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

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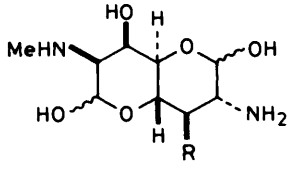
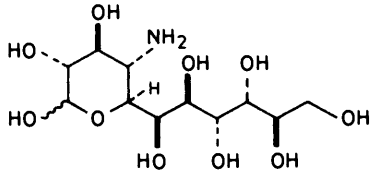
The stereochemical outcome of the osmium tetraoxide oxidation of a number of unsaturated carbohydrate derivatives, including (*E*)- and (*Z*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose (**6**) and (**9**), methyl (*Z*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranuronate (**8**), and 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-oct-7-enopyranose (**10**), has been examined. Such oxidations resulted in the preparation of the synthetically useful octose derivatives 1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (**18**) and 1,2:3,4:6,7-tri-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranose (**31**), as well as syntheses of L-*threo*-D-*galacto*-octitol (**14**), D-*erythro*-D-*galacto*-octitol (**21**), L-*erythro*-D-*galacto*-octitol (**29**), and D-*threo*-D-*galacto*-octitol (**35**).

The synthesis of sugars with carbon chains composed of more than six carbon atoms, the so-called higher-carbon sugars,[2] poses an interesting challenge.[2-4] Such syntheses require the formation of carbon–carbon bonds and control of the stereochemistry at each newly created stereocentre. The concept of asymmetric synthesis was first realised with the Kiliani–Fischer cyanohydrin reaction, which was used to extend the aldose chain by one carbon atom from the reducing end.[2,3] This procedure has been applied to most hexoses,[2,3] but, because of the asymmetric nature of the cyanohydrin synthesis, only a limited number of heptoses are available as substrates. In certain cases, syntheses were extended to give octose, nonose, and decose sugars, but the structures of many of these higher-carbon sugars remain unproved.[2] In recent times, the cyanohydrin procedure has been augmented by other methods;[5] these permit extension of the sugar chain by two or more carbon atoms in a single step, but seldom in a wholly predictable way, so that in spite of the long standing interest in higher-carbon sugars, only a handful of them containing eight or more carbon atoms are known.[2]

A resurgence of interest[5] in the synthesis of higher-carbon sugars has followed the discovery of important antibiotics containing such higher-carbon sugars as the amino-octodioses (**1**) (from apramycin[6] and oxyapramycin[7]) and the undecose hikosamine[8,9] (**2**) (from hikizimycin[9]). Our interest in the synthesis of these and other higher-carbon sugars of biological interest prompted an examination of the oxidation of various unsaturated sugar derivatives with osmium tetraoxide. In choosing this approach we were influenced by the knowledge that the osmylation of allylic alcohols and ethers proceeds with moderate to marked stereoselectivity, which can be predicted on an empirical basis.[10] Initially our efforts were directed towards the synthesis of octose sugars by extending the chain of the hexodialdose[11] (**3**) by two carbon atoms, as outlined in the Scheme. Unlike traditional methods, the carbon chain of the original hexose, in this instance D-galactose, is undergoing extension from the non-reducing end. This particular system has the unparalleled advantage in that the osmylation products (**4**) can be identified by chemical correlation with some of the few known octitols.[2]



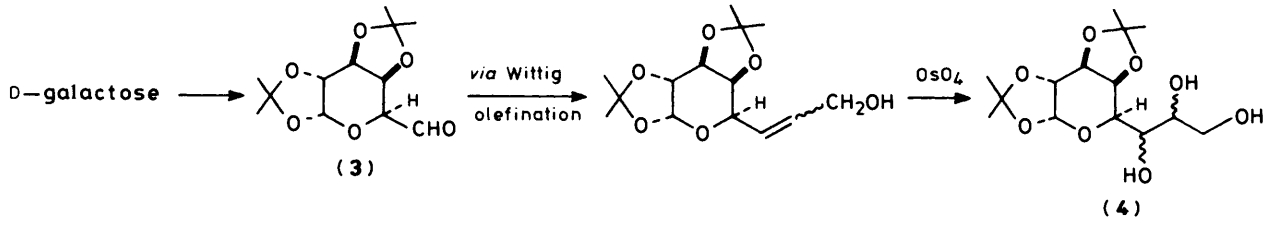
(**1**) R = H or OH



(**2**)

Results and Discussion

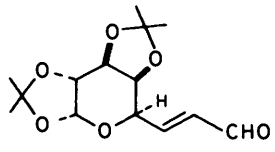
All the unsaturated precursors examined were prepared in a straightforward manner from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose[11] (**3**). Contrary to a previous report,[12] the dialdose derivative (**3**) reacted smoothly with (formylmethylene)triphenylphosphorane in refluxing ben-



(**3**) (**4**)

Scheme

zene to give the (*E*)-enal (**5**), which was originally prepared by another route.[12] On reduction with di-isobutylaluminium hydride in methylene dichloride at 0 °C, the (*E*)-enal (**5**) afforded (*E*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose (**6**), benzylation of which gave the compound (**7**). The reaction between the dialdose derivative (**3**) and (methoxycarbonylmethylene)triphenylphosphorane in methanol at *ca.* 4 °C furnished the (*Z*)-olefin (**8**), which then gave (*Z*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose (**9**) on reduction with lithium aluminium hydride. ^{1}H N.m.r. spectroscopy readily distinguished between the latter compound and the (*E*)-isomer (**6**) of established stereochemistry. Literature procedures were used in transforming the dialdose derivative (**3**) into 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-oct-7-enopyranose[13] (**10**) and (*Z*)-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose[14,15] (**11**).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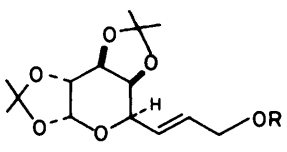
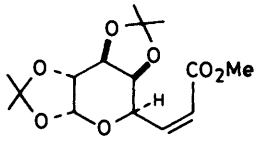

(**6**) R = H
(**7**) R = Bzl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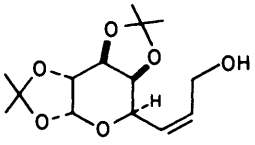
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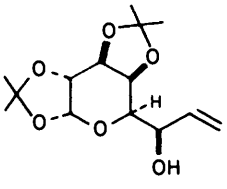
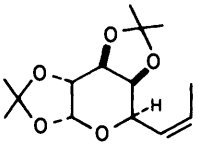
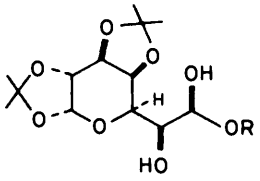
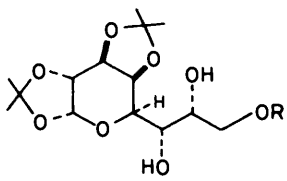
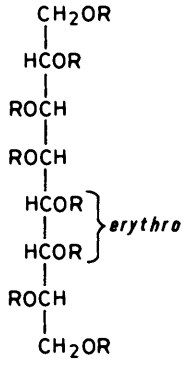

(**10**)


(**11**)

Catalytic osmylation[16] of the (*E*)-octenopyranose (**6**) produced a mixture containing 1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose* (**12**) and the α-D-*threo*-D-*galacto* isomer (**13**) in the ratio 7:1. In this and all subsequent oxidations, the ratios of the products were determined by integration over the resonances for the anomeric protons in the ^{1}H n.m.r. spectra. The stereochemistry of the principal product (**12**) was established by the isolation of L-*threo*-D-*galacto*-octitol (**14**) (45%) following acid hydrolysis of the mixture of the diacetals (**12**) and (**13**), and reduction of the resulting octoses.


(**12**) R = H
(**16**) R = Bzl


(**13**) R = H
(**17**) R = Bzl


(**14**) R = H
(**15**) R = Ac

Not only did the physical constants of this octitol and its octa-acetate (**15**) compare favourably with those of the D-enantiomers,[2,17] but, in agreement with the C_2-symmetry of the octitol (**14**), only four resonances, of roughly equal intensity, were observed in its ^{13}C n.m.r. spectrum (see Experimental section for details).

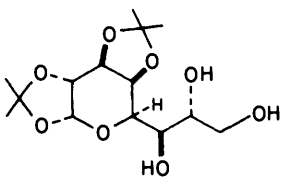
Catalytic osmylation[16] of the benzylated derivative (**7**) was less stereoselective, affording a mixture containing the diols (**16**) and (**17**) in the ratio 3:1. The octose derivatives (**12**) and (**13**) were obtained as a 3:1 mixture following debenzylation of the mixture of compounds (**16**) and (**17**).

When subjected to oxidation with osmium tetraoxide under catalytic conditions,[16] the (*Z*)-octenopyranose (**9**) produced a mixture containing 1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (**18**) and the β-L-*erythro*-D-*galacto* isomer (**19**) in the ratio 7:1, from which the former crystallised. Since the triol (**18**) was also obtained as the preponderant (even exclusive) product on similar osmylation of the terminal olefin[13] (**10**), its stereochemistry is firmly established. Acid hydrolysis of the triol (**18**) afforded crystalline D-*erythro*-D-*galacto*-octose[18] (**20**), which was reduced in a straightforward manner to D-*erythro*-D-*galacto*-octitol[18] (**21**). This octitol has been isolated[18] from the avocado (Calavo, Fuerte variety), where it occurs alongside the closely related D-*glycero*-D-*manno*-oct-2-ulose (**22**), and, like the parent octose (**20**), has been synthesised from D-*glycero*-D-*manno*-heptose using the cyanohydrin method.[2,18]

Oxidation of the (*Z*)-octenopyranose (**11**) with aqueous potassium permanganate is known[15] to yield exclusively 8-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (**23**). This compound was also formed exclusively and was isolated in 78% yield when the (*Z*)-octenopyranose (**11**) was subjected to catalytic osmylation. Thus, there appears to be nothing to choose between the two methods of oxidation as far as the stereoselectivity is concerned.

According to Kishi's empirical rule for osmylation,[10] the relative stereochemistry between the pre-existing hydroxy or alkoxy group and the adjacent, newly introduced hydroxy group of the major product is *erythro*. The observed dia-

* This compound is named according to the IUPAC–IUB Rules 'Tentative Rules for Carbohydrate Nomenclature,' *Biochemistry*, 1971, **10**, 3983; *Biochim. Biophys. Acta*, 1971, **244**, 223, which specify the highest numbered stereocentre (in this case C-7) as the reference atom regardless of chain length. This system requires compound (**13**), for example, to be named 1,2:3,4-di-*O*-isopropylidene-α-D-*threo*-D-*galacto*-octopyranose. According to the British–American Rules of Carbohydrate Nomenclature 'Rules of Carbohydrate Nomenclature,' *J. Chem. Soc.*, 1962, 5307; *J. Org. Chem.*, 1963, **28**, 281, compound (**12**) would be given the alternative name 1,2:3,4-di-*O*-isopropylidene-L-*threo*-α-D-*galacto*-octopyranose. Both names are unambiguous.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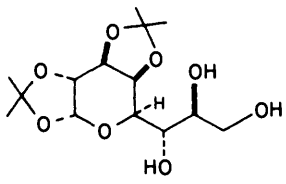
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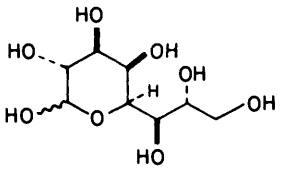
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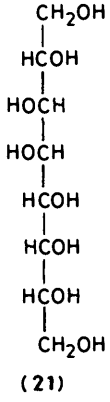
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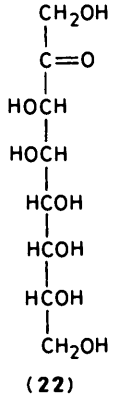
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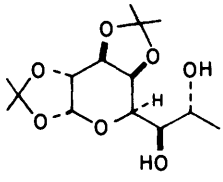
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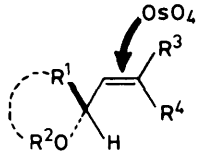
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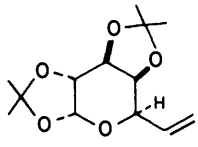
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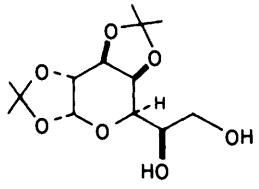
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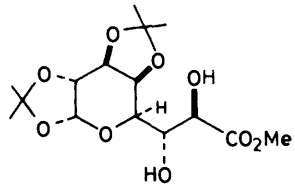
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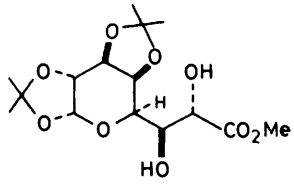
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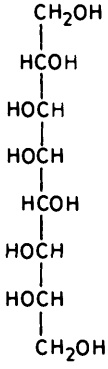
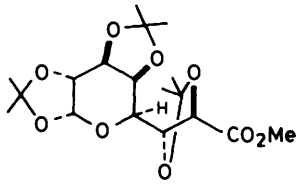

(29)

stereofacial selectivity may be explained by assuming that the molecule reacts in the sterically least compressed conformation (**24**).[10] The major product is formulated as arising from the preferential approach of osmium tetraoxide to the face of the olefinic bond opposite to that of the pre-existing hydroxy or alkoxy group. This *anti* selectivity is seen clearly in the conversion of the allylic alcohol (**10**) into the α-D-*erythro*-D-*galacto* derivative (**18**). For the pyranoid compounds (**6**), (**7**), (**9**), and (**11**), the osmylation reaction is regarded as being *anti* stereoselective with respect to the ring-oxygen atom, which seems to influence the streochemical outcome of the reaction in the same way as does an alkoxy group. In contemporary studies[19] the monosubstituted olefin (**25**) was also found to undergo preferential *anti* addition with respect to the ring-oxygen atom, yielding 1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-heptopyranose (**26**) as the principal product of osmylation. The *erythro* relationship between the ring-oxygen atom and the adjacent, newly introduced hydroxy group of the major product [*e.g.* (**12**)] is more easily perceived after the pyranose ring has been cleaved in the transformation into the corresponding alditol [*e.g.* (**14**)]. The steric argument based on the conformation (**24**) is not the only one able to accommodate the observed stereoselectivities; Danishefsky *et al.*[20] have provided an alternative rationalisation, which focuses on the role of stereoelectronic factors in the transition state, to account for the stereoselectivity found in the osmylation of a related pyranoid system. As with most reactions of this type, there is considerable uncertainty about how much the electrophilic attack is controlled by steric factors and how much by electronic factors.

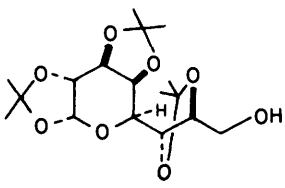
We found one exception to Kishi's formulation,[10] notably that catalytic osmylation[16] of the (*Z*)-octenopyranuronate (**8**) furnished a mixture containing methyl 1,2:3,4-di-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranuronate (**27**) and the α-D-*erythro*-D-*galacto* isomer (**28**) in the ratio 4:1. Reduction of this mixture with lithium aluminium hydride in tetrahydrofuran (THF) gave the triols (**18**) and (**19**) in the ratio 1:4, thereby establishing the diol (**27**) as the major product of the osmylation reaction. Acid hydrolysis of the mixture of triols (**18**) and (**19**) obtained in this way, and reduction of the resulting octoses, afforded L-*erythro*-D-*galacto*-octitol (**29**), whose physical constants showed the expected correspondence with those of the D-enantiomer.[2,21] Kishi and co-workers[10] have pointed out that the empirical rule for osmylation should be applied with caution to conjugated carbonyl compounds, since there are exceptions.

At this juncture, three of the four octitols that could be derived by two-carbon extension of the chain of the D-galactose derivative (**3**) had been prepared. The remaining octitol, namely D-*threo*-D-*galacto*-octitol (**35**), was eventually secured by way of epimerisation of 1,2:3,4:6,7-tri-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octodialdo-1,5-pyranose (**32**) at C-7. Treatment of the mixture containing the osmylation products (**27**) and (**28**) with 2-methoxypropene in methylene dichloride containing a catalytic amount of toluene-*p*-sulphonic acid (PTSA) afforded a mixture of the corresponding triacetals from which methyl 1,2:3,4:6,7-tri-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranuronate (**30**) crystallised upon the addition of hexane. Reduction of the octuronate (**30**) with lithium aluminium hydride in THF then gave the octose triacetal (**31**), which was oxidized with pyridinium chlorochromate (PCC)[22] to the key aldehyde (**32**). It appeared that the 6,7-*erythro*-aldehyde (**32**) suffered partial epimerisation to the 6,7-*threo*-aldehyde (**33**) either during oxidation or on subsequent chromatography on silica gel, since two overlapping doublets, attributable to the aldehydic protons, were observed at δ_H *ca.* 9.6 in the 90 MHz n.m.r. spectrum. Controlled reduction of the octuronate (**30**) with di-isobutylaluminium hydride also provided a virtually identical mixture of the aldehydes (**32**) and (**33**), although in substantially better yield. Essentially complete epimerisation of the 6,7-*erythro* derivative (**32**) to the more stable 6,7-*threo* derivative (**33**) was achieved using potassium carbonate in methanol.[23] Reduction of the aldehyde (**33**) with sodium

borohydride in ethanol then furnished 1,2:3,4:6,7-tri-*O*-isopropylidene-α-D-*threo*-D-*galacto*-octopyranose (**34**), which was converted into D-*threo*-D-*galacto*-octitol (**35**) following acid hydrolysis and reduction of the liberated octose.



(**30**)



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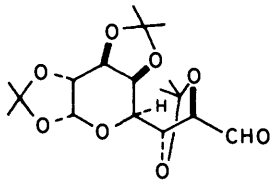

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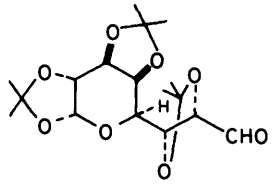

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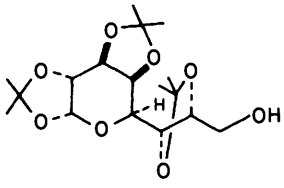
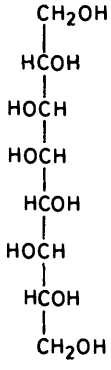


(**34**)



(**35**)

The foregoing examples demonstrate that the osmylation reaction can be used effectively in the synthesis of octose sugars. In most instances, the stereochemical outcome of the osmylation reactions can be predicted by Kishi's empircal rule,[10] the osmylation of the conjugate ester (**8**) providing a notable exception. The following paper describes further two-carbon extension of the chain of such octose sugars as (**18**) and (**33**) to provide decose derivatives.

Experimental

T.l.c. was performed on Kieselgel G, and spots were detected with 1% aqueous sulphuric acid. I.r. spectra were recorded for films or Nujol mulls with a Perkin-Elmer Infracord spectrophotometer. ^{1}H N.m.r. spectra were recorded for solutions in deuteriochloroform (internal tetramethylsilane) with a Bruker Spectrospin (90 MHz) spectrometer or by Edinburgh University n.m.r. service (360 MHz). ^{13}C N.m.r. spectra were recorded for solutions in [$^2H_6$]dimethyl sulphoxide (internal tetramethylsilane) with a Bruker WP-60 (15 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 are uncorrected. Light petroleum refers to the fraction boiling in the range 60—80 °C, unless otherwise indicated.

(E)-6,7-*Dideoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*oct*-6-*enodialdo*-1,5-*pyranose* (**5**).—A solution of the dialdose derivative[11] (**3**) (0.385 g, 1.49 mmol) and (formylmethylene)triphenylphosphorane[24] (0.5 g, 1.64 mmol) in anhydrous benzene (10 ml) was boiled under reflux for 4.5 h and was then concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (10:1) as eluant] gave the (E)-*enal* (**5**) (0.38 g, 90%), m.p. 94.5—95.5 °C (from light petroleum); $[\alpha]_D$ − 137° (*c* 1 in $CHCl_3$) {lit.,[12] m.p. 97.5—99.5 °C; $[\alpha]_D$ − 135° (*c* 1 in $CHCl_3$)}. The ^{1}H n.m.r. spectrum of the (*E*)-enal (**5**) was indistinguishable from that reported for an authentic sample prepared from the dialdose derivative (**3**) by another route.[12]

(E)-6,7-*Dideoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*oct*-6-*enopyranose* (**6**).—To a cooled (0 °C) and stirred solution of the enal (**5**) (0.568 g, 2 mmol) in anhydrous methylene dichloride (5 ml) under nitrogen was gradually added diisobutylaluminium hydride (3 ml of a M solution in methylene dichloride, 3 mmol) while the temperature of the solution was maintained at *ca.* 5 °C. The reaction mixture was stirred at 0 °C for 90 min, and the excess of the reagent was then destroyed by the dropwise addition of saturated aqueous ammonium chloride. The resulting solution was diluted with methylene dichloride (20 ml), filtered through glass wool, washed with a little water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on silica gel [methylene dichloride–acetone (2:1) as eluant] gave the (E)-*octenopyranose* (**6**) (0.4 g, 70%); an analytical sample had b.p. *ca.* 145 °C (bath) at 0.03 mmHg; $[\alpha]_D$ −108° (*c* 1 in $CHCl_3$) (Found: C, 58.9; H, 7.8. $C_{14}H_{22}O_6$ requires C, 58.7; H, 7.75%); δ_H 5.88 (2 H, m, CH=CH), 5.54 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 4.60 and 4.22 (6 H, dd and m, ratio 1:5, 2-, 3-, 4-, and 5-H, and 8-H_2), 2.67 (1 H, s, OH), and 1.52, 1.44, and 1.33 (12 H, 3 × s, ratio 1:1:2, 2 × CMe_2).

(E)-8-O-*Benzyl*-6,7-*dideoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*oct*-6-*enopyranose* (**7**).—To a stirred and cooled (0 °C) solution of the alcohol (**6**) (0.24 g, 0.84 mmol) in anhydrous THF (5 ml) was added sodium hydride (60% dispersion in mineral oil; 34 mg, 1.42 mmol) and the solution was then stirred at 0 °C for 30 min. After the addition of benzyl bromide (0.17 ml, 1.43 mmol), the reaction mixture was stirred at room temperature for 6 h, whereupon further quantities of sodium hydride (17 mg, 0.71 mmol) and benzyl bromide (0.1 ml, 0.84 mmol) were added. The reaction mixture was stirred overnight at room temperature, a few drops of methanol were then added to destroy the excess of the reagents, and the resulting solution was concentrated under reduced pressure. The residue was partitioned between chloroform and water, and the organic layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (20:1) as eluant] gave the *benzylated derivative* (**7**) (0.196 g, 62%); an analytical sample had b.p. *ca.* 157 °C (bath) at 0.01 mmHg; $[\alpha]_D$ −100° (*c* 1.1 in $CHCl_3$) (Found: C, 66.7; H, 7.55. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%); δ_H (*inter alia*) 7.35 (5 H, m, Ph), 5.91 (2 H, m, CH=CH), 5.58 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 4.52 (2 H, s, CH_2Ph), and 1.54, 1.47, and 1.33 (12 H, 3 × s, ratio 1:1:2, 2 × CMe_2).

Methyl (Z)-6,7-*Dideoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*oct*-6-*enopyranuronate* (**8**).—A solution of the dialdose derivative[11] (**3**) (3.53 g, 13.7 mmol) and (methoxycarbonylmethylene)triphenylphosphorane[25] (4.58 g, 13.7 mmol) in anhydrous methanol (90 ml) was kept at *ca.* 4 °C for 20 h and was then concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (20:1) as eluant] gave the *octenopyranuronate* (**8**) (3.95 g, 92%); an analytical sample had b.p. *ca.* 96 °C (bath) at 0.01 mmHg; $[\alpha]_D$ −121° (*c* 0.6 in $CHCl_3$) (Found: C, 57.2; H, 7.2. $C_{15}H_{22}O_7$ requires C, 57.3; H, 7.05%); δ_H (*inter alia*) 6.29 (1 H,

dd, $J_{6,7}$ 12, $J_{5,6}$ 7 Hz, 6-H), 5.88 (1 H, dd, $J_{5,7}$ 1.5 Hz, 7-H), 5.53 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 3.68 (3 H, s, CO_2Me), and 1.56, 1.45, and 1.30 (12 H, 3 × s, ratio 1:1:2, 2 × CMe_2).

(Z)-6,7-*Dideoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*oct*-6-*enopyranose* (**9**).—Lithium aluminium hydride (0.362 g, *ca.* 9.5 mmol) was added gradually to a cooled (0 °C) and stirred solution of the conjugate ester (**8**) (2.33 g, 7.4 mmol) in anhydrous THF (22 ml), and the reaction mixture was then stirred at room temperature for 4.5 h. Wet ethyl acetate was added to destroy the excess of the reagent, inorganic material was filtered off and washed thoroughly with ethyl acetate, and the filtrate and washings were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (5:1) as eluant] gave the (Z)-*octenopyranose* (**9**) (1.415 g, 67%); an analytical sample had b.p. *ca.* 140 °C (bath) at 0.05 mmHg; $[\alpha]_D$ −110° (*c* 1 in $CHCl_3$) (Found: C, 58.8; H, 7.7. $C_{14}H_{22}O_6$ requires C, 58.7; H, 7.75%); δ_H 5.80 (2 H, m, CH=CH), 5.54 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 4.62 and 4.22 (6 H, 2 × m, ratio 1:2, 2-, 3-, 4-, and 5-H, and 8-H_2), and 1.56, 1.47, and 1.33 (12 H, 3 × s, ratio 1:1:2, 2 × CMe_2).

Osmylation Experiments

General Procedure for Catalytic Osmylation.—The unsaturated sugar (1 equiv.), *N*-methylmorpholine *N*-oxide monohydrate (2 equiv.), and osmium tetraoxide (*ca.* 0.05—0.1 equiv.) were stirred in acetone–water (8:1; 5 ml/mmol of substrate) at room temperature until t.l.c. indicated that the reaction was complete. The reaction mixture was diluted with chloroform (50 ml/mmol of substrate), and the resulting solution was washed with 5M-hydrochloric acid (2 ml/mmol of substrate) and then shaken vigorously for several minutes with 45% aqueous sodium metabisulphite (3 ml/mmol of substrate). After being dried ($MgSO_4$), the chloroform solution was concentrated under reduced pressure. Percolation of the residue in an appropriate solvent through silica gel removed all the remaining impurities without effecting a separation of the osmylation products. After concentration, the ratio of the products was determined by integration over the resonances for the anomeric protons in the 90 or 360 MHz ^1H n.m.r. spectrum ($CDCl_3$).

(*a*) Catalytic osmylation of the (*E*)-octenopyranose (**6**) gave a mixture (56.5%) containing 1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose (**12**) [δ_H 5.51 (d, $J_{1,2}$ 5 Hz, 1-H)] and the α-D-*threo*-D-*galacto* isomer (**13**) [δ_H 5.58 (d, $J_{1,2}$ 5 Hz, 1-H)] in the ratio *ca.* 7:1, following purification on silica gel with methylene dichloride–acetone (1:1). This mixture was used to obtain L-*threo*-D-*galacto*-octitol (**14**) in a subsequent experiment.

(*b*) Catalytic osmylation of the benzylated derivative (**7**) produced a mixture (92%) containing 8-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose (**16**) [δ_H 5.47 (d, $J_{1,2}$ 5 Hz, 1-H)] and the α-D-*threo*-D-*galacto* isomer (**17**) [δ_H 5.54 (d, $J_{1,2}$ 5 Hz, 1-H)] in the ratio *ca.* 3:1, following purification on silica gel with ethyl acetate.

A solution of compounds (**16**) and (**17**) (0.14 g, 0.34 mmol) in methanol (10 ml) and glacial acetic acid (2.5 ml) containing 10% palladium–charcoal (0.28 g) was shaken overnight at room temperature under a slight overpressure of hydrogen. The catalyst and the solvent were then removed, and toluene was added to, and distilled from, the residue to remove the last traces of acetic acid. The residue was extracted with chloroform, and the extract was dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (72 mg, 66%) containing the triols (**12**) and (**13**) in the ratio *ca.* 3:1.

(*c*) Catalytic osmylation of the (*Z*)-octenopyranose (**9**) produced a mixture (67%) of 1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (**18**) [δ_H 5.52 (d, $J_{1,2}$ 5 Hz, 1-H)] and the β-L-*erythro*-D-*galacto* isomer (**19**) [δ_H 5.62 (d, $J_{1,2}$ 5 Hz, 1-H)] in the ratio 7:1, following purification on silica gel with methylene dichloride–acetone (1:2). Crystallisation from ethyl acetate–hexane gave the *triol* (**18**) (*ca.* 40%), m.p. 117—118 °C; $[\alpha]_D$ −61° (*c* 0.75 in $CHCl_3$) (Found: C, 52.4; H, 7.5. $C_{14}H_{24}O_8$ requires C, 52.5; H, 7.55%); δ_H (*inter alia*) 5.52 (1 H, d, $J_{1,2}$ 5 Hz, 1-H) and 1.56, 1.47, 1.37, and 1.33 (12 H, 4 × s, 2 × CMe_2).

(*d*) Similar osmylation of 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-oct-7-enopyranose[13] (**10**) gave the triol (**18**) (79%), which was indistinguishable (m.p., i.r. and ^1H n.m.r. spectra) from that prepared in (*c*). ^1H N.m.r. spectroscopy indicated that little, if any, of the other isomer was formed on osmylation of the compound (**10**).

(*e*) Catalytic osmylation of (*Z*)-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enopyranose[14,15] (**11**) yielded only 8-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (**23**) (78%), m.p. 152—153 °C (from chloroform–light petroleum); $[\alpha]_D$ −55.5° (*c* 1 in $CHCl_3$) {lit.,[15] m.p. 151—152 °C; $[\alpha]_D$ −57° (*c* 1.4 in $CHCl_3$)}.

(*f*) Catalytic osmylation of the (*Z*)-octenopyranuronate (**8**) yielded a mixture (83.5%) containing methyl 1,2:3,4-di-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranuronate (**27**) [δ_H 5.59 (d, $J_{1,2}$ 5 Hz, 1-H)] and the α-D-*erythro*-D-*galacto* isomer (**28**) [δ_H 5.44 (d, $J_{1,2}$ 5 Hz, 1-H)] in the ratio 4:1.

Lithium aluminium hydride (2.05 g, *ca.* 54 mmol) was added gradually to a cooled (0 °C) and stirred solution of the foregoing mixture of compounds (**27**) and (**28**) (3.64 g, 10.45 mmol) in anhydrous THF (38.5 ml), and the reaction mixture was then stirred at room temperature for 4 h. After processing [as described for compound (**9**)] and chromatography on silica gel [methylene dichloride–acetone (1:2) as eluant], the final residue (1.7 g, 51%) was shown (^1H n.m.r. spectroscopy) to contain the triols (**18**) and (**19**) in the ratio 1:4. This mixture was used to prepare L-*erythro*-D-*galacto*-octitol (**29**) in a subsequent experiment.

L-threo-D-galacto-*Octitol* (**14**).—A solution containing the triols (**12**) and (**13**) (0.47 g, 1.47 mmol) in trifluoroacetic acid (TFA)–water (9:1; 7.5 ml) was kept at room temperature for 15 min, and was then concentrated under reduced pressure with occasional addition of water. A stirred and cooled (0 °C) solution of the residue in water (25 ml) was treated with sodium borohydride (0.3 g, 7.9 mmol) for 3 h, sodium ions were then removed with Amberlite IR-120(H^+) resin (10 g), and the resin was filtered off and washed with water. During concentration of the filtrate and washings, the octitol began to crystallise out. After crystallisation was complete, L-*threo*-D-*galacto*-octitol (**14**) (0.16 g, 45%) was filtered off and recrystallised from hot water. The pure octitol (**14**) had m.p. 233—236 °C $[\alpha]_D$ *ca.* 0° (saturated solution in H_2O); its ^{13}C n.m.r. spectrum ([$^2H_6$]DMSO) contained resonances of roughly equal intensity at δ_C 70.34, 69.55, 68.64, and 63.29 {lit., (D-enantiomer)[2,17] m.p. 230 °C (corrected); $[\alpha]_D$ *ca.* 0° (saturated solution in H_2O)}.

L-threo-D-galacto-*Octitol Octa-acetate* (**15**).—A stirred suspension of the octitol (**14**) (0.103 g, 0.425 mmol) in anhydrous pyridine (3 ml) and acetic anhydride (2.5 ml) was heated at 100 °C for 3 h and, after having cooled, the clear solution was poured into ice–water. The precipitate was collected and recrystallised from aqueous ethanol to give the octa-acetate (**15**) (0.16 g, 65%), m.p. 143—145 °C; $[\alpha]_D$ −40° (*c* 1.1 in $CHCl_3$) {lit., (D-enantiomer)[17] m.p. 141 °C (corrected); $[\alpha]_D$ +40.4° (*c* 1.2 in $CHCl_3$)}.

D-erythro-D-galacto-*Octose* (**20**).—A solution of the triol (**18**) (0.4 g, 1.25 mmol) in M-sulphuric acid (15 ml) was heated at

100 °C for 5 h, cooled, and neutralised with Amberlite IR-45(HO^-) resin (16 g). The resin was filtered off and washed with water, and the filtrate and washings were combined and concentrated under reduced pressure. The residue crystallised from aqueous ethanol to give the octose (**20**) (0.181 g, 60%), m.p. 180—181.5 °C; $[\alpha]_D$ +42° (7 min) ⟶ +62° (final; *c* 1.1 in H_2O) {lit.,[18] m.p. 174—175 °C; $[\alpha]_D$ +45° (few minutes) ⟶ +64° (final; H_2O)}.

D-erythro-D-galacto-*Octitol* (**21**).—Sodium borohydride (0.336 g, 8.9 mmol) was added gradually to a stirred and cooled (0 °C) solution of the octose (**20**) (0.236 g, 0.98 mmol) in water (25 ml), and the reaction mixture was then stirred at 0 °C for 2 h. Sodium ions were removed with Amberlite IR-120(H^+) resin (11.5 g), and the resin was filtered off and washed thoroughly with water. The filtrate and washings were combined and concentrated under reduced pressure, and methanol was added to, and distilled from, the residue several times to remove boric acid. Recrystallisation of the resulting solid from aqueous ethanol gave the octitol monohydrate (**21**)·H_2O (0.205 g, 80%), m.p. 168—169 °C; $[\alpha]_D$ +2.5° (*c* 0.7 in H_2O) {lit.,[18] m.p. 169—170 °C (for the monohydrate); $[\alpha]_D$ −12° (acidified molybdate)}.

L-erythro-D-galacto-*Octitol* (**29**).—A solution of the triols (**18**) and (**19**) [prepared *via* osmylation of the (*Z*)-octenopyranuronate (**8**); 0.9 g, 2.8 mmol] in TFA–water (9:1, 14 ml) was kept at room temperature for 15 min, and was then concentrated under reduced pressure with occasional addition of water. A cooled (0 °C) solution of the resulting octoses in water (56 ml) was reduced with sodium borohydride (0.56 g, 14.8 mmol) as described in the previous experiment. Recrystallisation of the residue from aqueous ethanol gave the octitol (**29**) (0.295 g, 43%), m.p. 153—154.5 °C; $[\alpha]_D$ −2.5° (*c* 0.6 in H_2O) {lit. (D-enantiomer),[21] m.p. 153—154 °C; $[\alpha]_D$ +2.4° (*c* 4 in H_2O)}.

Methyl 1,2:3,4:6,7-*Tri*-O-*isopropylidene*-β-L-erythro-D-galacto-*octopyranuronate* (**30**).—A solution of the esters (**27**) and (**28**) [prepared by osmylation of compound (**8**); 20.1 g, 57.7 mmol) in methylene dichloride (550 ml) containing 2-methoxypropene (28 ml, 0.292 mol) and PTSA monohydrate (0.5 g) was stirred at room temperature for 1 h. The solution was washed successively with saturated aqueous sodium hydrogen carbonate (100 ml) and water (2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (20:1) as eluant] afforded a mixture of the corresponding triacetals. Crystallisation from hexane gave the *triacetal* (**30**) (13.61 g, 61%), m.p. 130.5—131.5 °C (after further recrystallisation from hexane); $[\alpha]_D$ −81° (*c* 1.1 in $CHCl_3$) (Found: C, 55.8; H, 7.0. $C_{18}H_{28}O_9$ requires C, 55.7; H, 7.3%); δ_H (*inter alia*) 5.61 (1 H, d, $J_{1,2}$ 5 Hz, 1-H) 3.76 (3 H, s, CO_2Me), and 1.62, 1.51, 1.47, 1.42, and 1.33 (18 H, 5 × s, ratio 1:1:1:1:2, 3 × CMe_2).

1,2:3,4:6,7-*Tri*-O-*isopropylidene*-β-L-erythro-D-galacto-*octopyranose* (**31**).—Lithium aluminium hydride (0.167 g, *ca.* 4.4 mmol) was added gradually to a stirred solution of the ester (**30**) (0.3 g, 0.77 mmol) in anhydrous THF (3 ml) at room temperature, the reaction mixture was stirred for 4 h, and the excess of the reagent was then destroyed by the dropwise addition of wet ethyl acetate. Inorganic material was filtered off and washed thoroughly with ethyl acetate, and the filtrate and washings were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (2:1) as eluant] furnished the *triacetal* (**31**) (0.245 g, 88%), which crystallised on trituration with light petroleum (b.p. 40—60 °C). After recrystallisation from ethyl acetate–light petroleum (b.p. 40—60 °C), the triacetal (**31**) had m.p. 99—100.5 °C; $[\alpha]_D$ −91 (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 480 cm^{-1} (OH) (Found: C, 56.4; H, 8.0. $C_{17}H_{28}O_8$ requires C, 56.65; H, 7.8%); δ_H (*inter alia*) 5.61 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 1.52, 1.48, 1.47, 1.38, and 1.31 (18 H, 5 × s, ratio 1:1:1:1:2, 3 × CMe_2).

1,2:3,4:6,7-*Tri*-O-*isopropylidene*-α-D-threo-D-galacto-*octodialdo*-1,5-*pyranose* (**33**).—A solution of the triacetal (**31**) (0.69 g, 1.9 mmol) in anhydrous methylene dichloride (5 ml) was added to a stirred solution of PCC[22] (1.23 g, 5.7 mmol) in anhydrous methylene dichloride (8 ml) containing powdered 3Å molecular sieves[26] (1 g) at room temperature. The reaction mixture was stirred for 2.5 h and then poured into anhydrous diethyl ether (85 ml). The supernatant solution was decanted from the spent oxidant and concentrated under reduced pressure. The residue was extracted with diethyl ether, and the ethereal solution was filtered and concentrated; this procedure was repeated (with charcoaling). Purification of the residue on silica gel [methylene dichloride–acetone (10:1) as eluant] gave a mixture (0.494 g, 72%) containing the aldehydes (**32**) and (**33**), as judged from the presence of two overlapping doublets (*J* 3 Hz) at δ_H *ca.* 9.6 in its ^1H n.m.r. spectrum.

Alternatively, the following procedure could be used. To a cooled (−78 °C) and stirred solution of the ester (**30**) (0.388 g, 1 mmol) in anhydrous methylene dichloride (6 ml) under nitrogen was gradually added di-isobutylaluminium hydride (1 ml of a M solution in methylene dichloride, 1 mmol). The reaction mixture was stirred at −78 °C for 3 h, diluted with methylene dichloride, and poured into ice–water. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (10:1) as eluant] gave a mixture of the aldehydes (**32**) and (**33**) (0.32 g, 89%), whose ^1H n.m.r. spectrum was virtually superimposable on that of the products obtained in the previous experiment.

A solution of the foregoing aldehydes (0.4 g, 1.1 mmol) in anhydrous methanol (8 ml) containing anhydrous potassium carbonate (0.52 g, 3.8 mmol) was stirred at room temperature for 2 h and then filtered. The filtrate was neutralised with saturated aqueous ammonium chloride, and was then concentrated under reduced pressure. The residue was extracted with chloroform, and the extract was washed with a small volume of water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (10:1) as eluant] gave the *threo*-aldehyde (**33**) (0.321 g, 80%), $[\alpha]_D$ *ca.* −55° (*c* 1.7 in $CHCl_3$); δ_H 9.62 (1 H, d, $J_{7,8}$ 3 Hz, CHO), 5.58 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 4.68—3.82 (6 H, m, 2-, 3-, 4-, 5-, 6-, and 7-H), and 1.53, 1.49, 1.47, 1.43, 1.33, and 1.30 (18 H, 6 × s, 3 × CMe_2).

1,2:3,4:6,7-*Tri*-O-*isopropylidene*-α-D-threo-D-galacto-*octopyranose* (**34**).—Sodium borohydride (0.123 g, 3.2 mmol) was added gradually to a solution of the dialdose derivative (**33**) (0.53 g, 1.48 mmol) in ethanol (8 ml), and the reaction mixture was stirred for 2 h at room temperature before the solvent was removed under reduced pressure. The residue was extracted with chloroform, and the extract was washed with a small volume of water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (5:1) as eluant] furnished the *octopyranose triacetal* (**34**) (0.49 g, 92%), $[\alpha]_D$ −55.5° (*c* 1.2 in $CHCl_3$) (Found: C, 56.8; H, 8.2. $C_{17}H_{28}O_8$ requires C, 56.65; H, 7.8%); δ_H (*inter alia*) 5.60 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 1.53, 1.47, 1.45, and 1.34 (18 H, 4 × s, ratio 1:1:2:2, 3 × CMe_2).

D-threo-D-galacto-*Octitol* (**35**).—A solution of the triacetal (**34**) (0.6 g, 1.66 mmol) in TFA–water (9:1; 8.5 ml) was kept at room temperature for 15 min, and was then concentrated under

reduced pressure with occasional addition of water. A cooled (0 °C) solution of the resulting octose in water (28 ml) was reduced with sodium borohydride (0.34 g, 9 mmol) as described previously. The final residue crystallised after methanol had been distilled from it several times. Recrystallisation from aqueous ethanol gave the *octitol* (**35**) (0.205 g, 51%), m.p. 168—169 °C; $[\alpha]_D$ −0.55° (*c* 1.1 in H_2O) (Found: C, 39.7; H, 7.6. $C_8H_{18}O_8$ requires C, 39.7; H, 7.5%).

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