Higher-carbon Sugars. Part 6.[1] The Synthesis of Some Octose Sugars *via* the Epoxidation of Unsaturated Precursors

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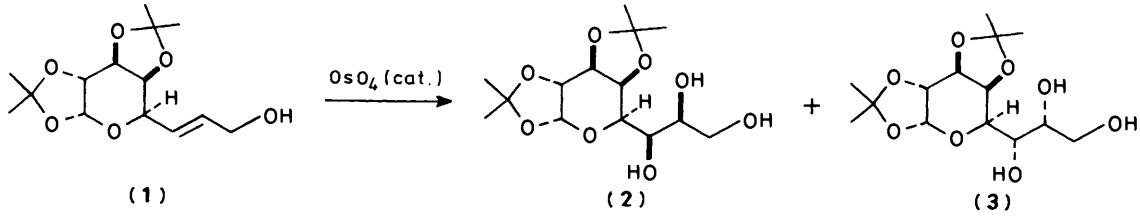
Titanium-catalysed asymmetric epoxidation of (*E*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose (**1**) with di-isopropyl L-(+)-tartrate afforded 6,7-anhydro-1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose (**4**), which was identified by its conversion on basic hydrolysis into 1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (**6**) *via* preferential ring-opening of the Payne-rearrangement product (**5**) at the terminal position. Oxidation of (**1**) with *m*-chloroperbenzoic acid gave principally the isomeric epoxy alcohol (**8**), which basic hydrolysis similarly transformed into 1,2:3,4-di-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranose (**10**). The latter sequence of reactions also yielded 1,2:3,4-di-*O*-isopropylidene-α-D-*threo*-D-*galacto*-octopyranose (**3**) from (*Z*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose (**12**). D-*erythro*-D-*galacto*-Octitol (**7**), L-*erythro*-D-*galacto*-octitol (**11**), and D-*threo*-D-*galacto*-octitol (**16**) are accessible from the protected octoses (**6**), (**10**), and (**3**), respectively.

In a previous paper[2] in this series, we described the synthesis of some octose sugars *via* the OsO_4-catalysed bishydroxylation of unsaturated precursors. Catalytic osmylation of (*E*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose (**1**), for example, furnished a mixture of 1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose (**2**) and the α-D-*threo*-D-*galacto* isomer (**3**) in the ratio 7:1, respectively. A number of useful reference compounds provided by this study[2] has enabled us to examine an alternative route to octose sugars *via* the epoxidation of the same unsaturated precursors.

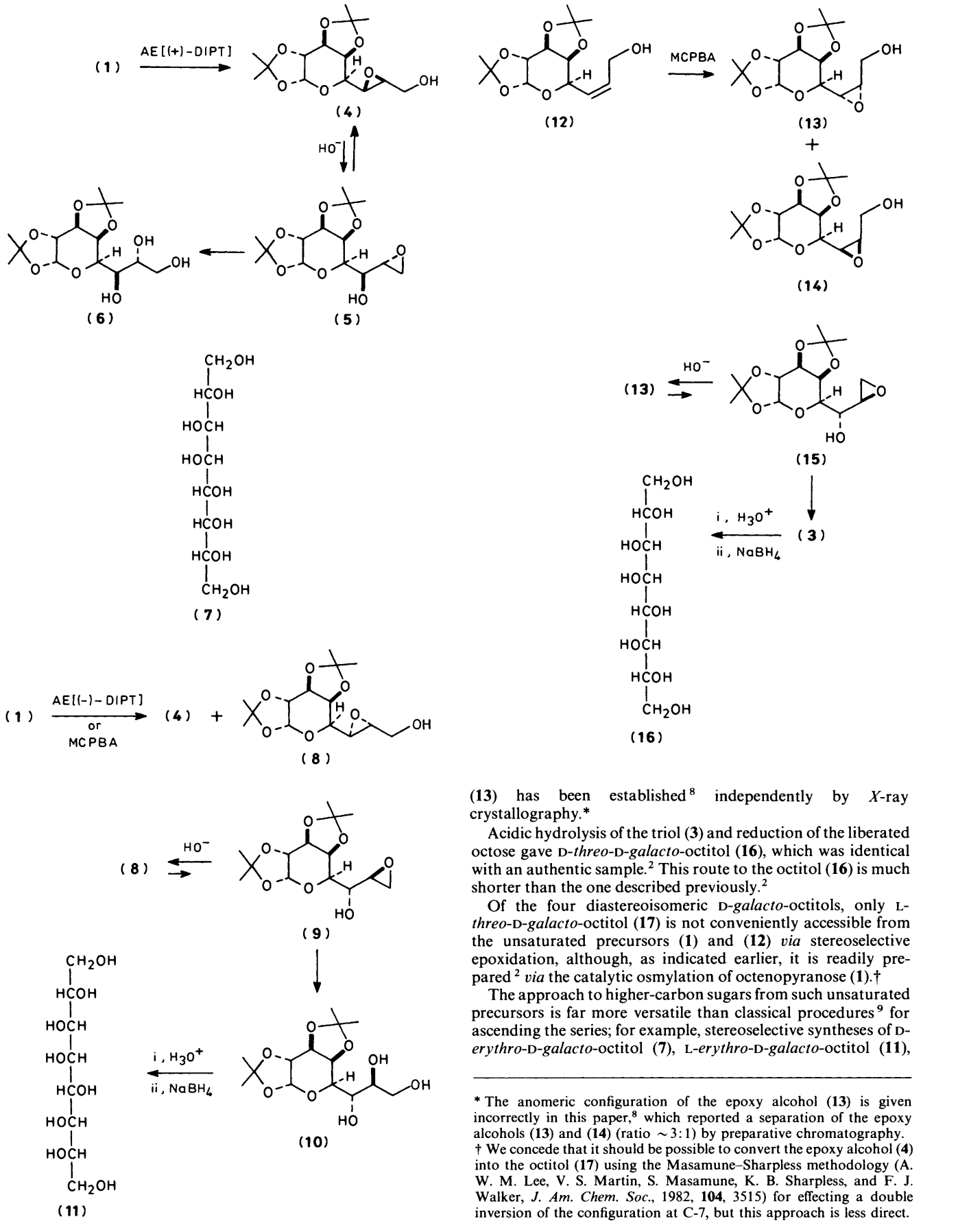


Results and Discussion

Titanium-catalysed asymmetric epoxidation (AE)[3,4] of the (*E*)-allylic alcohol (**1**) with di-isopropyl L-(+)-tartrate [(+)-DIPT] at −23 °C readily gave a single epoxy alcohol, which was assigned as 6,7-anhydro-1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose (**4**) on the assumption that the diastereofacial selectivity of the reagent[3] would overcome the chirality already existing in compound (**1**). This assignment was confirmed when hydrolysis of the epoxy alcohol (**4**) with sodium hydroxide in aqueous 1,4-dioxane afforded 1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose[2] (**6**), which, by analogy,[5] was considered to arise by preferential ring-opening of the Payne-rearrangement[6] product (**5**) at the terminal position with hydroxide ion. Thus, the configuration at C-7 is inverted in the conversion of (**4**) into (**6**). Acidic hydrolysis of the triol (**6**) has already been shown to give the parent octose, reduction of which provided D-*erythro*-D-*galacto*-octitol (**7**).[2] This octitol has been isolated[7] from the avocado (Calavo, Fuerte variety), and was originally synthesised from D-*glycero*-D-*manno*-heptose using the cyanohydrin method.[7]

By contrast, titanium-catalysed epoxidation[3,4] of the (*E*)-allylic alcohol (**1**) with di-isopropyl D-(−)-tartrate [(−)-DIPT] at −23 °C was incomplete after 8 days and furnished a mixture of epoxide (**4**) and 6,7-anhydro-1,2:3,4-di-*O*-isopropylidene-α-D-*threo*-D-*galacto*-octopyranose (**8**), which was shown (^{1}H n.m.r. spectroscopy) to contain only a marginal excess of (**8**). Oxidation of compound (**1**) with *m*-chloroperbenzoic acid (MCPBA) at 0 °C, on the other hand, gave a mixture of the epoxy alcohols (**4**) and (**8**) in the ratio ~1:3, respectively, from which compound (**8**) was obtained by crystallisation, although traces of the isomeric epoxy alcohol (**4**) persisted even after several recrystallisations. Basic hydrolysis of the epoxy alcohol (**8**) gave, *via* preferential ring-opening of the Payne-rearrangement[6] product (**9**) at the terminal position, 1,2:3,4-di-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranose (**10**) (identified by ^{1}H n.m.r. spectroscopy[2]). Some (≤8%) of the isomeric triol (**6**) (identified by ^{1}H n.m.r. spectroscopy[2]) was also formed in this reaction, either from the small proportion of compound (**4**) contaminating the epoxy alcohol (**8**) or, possibly, by ring-opening of epoxide (**8**) at C-6. Acidic hydrolysis of the triol (**10**) and reduction of the resulting octose gave L-*erythro*-D-*galacto*-octitol (**11**), which was identical with an authentic sample.[2]

Not unexpectedly,[3-5] the titanium-catalysed epoxidations of (*Z*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose[2] (**12**) with either (+)- or (−)-DIPT at −23 °C were too slow to be practical, but compound (**12**) reacted readily with MCPBA at 0 °C to produce a mixture of 6,7-anhydro-1,2:3,4-di-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranose (**13**) and the α-D-*erythro*-D-*galacto* isomer (**14**) in the ratio ~3:1, respectively. The epoxy alcohol (**13**) was obtained from this mixture by crystallisation. The structure assigned to the epoxy alcohol (**13**) was based, as before, on the isolation of 1,2:3,4-di-*O*-isopropylidene-α-D-*threo*-D-*galacto*-octopyranose (**3**), formed *via* the terminal epoxide (**15**), following basic hydrolysis. The structure of the epoxy alcohol



(13) has been established[8] independently by *X*-ray crystallography.*

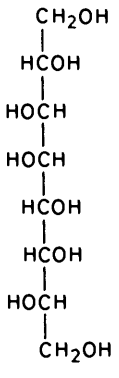
Acidic hydrolysis of the triol (3) and reduction of the liberated octose gave D-*threo*-D-*galacto*-octitol (16), which was identical with an authentic sample.[2] This route to the octitol (16) is much shorter than the one described previously.[2]

Of the four diastereoisomeric D-*galacto*-octitols, only L-*threo*-D-*galacto*-octitol (17) is not conveniently accessible from the unsaturated precursors (1) and (12) *via* stereoselective epoxidation, although, as indicated earlier, it is readily prepared[2] *via* the catalytic osmylation of octenopyranose (1).†

The approach to higher-carbon sugars from such unsaturated precursors is far more versatile than classical procedures[9] for ascending the series; for example, stereoselective syntheses of D-*erythro*-D-*galacto*-octitol (7), L-*erythro*-D-*galacto*-octitol (11),

* The anomeric configuration of the epoxy alcohol (13) is given incorrectly in this paper,[8] which reported a separation of the epoxy alcohols (13) and (14) (ratio ~3:1) by preparative chromatography.

† We concede that it should be possible to convert the epoxy alcohol (4) into the octitol (17) using the Masamune–Sharpless methodology (A. W. M. Lee, V. S. Martin, S. Masamune, K. B. Sharpless, and F. J. Walker, *J. Am. Chem. Soc.*, 1982, **104**, 3515) for effecting a double inversion of the configuration at C-7, but this approach is less direct.



(17)

and L-*threo*-D-*galacto*-octitol (**17**) can be achieved from a single precursor (**1**) by way of either catalytic osmylation or epoxidation.

Experimental

T.l.c. was performed on Kieselgel G, and spots were detected with 1% aqueous sulphuric acid. ^{1}H N.m.r. spectra were recorded for solutions in deuteriochloroform (internal tetramethylsilane) with a Bruker Spectrospin (90 MHz) spectrometer. A Perkin-Elmer Model 141 automatic polarimeter and 1 dm tubes were used for the measurement of specific optical rotations. M.p.s were measured on a Reichert melting point apparatus and are uncorrected.

6,7-*Anhydro*-1,2:3,4-*di*-O-*isopropylidene*-β-L-threo-D-galacto-*octopyranose* (**4**).—A 100 ml round-bottom flask equipped with a Teflon-coated bar magnet was oven-dried and then fitted with a serum cap and flushed with nitrogen. The flask was charged with anhydrous methylene dichloride (25 ml, distilled from calcium hydride) and cooled to −23 °C (solid CO_2–carbon tetrachloride). Titanium(IV) isopropoxide (1.12 ml, 3.76 mmol) and (+)-DIPT (1.11 g, 4.74 mmol) were then added in turn by syringe, and the mixture was stirred for 5 min prior to the addition of solutions of octenopyranose (**1**)[2] (0.9 g, 3.14 mmol) in anhydrous methylene dichloride (5 ml) and 3M *t*-butyl hydroperoxide in toluene[10] (3.15 ml, 9.45 mmol). The flask was then stoppered and kept overnight in a freezer at −23 °C. It was then placed in a cooling bath at −23 °C, and 10% aqueous tartaric acid (8 ml) was added to the stirred solution. The mixture, containing the solidified aqueous layer, was stirred at −23 °C for 30 min and then at room temperature for 1 h. After dilution with methylene dichloride, the organic layer was separated, washed with a little water, dried (Na_2SO_4), and concentrated under reduced pressure. A solution of the residue in diethyl ether (24 ml) was cooled (0 °C) and stirred with M sodium hydroxide (9.6 ml) for 30 min. More ether was then added, and the ethereal layer was separated, washed with a little aqueous sodium chloride, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (2:1) as eluant] gave the *epoxy alcohol* (**4**) (0.627 g, 66%), $[\alpha]_D$ −90° (*c* 1 in $CHCl_3$) (Found: C, 55.9; H, 7.2. $C_{14}H_{22}O_7$ requires C, 55.6; H, 7.3%); δ_H 5.53 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 3.22 (2 H, m, CH−CHO), and 1.47, 1.36, and 1.31 (12 H, 3 s, proportions 2:1:1, 2 × CMe_2).

1,2:3,4-*Di*-O-*isopropylidene*-α-D-erythro-D-galacto-*octopyranose* (**6**).—A solution of epoxide (**4**) (0.273 g, 0.9 mmol) in a mixture of 0.5M sodium hydroxide (5 ml) and 1,4-dioxane (1 ml) in a sealed tube was heated overnight at ~70 °C, and, after having cooled, the dark brown hydrolysate was diluted with water and neutralised with Amberlite IR-120(H^+) resin (1 g). The resin was filtered off and washed with water, and the filtrate and washings were combined and concentrated under reduced pressure. The residue was extracted with chloroform, and the extract was dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (1:2) as eluant] gave the triol (**6**) (0.168 g, 58%), m.p. 117—118 °C (from ethyl acetate–hexane); $[\alpha]_D$ −61° (*c* 0.65 in $CHCl_3$) {lit.,[2] m.p. 117—118 °C; $[\alpha]_D$ −61° (*c* 0.75 in $CHCl_3$)}.

6,7-*Anhydro*-1,2:3,4-*di*-O-*isopropylidene*-α-D-threo-D-galacto-*octopyranose* (**8**).—MCPBA (85%; 0.515 g, 2.54 mmol) was added gradually to a cooled (0 °C) and stirred solution of compound (**1**)[2] (0.527 g, 1.84 mmol) in anhydrous methylene dichloride (30 ml), and the reaction mixture was then kept overnight in a refrigerator (~0 °C). After dilution with methylene dichloride (30 ml), the solution was washed successively with M sodium hydroxide (2 × 3 ml) and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated under reduced pressure. ^{1}H N.m.r. spectroscopy showed that the epoxy alcohols (**4**) and (**8**) had been formed in the ratio ~1:3, respectively. Crystallisation from diethyl ether–hexane gave the *epoxy alcohol* (**8**) (0.322 g, 58%), m.p. 97—98 °C; $[\alpha]_D$ ~ −65.6 °C (*c* 1.2 in $CHCl_3$) (Found: C, 55.0; H, 7.2. $C_{14}H_{22}O_7$ requires C, 55.6; H, 7.3%); δ_H 5.58 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 3.22 (2 H, m, CH−CHO), and 1.47, 1.33, and 1.31 (12 H, 3 s, proportions 2:1:1, 2 × CMe_2). This material contained traces of the isomeric epoxy alcohol (**4**) (^{1}H n.m.r. evidence) that persisted even after several recrystallisations.

1,2:3,4-*Di*-O-*isopropylidene*-β-L-erythro-D-galacto-*octopyranose* (**10**).—A solution of compound (**8**) (0.349 g, 1.15 mmol) in a mixture of 0.5M sodium hydroxide (5 ml) and 1,4-dioxane (1 ml) in a sealed tube was heated for 18 h at ~70 °C, and the hydrolysate was then processed as described previously. Chromatography of the final residue on silica gel [methylene dichloride–acetone (1:2) as eluant] gave the triol (**10**) (~0.192 g, ~52%), $[\alpha]_D$ ~ −52° (*c* 1 in $CHCl_3$), contaminated with a small proportion (≤8%) of the isomeric triol (**6**); δ_H [for (**10**)] 5.62 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 1.53, 1.47, and 1.33 (12 H, 3 s, proportions 1:1:2, 2 × CMe_2).

Hydrolysis of compound (**10**) and reduction of the resulting octose, as described later for the preparation of octitol (**16**), afforded L-*erythro*-D-*galacto*-octitol (**11**) (58%), m.p. (from aqueous ethanol) and mixed m.p. 153—154 °C (lit.,[2] 153—154.5 °C).

6,7-*Anhydro*-1,2:3,4-*di*-O-*isopropylidene*-β-L-erythro-D-galacto-*octopyranose* (**13**).—MCPBA (85%; 1.56 g, 7.68 mmol) was added gradually to a cooled (0 °C) and stirred solution of compound (**12**)[2] (1.59 g, 5.55 mmol) in anhydrous methylene dichloride (84 ml), and the reaction mixture was then kept overnight in a refrigerator (~0 °C). Work-up, as previously described, afforded a mixture shown (^{1}H n.m.r. spectroscopy) to contain the epoxy alcohols (**13**) and (**14**) in the ratio ~3:1. Crystallisation from diethyl ether–hexane gave the epoxy alcohol (**13**) (0.701 g, 42%), m.p. 124—125.5 °C; $[\alpha]_D$ −82.5° (*c* 1.3 in $CHCl_3$) {lit.,[8] m.p. 122—124 °C; $[\alpha]_D$ −83° (*c* 0.6 in $CHCl_3$)}.

1,2:3,4-*Di*-O-*isopropylidene*-α-D-threo-D-galacto-*octopyranose* (**3**).—A solution of compound (**13**) (0.336 g, 1.11 mmol) in 0.5M sodium hydroxide (5 ml) containing 1,4-dioxane (1 ml) was heated at ~70 °C for 18 h, and the hydrolysate was processed as described previously. Chromatography of the final residue on silica gel [methylene dichloride–acetone (1:2) as

eluant] gave the *triol* (**3**) (0.229 g, 64%), m.p. 140—141 °C (from ethyl acetate–hexane); $[\alpha]_D$ −59° (*c* 0.8 in $CHCl_3$) (Found: C, 52.6; H, 7.4. $C_{14}H_{24}O_8$ requires C, 52.5; H, 7.55%); δ_H 5.58 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 1.53, 1.43, and 1.32 (12 H, 3 s, proportions 1:1:2, 2 × CMe_2).

D-threo-D-galacto-*Octitol* (**16**).—A solution of the pyranose (**3**) (0.72 g, 2.25 mmol) in trifluoroacetic acid–water (9:1, 11 ml) was kept for 15 min at room temperature, and it was then concentrated under reduced pressure with occasional additions of water. To a cooled (0 °C) and stirred solution of the residue in water (34 ml) was gradually added sodium borohydride (0.4 g, ~10.6 mmol), and the reaction mixture was stirred at 0 °C for 2 h and then overnight at room temperature. Sodium ions were removed with Amberlite IR-120(H^+) resin (14 g), and the resin was filtered off and washed with water. The filtrate and washings were combined and concentrated under reduced pressure, and methanol was evaporated several times from the residue to remove boric acid. Two recrystallisations from aqueous ethanol furnished the pure octitol (**16**) (0.32 g, 59%), m.p. and mixed m.p. 167.5—168.5 °C (lit.,[2] 168—169 °C).

Acknowledgements

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