109° (from isopropyl ether–light petroleum), $[\alpha]_D$ −55°. ^{1}H-N.m.r. data: δ 4.43 (m, 1 H, H-1), 4.22 (bs, 1 H, H-4), 3.75 (m, 3 H, H-5,6,6'), 3.52 (s, 3 H, OMe), 1.95 (m, 5 H, H-2,2',3,3' and OH).

Anal. Calc. for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82. Found: C, 37.22; H, 5.75.

*Methyl 2,3,4-trideoxy-α-*D-glycero-*hexopyranoside* (**10**) *and -β-*D-glycero-*hexopy-*

ranoside (**11**). — (*a*) *From compound* **8**. The aldehyde **8** (0.59 g, 3.44 mmol) was treated with 1.5% methanolic hydrogen chloride (30 mL) and processed as described above. Flash-column chromatography (light petroleum ethyl acetate, 3:2) of the crude product gave **10** (0.243 g, 48.6%), $[\alpha]_D$ +149°; lit.[8] +126°, lit.[13] $[\alpha]_D$ +137°. ^{1}H-N.m.r. data: δ 4.73 (bs, 1 H, H-1), 3.80 (m, 1 H, H-5), 3.55 (m, 2 H, H-6,6'), 3.37 (s, 3 H, OMe), 2.2 (bs, 1 H, OH), 2.2–1.37 (m, 6 H, H-2,2',3,3',4,5).

A solution of **10** (67 mg) in pyridine (2 mL) was treated with 3,5-dinitrobenzoyl chloride (113 mg) and processed in the usual manner to give **12** (89 mg, 57%), m.p. 108–109° (from isopropyl ether), $[\alpha]_D$ +68°. ^{1}H-N.m.r. data: δ 9.25 (m, 3 H, aromatic H), 4.80 (m, 1 H, H-1), 4.45 (d, 2 H, H-6,6'), 4.20 (m, 1 H, H-5), 3.42 (s, 3 H, OMe), 1.72 (m, 6 H, H-2,2',3,3',4,4').

Anal. Calc. for $C_{14}H_{16}N_2O_8$: C, 49.42; H, 4.74; N, 8.23. Found: C, 49.54; H, 4.62; N, 8.43.

Further elution gave a mixture of **10** and **11** (40.6 mg, 8%), followed by pure (g.l.c.) **11** (73 mg, 15%), $[\alpha]_D$ −75°. ^{1}H-N.m.r. data: δ 4.37 (m, 1 H, H-1), 3.60 (bs, 3 H, H-5,6,6'), 3.48 (s, 3 H, OMe), 2.07–1.20 (m, 7 H, H-2,2',3,3',4,4' and OH).

Treatment of **11** with 3,5-dinitrobenzoyl chloride/pyridine in the usual manner gave **13** (37%), m.p. 93–95° (from isopropyl ether), $[\alpha]_D$ −32°. ^{1}H-N.m.r. data: δ 9.20 (m, 3 H, aromatic H), 4.45 (m, 3 H, H-1,6,6'), 3.87 (m, 1 H, H-5), 3.47 (s, 3 H, OMe), 1.68 (m, 6 H, H-2,2',3,3',4,4').

Anal. Calc. for $C_{14}H_{16}N_2O_8$: C, 49.42; H, 4.74; N, 8.23. Found: C, 49.22; H, 5.00; N, 8.29.

(*b*) *From compound* **20**. A solution of **20** (0.266 g) in methanol (20 mL) was treated with anhydrous sodium acetate (0.26 g) and palladised charcoal (10%, 20 mg), and then hydrogenated (1 atm) for a total of 14 h. After 6.5 h and 11.5 h, the mixture was treated with additional amounts (10 mg) of the catalyst. The mixture was filtered, the inorganic material was washed with methanol (2 × 10 mL), and the combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in dichloromethane (25 mL) was washed with water, the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give **10** (0.154 g, 89.3%), $[\alpha]_D$ +142°.

(*c*) *From compound* **21**. Treatment of **12** (56 mg) in the above manner gave **11** (23 mg, 63%), $[\alpha]_D$ −72°.

(*4S,5R*)-*5,6-Isopropylidenedioxy-4*-p-*toluenesulfonyloxyhexanal* (**26**). A solution of the tosylate **4** (0.5 g, 1.46 mmol) in toluene (5 mL) was treated with di-isobutylaluminium hydride (1.8 mL) at −78° for 1.75 h, and then processed as described above. Column chromatography (light petroleum–ethyl acetate, 3:1) of the product gave **26** (0.366 g, 79.5%), $[\alpha]_D$ −6.7°, as a very unstable oil. ^{1}H-N.m.r. data: δ 9.75 (s, 1 H, CHO), 7.35–7.80 (q_{AB}, 4 H, aromatic H), 4.65 (m, 1 H, H-4), 3.90 (m, 3 H, H-5,6,6'), 2.57 (t, 2 H, H-2,2'), 2.45 (s, 3 H, CH_3), 1.98 (m, 2 H, H-3,3'), 1.32 and 1.30 (2 s, each 3 H, CMe_2).

Methyl 2,3-dideoxy-4-O-p-*toluenesulfonyl*-α-D-glycero-*hexopyranoside* (**27**) *and* -β-D-glycero-*hexopyranoside* (**28**). — A solution of freshly prepared aldehyde **26** (1.78 g,

5.20 mmol) in methanolic 1.5% hydrogen chloride (170 mL) was stirred overnight at room temperature, then neutralised by careful addition of sodium hydrogen carbonate, and filtered. The inorganic material was washed with methanol (2 × 30 mL), and the combined filtrate and washings were concentrated *in vacuo*. Flash-column chromatography of the residue gave a mixture of **27** and **28** as a homogeneous (t.l.c.) oil (1.21 g, 76%), $[\alpha]_D$ +83°. ^{1}H-N.m.r. data: δ 7.80–7.33 (q_{AB}, 4 H, aromatic H), 4.50 (m, 2 H, H-1,4), 3.57 (m, 3 H, H-5,6,6'), 3.38 and 3.30 (2 s, each 3 H; OMe_β and OMe_α, 1:4), 2.43 (s, 4 H, aromatic CH_3, OH), 1.73 (m, 4 H, H-2,2',3,3').

*Methyl 2,3-dideoxy-6-*O*-*p*-nitrobenzoyl-4-*O*-*p*-toluenesulfonyl-*α*-*D*-glycero-hexopyranoside* (**29**) *and -β-*D*-glycero-hexopyranoside* (**30**). — A solution of the foregoing product (0.263 g) in pyridine (2 mL) was treated with *p*-nitrobenzoyl chloride (0.18 g) and processed in the usual manner to give a mixture of **29** and **30** (0.28 g, 75%), m.p. 117–120.5° (from ethanol), $[\alpha]_D$ +70°. ^{1}H-N.m.r. data: δ 8.23 (q_{AB}, 4 H, *J* 12 Hz and 8 Hz, aromatic H), 7.77 and 7.23 (q_{AB}, 4 H, *J* 9 Hz, aromatic H), 4.50–3.98 (m, 5 H, H-1,4,5,6,6'), 3.40 and 3.32 (2 s, each 3 H; OMe_β and OMe_α, 1:4), 2.33 (s, 3 H, aromatic CH_3), 1.98 (m, 4 H, H-2,2',3,3').

Anal. Calc. for $C_{21}H_{23}NO_9S$: C, 54.19; H, 4.98; N, 3.01; S, 6.89. Found: C, 53.83; H, 5.08; N, 2.54; S, 7.36.

*Methyl 2,3-dideoxy-4,6-di-*O*-*p*-toluenesulfonyl-α-*D*-glycero-hexopyranoside* (**31**) *and -β-*D*-glycero-hexopyranoside* (**32**). — To a solution of **27**/**28** (1.19 g) in dry pyridine (5 mL) at −18° was added tosyl chloride (0.935 g). The mixture was stored overnight at 5°, treated with ice–water (1 mL), and, after 5 min, poured into ice–water (100 mL). The crude product was recrystallised from propan-2-ol to give a mixture of **31** and **32** (1.54 g, 87%), m.p. 103–132°, $[\alpha]_D$ +60.5°; lit.[17] m.p. (compound **32**) 136–138°. ^{1}H-N.m.r. data: δ 7.75–7.31 (q_{AB}, 8 H, aromatic H), 4.13 (m, 5 H, H-1,4,5,6,6'), 3.30 and 3.23 (2 s, each 3 H, OMe_β and OMe_α, 1:4), 2.42 (s, 6 H, aromatic CH_3), 1.80 (m, 4 H, H-2,2',3,3').

Anal. Calc. for $C_{21}H_{26}O_8S_2$: C, 53.60; H, 5.57; S, 13.63. Found: C, 53.42; H, 5.82; S, 14.22.

*Methyl 2,3,6-trideoxy-α-*D*-glycero-hexopyranoside and -β-*D*-glycero-hexopyranoside* (*methyl α-D- and β-D-amicetoside*, **24** *and* **25**). — A mixture of **31** and **32** (1.59 g, 3.38 mmol) was added portionwise to a stirred suspension of lithium aluminium hydride (900 mg, 23.7 mmol) in dry ether (100 mL), maintained under nitrogen. The mixture was stirred overnight at room temperature, and processed in the manner described previously[1]. Flash-column chromatography (light petroleum–ethyl acetate, 3:2) of the residue gave **24** (0.242 g, 49%), $[\alpha]_D$ +154°; lit.[11] $[\alpha]_D$ +142° (water). ^{1}H-N.m.r. data: δ 4.63 (bs, 1 H, H-1), 3.40 (m, 2 H, H-4,5), 3.35 (s, 3 H, OCH_3), 1.75 (m, 5 H, H-2,2',3,3' and OH), 1.23 (d, 3 H, CH_3).

Treatment of **24** with 3,5-dinitrobenzoyl chloride in pyridine yielded, after recrystallisation from isopropyl ether, the 3,5-dinitrobenzoate **33**, m.p. 98.5–101°, $[\alpha]_D$ +126°; lit.[11] m.p. 100–101°, $[\alpha]_D$ +134°.

Further elution then gave **25** (97.5 mg, 20%), $[\alpha]_D$ −22°; lit.[17] $[\alpha]_D$ −21.9°. ^{1}H-N.m.r. data: δ 4.38 (m, 1 H, H-1), 3.47 (s, 3 H, OMe), 3.32 (m, 2 H, H-4,5), 1.75 (m, 5 H, H-2,2',3,3' and OH), 1.30 (d, 3 H, CH_3).

Treatment of **25** with 3,5-dinitrobenzoyl chloride in pyridine yielded, after recrystallisation from propan-2-ol and then methanol, the 3,5-dinitrobenzoate **34**, m.p. 117–120°, $[\alpha]_D$ +0.8°. ^{1}H-N.m.r. data: δ 9.25 (t, 1 H, aromatic H), 9.13 (d, 2 H, aromatic H), 4.87 (m, 1 H, H-4), 4.56 (m, 1 H, H-1), 3.77 (m, 1 H, H-5), 3.52 (s, 3 H, OMe), 1.86 (m, 4 H, H-2,2',3,3'), 1.35 (d, 3 H, CH_3).

Anal. Calc. for $C_{14}H_{16}N_2O_8$: C, 49.42; H, 4.74; N, 8.23. Found: C, 49.69; H, 4.69; N, 8.25.

Further elution gave a mixture of **24** and **25** (37.5 mg, 8%), which was not treated further.

Treatment of either **24** or **25** in 2M hydrochloric acid with 2,4-dinitrophenylhydrazine[11,18] yielded the hydrazone **35**, m.p. 153.5–156°, $[\alpha]_D$ −8° (pyridine); lit. m.p. 154–155.5°, $[\alpha]_D$ −9.8° (ref. 11); m.p. 156–157°, $[\alpha]_D$ −10° (ref. 14).

(5S)-*5,6-Isopropylidenedioxyhexanol* (**38**). – (*a*) *From* **6**. A solution of **6** (1.71 g, 6.01 mmol) in 1,2-dimethoxyethane (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (1.39 g, 6 mol. equiv.) in 1,2-dimethoxyethane (10 mL). The mixture was boiled under reflux for 16 h under nitrogen, then cooled (0°), treated dropwise with water (6.5 mL), followed by anhydrous magnesium sulfate (4 g), stirred for 30 min, filtered through a thin layer of anhydrous magnesium sulfate, and concentrated *in vacuo*. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue gave **38** (0.865 g, 82%) as an oil, $[\alpha]_D$ +18°. ^{1}H-N.m.r. data: δ 4.08 (m, 2 H, H-1,1'), 3.55 (m, 3 H, H-5,6,6'), 1.87 (m, 6 H, H-2,2',3,3',4,4'), 1.40 and 1.33 (2 s, each 3 H, CMe_2).

(*b*) *From* **7**. A solution of **7** (1.307 g, 6.47 mmol) in 1,2-dimethoxyethane (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.49 g, 2 mol. equiv.) in 1,2-dimethoxyethane (10 mL). The mixture was boiled under reflux for 2 h, under nitrogen, and processed as in (*a*) to give **38** (1.12 g, 99%), $[\alpha]_D$ +18°.

A stirred solution of **38** (0.858 g, 4.93 mmol) in pyridine (4 mL) at 0° was treated with tosyl chloride. The mixture was stored overnight at 5°, treated with ice–water (1 mL), and, after 5 min, poured into ice–water (100 mL). The mixture was extracted with dichloromethane (2 × 70 mL), and the combined extracts were washed successively with 2M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (light petroleum–ethyl acetate, 3:1) of the crude product gave syrupy **40** (1.24 g, 77%), $[\alpha]_D$ +8.7°. ^{1}H-N.m.r. data: δ 7.80–7.35 (q_{AB}, 4 H, aromatic H), 4.05 (m, 4 H, H-1,1',6,6'), 3.50 (m, 1 H, H-5), 2.43 (s, 3 H, tosyl Me) 1.58 (m, 6 H, backbone H), 1.37 and 1.32 (2 s, each 3 H, CMe_2)

(5S)-*1,5,6-Hexanetriol* (**37**). — A solution of **38** (0.283 g) in aqueous 80% acetic acid (10 mL) was set aside at room temperature for 4 days, then concentrated *in vacuo*, and water (3 × 10 mL) was distilled *in vacuo* from the residue. Column chromatography (1,2-dimethoxyethane–light petroleum, 3:2) of the residue (0.26 g) yielded pure (g.l.c.) **37** (0.233 g, 97%) as an oil, $[\alpha]_D$ −3.4°.

The tris(*p*-nitrobenzoate) (**39**, 47%) of **37** had m.p. 120–121° (from ethanol–ethyl acetate), $[\alpha]_D$ +8.6°.

Anal. Calc. for $C_{27}H_{23}N_3O_{12}$: C, 55.77; H, 3.99; N, 7.23. Found: C, 55.84; H, 4.11; N, 7.14.

(2S)-*1,2-Hexanediol* (**36**). — A solution of **40** (1.89 g, 5.76 mmol) in dry oxolane (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.876 g, 4 mol. equiv.) in oxolane (20 mL). The mixture was boiled under reflux for 2 h under nitrogen, cooled (0 °), treated dropwise with water (3.5 mL), followed by anhydrous magnesium sulfate (4 g), and filtered through a layer of anhydrous sodium sulfate (1 cm). The inorganic material was washed with oxolane (5 mL) and ether (10 mL), and the combined filtrate and washings were concentrated at atmospheric pressure to ~ 10 mL. The residue was treated with aqueous 33% acetic acid (15 mL), the mixture was set aside at room temperature for 3 days and then concentrated *in vacuo*, and toluene (3 × 10 mL) was distilled *in vacuo* from the residue. Column chromatography (ethyl acetate–light petroleum, 3:1) of the residue (0.667 g) yielded **36** (0.476 g, 70%) as a pure (g.l.c.) oil, $[\alpha]_D$ −17.5° (*c* 13, ethanol); lit. $[\alpha]_D$ −15.2° (ref. 25); −15.1° (ref. 27). ^{1}H-N.m.r. data: δ 3.45 (m, 5 H, H-5,6,6′ and OH), 1.40 (bs, 6 H, H-2,2′,3,3′,4,4′), 0.92 (m, 3 H, CH_3).

A solution of **36** (100 mg) in dry pyridine (4 mL) was treated with *p*-nitrobenzoyl chloride (350 mg) and set aside for 4 days. The crude product (328 mg), obtained after conventional work-up, was recrystallised from propan-2-ol to give **42** (282 mg, 80%), m.p. 119–120.5°, $[\alpha]_D$ +32.5°; lit.[28] (for the racemate) m.p. 100.2–100.8°. ^{1}H-N.m.r. data: δ 8.25 (m, 8 H, aromatic H), 5.57 (m, 1 H, H-5), 4.60 (m, 2 H, H-6,6′), 1.87 (m, 2 H, H-4,4′), 1.48 (m, 4 H, H-2,2′,3,3′), 0.93 (m, 3 H, CH_3).

Anal. Calc. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.62; H, 4.85; N, 6.59.

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