Carbohydrate Research, 136 (1985) 77–89
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF FOUR NEW DIASTEREOISOMERS OF DL-5-HYDROXYMETHYL-1,2,3,4-CYCLOHEXANETETROL*

SEIICHIRO OGAWA†, YOSHIKI TSUKIBOSHI, YOSHIKAZU IWASAWA, AND TETSUO SUAMI
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223 (Japan)

(Received April 30th, 1984; accepted for publication, June 30th, 1984)

ABSTRACT

Four new diastereoisomers of the pseudo-sugar DL-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol, having (1,2,3,4/5)- (**2**), (1,5/2,3,4)- (**3**), (1,2,3/4,5)- (**4**), and (1,2,4,5/3)-configurations (**5**), have been synthesised by unambiguous sequences from readily available pseudo-sugars. Acetonation of DL-(1,2,4/3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol with 2,2-dimethoxypropane in *N,N*-dimethylformamide in the presence of toluene-*p*-sulfonic acid gave the 1,2:4,7-di-*O*-isopropylidene derivative (**9**) in good yield. Oxidation of HO-3 in **9** with ruthenium tetraoxide in chloroform gave the ketone **11**, which was catalytically hydrogenated to give the 3-epimer (**12**) of **9**. Deprotection of **12** gave the 1,2,3,4/5-isomer **2** in good yield. Likewise, compounds **3** and **4** were synthesised from (1,3,5/2,4)- and (1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol, respectively. Compound **5** was obtained by catalytic hydrogenation of DL-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol.

INTRODUCTION

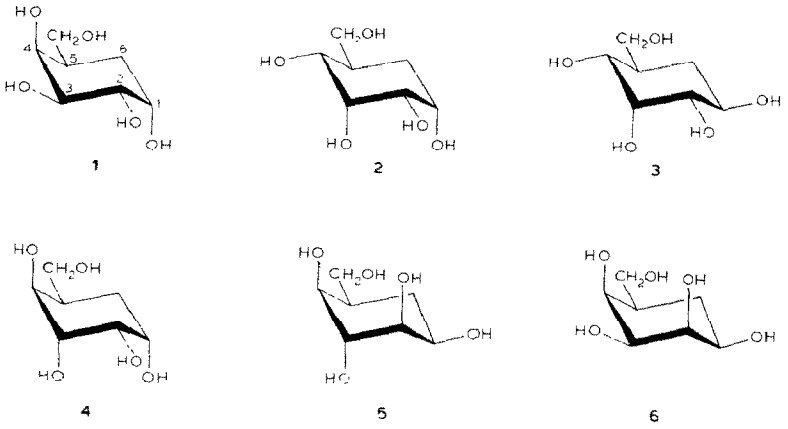
Much interest has been stimulated in the chemical and biological properties of pseudo-sugars**, carbocyclic analogues of hexopyranoses, since pseudo-α-D-galactose [**1**, (1*S*)-(1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol] was discovered[2] as an antibacterial substance from the fermentation broth of *Streptomyces* sp. MA-4145.

Sixteen diastereoisomers (racemic) are theoretically possible for pseudo-sugars and eleven, including racemic **1**, have so far been synthesised and fully characterised[3–9]. The isomers having the *α-allo* (**2**), *β-allo* (**3**), *α-gulo* (**4**), *β-ido* (**5**), and *β-talo* configurations (**6**) were hitherto unknown. Recently, a key synthetic

*Pseudo-sugars, Part XI. For Part X, see ref. 1.
†To whom correspondence should be addressed.
**The term "pseudo-sugar" was first proposed by McCasland *et al.*[3], who synthesised pseudo-α-DL-talose, DL-(1/2,3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol, the first pseudo-sugar.

0008-6215/85/$ 03.30

intermediate, 7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid has been optically resolved, and **1** has been synthesised[10] therefrom, thereby allowing the establishment of the absolute configuration.



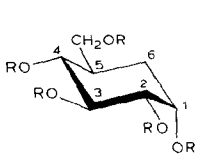
All compounds described in this paper are racemic, and, for convenience, the formulas depict only one of the respective enantiomers except for **1**.

We now describe an unambiguous synthesis of three new racemic isomers, **2–4**, starting from readily available pseudo-sugars, mainly by inversion of the configuration of the isolated hydroxyl group by an oxidation–reduction sequence. The isomer **5** was obtained by catalytic hydrogenation of the unsaturated pseudo-sugar **39**.

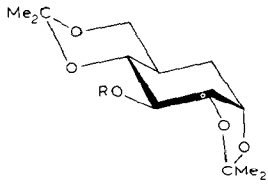
RESULTS AND DISCUSSION

Reaction of DL-(1,2,4/3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**8**), prepared by *O*-deacetylation of the corresponding penta-acetate[9] (**7**), with a large excess of 2,2-dimethoxypropane in *N,N*-dimethylformamide in the presence of toluene-*p*-sulfonic acid at 60° for 6 h gave 50% of the crystalline 1,2:4,7-di-*O*-isopropylidene derivative (**9**). In the ^{1}H-n.m.r. spectrum of the acetate **10** of **9**, the H-3 resonance appeared at δ 5.01 as a doublet of doublets (J 7.5 and 10 Hz), in accord with the assigned structure. Oxidation of **9** with a small amount of ruthenium tetraoxide in chloroform in the presence of aqueous 5% sodium metaperiodate and excess of sodium hydrogencarbonate at 0–5° for 7.5 h gave 80% of the ketone **11**, which had i.r. carbonyl absorption at 1732 cm^{-1}. Catalytic hydrogenation of **11** in ethanol in the presence of Raney nickel T-4[11] gave 97% of the hydroxy compound **12**. The ^{1}H-n.m.r. spectrum of the acetate **13** of **12** showed a narrow doublet of doublets of δ 5.33 (J 1.8 and 5.4 Hz) for H-3. Treatment of **12** with aqueous 70% acetic acid at room temperature for 17 h and acetylation of the

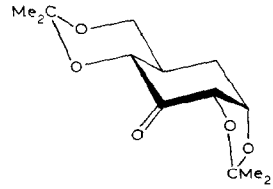
product gave 49% of the crystalline penta-acetate **14** of **2**, the structure of which was confirmed by the ^{1}H-n.m.r. data. Thus, the signals due to H-1,2,3,4 appeared at δ 5.38 (q, J 3.6 Hz), 4.99 (t, J 3.3 Hz), 5.51 (t, J 3.4 Hz), and 4.22 (dd, J 3.3 and 9.8 Hz), respectively, indicating an *e,a,e,a,a* assignment for H-1,2,3,4,5. *O*-Deacetylation of **14** with methanolic sodium methoxide gave syrupy **2** in quantitative yield.



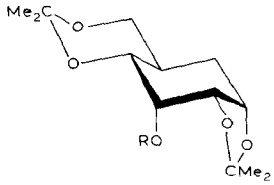
7 R = Ac
8 R = H



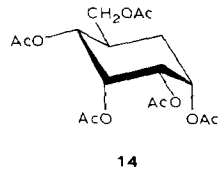
9 R = H
10 R = Ac



11



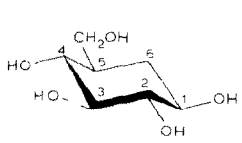
12 R = H
13 R = Ac



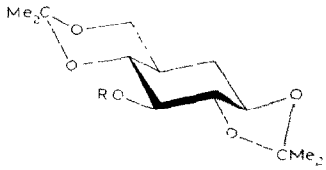
14

Likewise, acetonation of DL-(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol[7,8] (**15**) gave crystalline 1,2:4,7- (**16**, 26%) and 2,3:4,7-di-*O*-isopropylidene derivatives (**17**, 39%) after chromatography on silica gel. The ^{1}H-n.m.r. spectrum of the acetate **18** of **16** contained a triplet (δ 5.13, J 9.3 Hz) due to the proton in the HCOAc group, consistent with the structure assigned. For the acetate **19** of **17**, the corresponding resonance appeared at δ 4.99 (td, J 5.2, 10.2, and 10.2 Hz), suggesting that the acetoxyl group was located at position 1. Oxidation of **16** and **17** with ruthenium tetraoxide gave the crystalline ketones **20** and **24** in yields of 80 and 70%, respectively, the i.r. and ^{1}H-n.m.r. spectral data of which supported the structures assigned. Catalytic hydrogenation of **20** in the presence of Raney nickel gave the hydroxy compound **21** as the main product (36%, after crystallisation). In the ^{1}H-n.m.r. spectrum of the acetate **22** of **21**, the H-3 signal appeared at δ 5.65 (t, J 2.9 Hz), indicative of the axial orientation of the acetoxyl group. Deacetonation of **21** followed by acetylation gave 62% of the penta-acetate **23** of **3**, the ^{1}H-n.m.r. spectrum of which showed signals [δ 5.59 (t, J 2.7 Hz), 5.20 (td, J 4.9, 10.5, and 10.5 Hz), 5.03 (dd, J 2.7 and 10.5 Hz), 4.88 (dd, J 2.7 and 11.4 Hz)] which were attributed to H-1,2,3,4, respectively, consistent with the assigned structure. Deacetylation of **23** gave 53% of crystalline **3**.

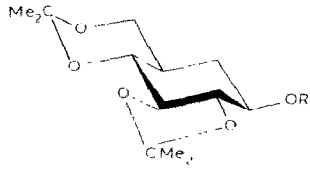
On the other hand, catalytic hydrogenation of **24** gave 31% of a new hydroxy



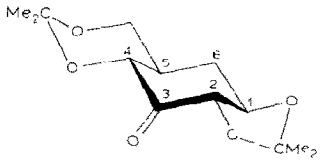
15



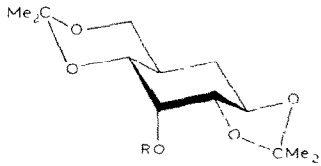
16 R = H
18 R = Ac



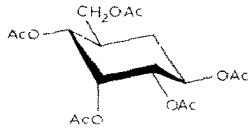
17 R = H
19 R = Ac



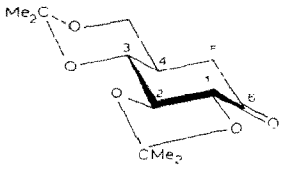
20



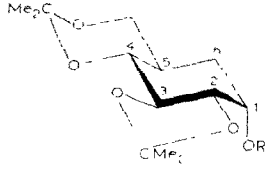
21 R = H
22 R = Ac



23



24



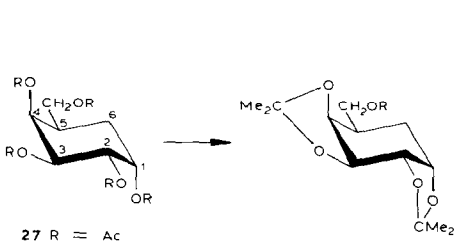
25 R = H
26 R = Ac

compound (**25**) together with **17** (16%), after chromatography. Compound **25** was the C-1 epimer of **17** since acetylation gave a product (**26**), the ^{1}H-n.m.r. spectrum of which showed a quartet (δ 5.45, J 3 Hz) ascribable to H-1*e*. Deprotection of **25**, followed by acetylation, gave **7**.

Compounds **17, 24,** and **25** are potentially useful synthetic intermediates for the preparation of pseudo-glucopyranose compounds.

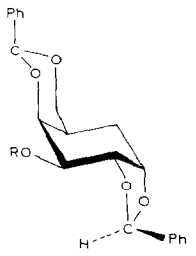
DL-(1,2/3,4,5)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol (**28**), obtained by *O*-deacetylation of its penta-acetate[8] (**27**), was acetonated to give 57% of a single compound, namely, the syrupy 1,2:3,4-di-*O*-isopropylidene derivative (**29**). The ^{1}H-n.m.r. spectrum of the acetate **30** of **29** contained a multiplet at δ 4.12–3.90 attributed to the C-7 acetoxymethylene protons, confirming the assigned structure. T.l.c. showed that **29** was thermodynamically the most stable isomer formed by acetonation of **28** and that two other isomers were isolable after the kinetic phase.

In order to prepare a protected derivative other than **29**, benzylidenation of **28** was studied. Treatment of **28** with a large excess of α,α-dimethoxytoluene in *N,N*-dimethylformamide in the presence of toluene-*p*-sulfonic acid at 55° for 9 h gave the di-*O*-benzylidene derivatives **31** (25%) and **32** (22%), which were isolated

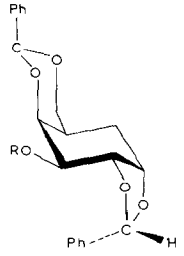


27 R = Ac
28 R = H

29 R = H
30 R = Ac



31 R = H
33 R = Ac

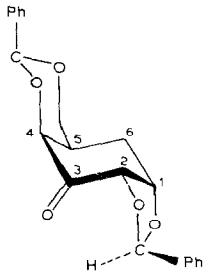


32 R = H
34 R = Ac

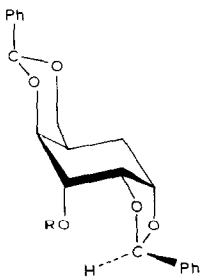
by chromatography. In the ^{1}H-n.m.r. spectra of the acetates **33** and **34** of **31** and **32**, respectively, the protons of the HCOAc groups resonated at δ 5.11 (dd, $J_{1,2}$ 3, $J_{3,4}$ 8.4 Hz) and 4.95 (dd, $J_{1,2}$ 4, $J_{3,4}$ 7.8 Hz), indicating the presence of an acetoxyl group at position 3 in each compound. The dioxolane acetal protons of **31** and **32** resonated at δ values higher than those of the corresponding protons of **32** and **34**. Therefore, on the basis of the rule proposed by Baggett *et al.*[12,13], **31** and **32**, and **32** and **34**, were tentatively assigned *exo*- and *endo*-phenyl structures, respectively, for the 1,2-*O*-benzylidene group. For convenience, **31** was used for further synthetic work.

Oxidation of **31** with ruthenium tetraoxide gave 65% of the crystalline ketone **35**, the structure of which was supported by i.r. and ^{1}H-n.m.r. spectral data. Reduction of **35** with sodium borohydride in methanol gave **31** (26%) and the new hydroxy compound **36** (55%), which were isolated by chromatography. In the ^{1}H-n.m.r. spectrum of the acetate **37** of **36**, the H-3 signal appeared at δ 5.31 (t, J 4.2 Hz), in accord with the assigned structure. Debenzylidenation of **37** and acetylation of the product gave 78% of the crystalline penta-acetate (**38**) of **4**. The ^{1}H-n.m.r. spectrum contained a complex multiplet for the four ring protons. Deacetylation of **38** gave crystalline **4** in good yield.

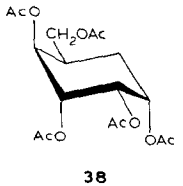
The new pseudo-sugar **5** was obtained from the readily accessible[14] DL-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (**39**) by catalytic hydrogenation in methanol over Pd/C, which minimised the formation of by-products, mainly, de-



35

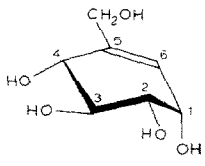


36 R = H
37 R = Ac

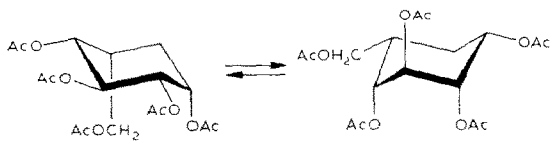


38

hydroxy compounds. Chromatography of the acetylated products of hydrogenation gave 60% of the penta-acetate **40** of **5**, the ^{1}H-n.m.r. spectrum of which could not be analysed. However, the structure of **40** was assigned tentatively on the basis of the fact that it differed from **7** and penta-acetates of the known pseudo-sugars.



39



40

The last remaining pseudo-sugar **6**, having the (1,2,3,4,5/0)-configuration, should be accessible from **5** following essentially the procedure described here, and this work is in progress.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 capillary melting-point apparatus and are uncorrected. I.r. spectra were recorded with a Hitachi HPL-225 spectrophotometer. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian EM-390 (90 MHz) spectrometer. T.l.c. was performed on Wakogel B-10 (Wako Co., Osaka, Japan) with detection by charring with 10% sulfuric acid. Column chromatography was conducted on Wakogel C-200 (200 Mesh) or Wakogel C-300 (300 Mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <50° under diminished pressure.

DL-*(1,2,4/3,5)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol* (**8**). — A mixture of DL-(1,2,4/3,5)-5-acetoxymethyl-1,2,3,4-tetra-acetoxycyclohexane[9] (**7**; 100 mg, 0.26 mmol) and methanol (3 mL) containing methanolic M sodium methoxide (0.5 mL) was stirred at room temperature for 90 min, neutralised with Amberlite IR-120B (H^+) resin, and concentrated to give **8** (39 mg, 84%). Recrystallisation from aqueous ethanol gave needles, m.p. 146–147°.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.15; H, 7.75.

*(1*SR*,2*SR*,3*RS*,8*RS*,10*SR*)-5,5,12,12-Tetramethyl-4,6,11,13-tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-ol* [**9**, *1,2:4,7-di-*O*-isopropylidene derivative of* DL-*(1,2,4/3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — A mixture of **8** (696 mg, 3.91 mmol), dry *N,N*-dimethylformamide (16 mL), 2,2-dimethoxypropane (9.6 mL), and toluene-*p*-sulfonic acid monohydrate (5 mg) was stirred at 60° for 6 h under slightly diminished pressure. T.l.c. (1:2 2-butanone–toluene) then indicated the conversion of **8** into a single product (R_F 0.35). Sodium hydrogencarbonate (0.1 g) was added, the mixture was concentrated, and a solution of the residue in ethyl acetate (70 mL) was washed with water, dried, and concentrated. The residue was recrystallised from ethanol to give **9** as needles (505 mg, 50.3%), m.p. 146.5–

147.5°. ^{1}H-N.m.r. data: δ 4.25 (narrow m, 1 H, H-1), 3.93 (dd, 1 H, $J_{1,2}$ 5.4, $J_{2,3}$ 6.6 Hz, H-2), 3.70 (dd, 1 H, $J_{5,7}$ 5.7, J_{gem} 10.5 Hz, H-7), 3.61 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 3.51 (t, 1 H, $J_{5,7'}$ 10.5 Hz, H-7'), 3.28 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 1.50, 1.43, 1.40, and 1.43 (4s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.30; H, 8.48.

Compound **9** (20 mg) was treated with acetic anhydride (1 mL) in pyridine (1 mL) at room temperature overnight. The reaction mixture was then concentrated and the product was purified by elution from a short column of alumina with chloroform to give the acetate **10** as a syrup (21 mg, 90%). ^{1}H-N.m.r. data: δ 5.01 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 10 Hz, H-3), 4.23 (narrow m, 1 H, H-1), 3.94 (dd, 1 H, $J_{1,2}$ 4.1 Hz, H-2), 3.75 (dd, 1 H, $J_{5,7}$ 5.3, J_{gem} 10.5 Hz, H-7), 3.47 (t, 1 H, $J_{5,7'}$ 10.5 Hz, H-7'), 3.38 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 2.03 (s, 3 H, OAc), 1.51, 1.35, and 1.30 (3 s, 3, 3, and 6 H, 2 CMe_2).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.25; H, 7.84.

(1SR,3RS,8RS,10SR) - 5,5,12,12 - Tetramethyl - 4,6,11,13 - tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-one [**11**, *1,2:4,7-di-O-isopropylidene derivative of* DL-*(1,2,4/5)-5-hydroxymethyl-3-oxo-1,2,4-cyclohexanetriol*]. — To a solution of **9** (203 mg, 0.79 mmol) in ethanol-free chloroform (6 mL) was added sodium hydrogencarbonate (0.5 g), aqueous 5% sodium metaperiodate (8 mL), and ruthenium tetraoxide (5 mg), and the mixture was vigorously stirred at 0–5° for 7.5 h. T.l.c. (1:2 acetone–hexane) then indicated the conversion of **9** into a single product (R_F 0.33). 2-Propanol (4 mL) was added, and, after 0.5 h, the precipitate was removed, and the organic layer was washed with water, dried, and concentrated to give **11** (179 mg, 89%). Recrystallisation from ethanol gave thin needles, m.p. 160–162°; ν_{max}^{KBr} 1732 cm^{-1} (C=O). ^{1}H-N.m.r. data: δ 4.50 (m, 1 H, H-1), 4.36 (d, 1 H, $J_{1,2}$ 5.6 Hz, H-2), 4.23 (d, 1 H, $J_{4,5}$ 11.3 Hz, H-4), 4.00–3.57 (m, 2 H, CH_2O), 1.46, 1.44, 1.39, and 1.34 (4 s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.66; H, 7.74.

(1SR,2RS,3RS,8RS,10SR)-5,5,12,12-Tetramethyl-3,5,11,13-tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-ol [**12**, *1,2:4,7-di-O-isopropylidene derivative of* DL-*(1,2,3,4/5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — A solution of **11** (110 mg, 0.43 mmol) in ethanol (5 mL) was hydrogenated in the presence of Raney nickel T-4[11] (1 g) at room temperature for 15 h (initial hydrogen pressure of 3.2 kg/cm^2). T.l.c. (1:2 acetone–hexane) then indicated the formation of a single product (R_F 0.54). The mixture was filtered and concentrated to give **12** (108 mg, 97.4%). Recrystallisation from ethanol gave prisms, m.p. 153–154°. ^{1}H-N.m.r. data: δ 4.30 (t, 1 H, $J_{1,2} = J_{1,6} = 4.5$ Hz, H-1), 4.08 (t, 1 H, $J_{2,3} = J_{3,4} = 5$ Hz, H-3), 3.91 (t, 1 H, H-2), 3.83 (dd, 1 H, $J_{4,5}$ 12 Hz, H-4), 3.50 (dd, 1 H, $J_{5,7}$ 4.1, J_{gem} 10.8 Hz, H-7), 3.43 (dd, 1 H, $J_{5,7'}$ 13 Hz, H-7'), 1.57, 1.43, and 1.37 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.66; H, 8.39.

Acetylation of **12** (35 mg), as for **9**, and elution of the product from a column of silica gel (3 g) with 1:7 2-butanone–toluene gave the acetate **13** (38 mg, 93%). Recrystallisation from ethanol gave prisms, m.p. 119–119.5°. ^{1}H-N.m.r. data: δ

5.33 (dd, 1 H, $J_{2,3}$ 5.4, $J_{3,4}$ 1.8 Hz, H-3), 4.27 (dt, 1 H, $J_{1,2} = J_{1,6} = J_{1,6'} = 5.4$ Hz, H-1), 4.18 (t, 1 H, H-2), 3.83 (dd, 1 H, $J_{5,7}$ 5.7, J_{gem} 12 Hz, H-7), 3.52 (dd, 1 H, $J_{5,7'}$ 7.5 Hz, H-7'), 3.14 (dd, 1 H, $J_{4,5}$ 11.2 Hz, H-4), 2.13 (s, 3 H, OAc), 1.48, 1.42, and 1.33 (3 s, 3, 3, and 6 H, 2 CMe_2).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.72; H, 7.91.

DL-*(1,2,3,4/5)-5-Acetoxymethyl-1,2,3,4-tetra-acetoxycyclohexane* (**14**). — A mixture of **12** (50 mg, 0.19 mmol) and aqueous 70% acetic acid (5 mL) was stirred at room temperature for 17 h and then concentrated, the residue was acetylated, and the product was eluted from a column of silica gel (3 g) with 1:5 2-butanone–toluene. Recrystallisation of the product from ethanol then gave **14** as needles (137 mg, 49%), m.p. 120–121°. ^{1}H-N.m.r. data: δ 5.51 (t, 1 H, $J_{2,3} = J_{3,4} = 3.4$ Hz, H-3), 5.38 (q, 1 H, $J_{1,2} = J_{1,6} = J_{1,6'} = 3.6$ Hz, H-1), 4.99 (t, 1 H, H-2), 4.90 (dd, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.22 (dd, 1 H, $J_{5,7}$ 4.4, J_{gem} 11.3 Hz, H-7), 3.98 (dd, 1 H, $J_{5,7'}$ 4.2 Hz, H-7'), 2.13, 2.10, 2.06, 2.01, and 1.98 (5 s, each 3 H, 5 OAc).

Anal. Calc. for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23. Found: C, 52.58; H, 6.20.

DL-*(1,2,3,4/5)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol* (**2**). — Compound **14** (51 mg, 0.13 mmol) was treated with methanolic M sodium methoxide (10 mL) at room temperature for 1.5 h. The reaction mixture was neutralised by passage through a short column of Amberlite IR-120B (H^+) resin and concentrated to give **2** as a syrup (23 mg, 100%).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.05; H, 7.73.

DL-*(1,3,5/2,4)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol* (**15**). — (1,3,5/2,4)-5-Acetoxymethyl-1,2,3,4-tetra-acetoxycyclohexane[7,8] (1.37 g, 3.53 mmol) was *O*-deacetylated as described above for the preparation of **8**, to give **15** as a syrup (580 mg, 100%). Crystallisation from aqueous ethanol gave prisms, m.p. 132–133°.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.36; H, 7.76.

*(1*SR*,2*SR*,3*RS*,8*RS*,10*RS*)-5,5,12,12-Tetramethyl-4,6,11,13-tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-ol and (1*SR*,2*RS*,7*RS*,9*RS*,10*SR*)-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo[8.3.0.0^{2,7}]tridecan-9-ol [1,2:4,7-* (**16**) *and 2,3:4,7-di-O-isopropylidene derivatives* (**17**) *of* DL-*(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — To a solution of **15** (298 mg, 1.67 mmol) in dry *N*,*N*-dimethylformamide (6 mL) was added 2,2-dimethoxypropane (4 mL) and toluene-*p*-sulfonic acid monohydrate (5 mg), and the mixture was stirred at 60° for 6 h under slightly diminished pressure. T.l.c. (1:2 2-butanone–toluene) then revealed two major products (R_F 0.68 and 0.62), which were isolated essentially by the general procedure used for **9**. Elution of the mixture from a column of silica gel (4 g) with 1:8 2-butanone–toluene gave, first, **17** as needles, m.p. 160.5–161.5° (from ethanol). ^{1}H-N.m.r. data: δ 4.00–3.23 (m, 6 H, H-1,2,3,4 and CH_2O), 1.51, 1.45, and 1.43 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.58; H, 8.42.

The second fraction was **16**, needles (111 mg, 25.6%), m.p. 137–138°. ^{1}H-N.m.r. data: δ 3.87–3.21 (m, 6 H, H-1,2,3,4 and CH_2O), 1.45, 1.44, and 1.41 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.38; H, 8.49.

The acetate **19** of **17** was a syrup. ^{1}H-N.m.r. data: δ 4.22 (td, 1 H, $J_{1,2} = J_{1,6} = 10.5$, $J_{1,6'}$ 5.2 Hz, H-1), 3.94–3.50 (m, 5 H, H-2,3,4 and CH_2O), 3.08 (s, 3 H, OAc), 1.52, 1.47, and 1.46 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.20; H, 7.77.

The acetate **19** of **17** was a syrup. ^{1}H-N.m.r. data: δ 4.22 (td, 1 H, $J_{1,2} = J_{1,6} = 10.5$, $J_{1,6'}$ 5.2 Hz, H-1), 3.94–3.50 (m, 5 H, H-2,3,4 and CH_2O), 3.08 (s, 3 H, OAc), 1.52, 1.47, and 1.46 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Found: C, 59.67; H, 7.90.

*(1*SR,*3*RS,*8*RS,*10*RS*) - 5,5,12,12 - Tetramethyl - 4,6,11,13 - tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-one* [**20**, *1,2:4,7-di-*O*-isopropylidene derivative of* DL*-(1,5/2,4)-5-hydroxymethyl-3-oxo-1,2,4-cyclohexanetriol*]. — Compound **16** (165 mg, 0.64 mmol) was oxidised with ruthenium tetraoxide, as in the preparation of **9**, to give **20** (162 mg, 99%) as thin needles, m.p. 154–155° (from ethanol); ν_{max}^{KBr} 1752 cm^{-1} (C=O). ^{1}H-N.m.r. data: δ 4.34 (dd, 1 H, *J* 2.2 and 10.5 Hz, H-2), 4.13 (dd, 1 H, *J* 2.2 and 9.8 Hz, H-4), 3.94–3.53 (m, 3 H, H-1 and CH_2O), and 1.48 (s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.70; H, 7.85.

*(1*SR,*2*RS,*3*RS,*8*RS,*10*RS*)-5,5,12,12-Tetramethyl-4,6,11,13-tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-ol* [**21**, *1,2:4,7-di-*O*-isopropylidene derivative of* DL*-(1,5/2,3,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — Compound **20** (131 mg, 0.51 mmol) was hydrogenated, as in the preparation of **12**, to give **21** as prisms (48 mg, 36%), m.p. 99–100° (from ethyl acetate–hexane). ^{1}H-N.m.r. data: δ 4.34 (t, 1 H, $J_{2,3} = J_{3,4} = 2$ Hz, H-3), 4.05 (td, 1 H, $J_{1,2}$ 4.2, $J_{1,6} = J_{1,6'} = 9.6$ Hz, H-1), 3.87–3.21 (m, 3 H, H-2 and CH_2O), 3.31 (dd, 1 H, $J_{4,5}$ 9.6 Hz, H-4), and 1.43 (s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.69; H, 8.36.

Compound **21** (88 mg) was acetylated in the usual way, and the product was purified by elution from a column of silica gel with 1:7 2-butanone–toluene to give the acetate **22** (92 mg, 69.5%) as prisms, m.p. 137–138° (from ethanol). ^{1}H-N.m.r. data: δ 5.65 (t, 1 H, $J_{2,3} = J_{3,4} = 2.9$ Hz, H-3), 4.10–3.30 (m, 5 H, H-1,2,4 and CH_2O), 1.40 and 1.37 (2 s, each 6 H, 2 CMe_2).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.88; H, 7.87.

DL*-(1,5/2,3,4)-5-Acetoxymethyl-1,2,3,4-tetra-acetoxycyclohexane* (**23**). — Compound **22** (120 mg, 0.47 mmol) was treated with aqueous 70% acetic acid (5 mL) at room temperature for 5 h. The mixture was concentrated and the product was acetylated in the usual way. Crystallisation from ethanol then gave **23** as prisms (112 mg, 62%), m.p. 110–111°. ^{1}H-N.m.r. data: δ 5.59 (t, 1 H, $J_{2,3} = J_{3,4} = 2.7$ Hz, H-3), 5.20 (dd, 1 H, $J_{1,2} = J_{1,6} = 10.5$, $J_{1,6'}$ 4.9 Hz, H-1), 5.03 (dd, 1 H, H-2), 4.88 (dd, 1 H, $J_{4,5}$ 11.4 Hz, H-4), 4.15–3.96 (m, 2 H, CH_2OAc), 2.14, 2.05, 2.04, and 2.00 (4 s, 3, 3, 3, and 6 H, 5 OAc).

Anal. Calc. for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23. Found: C, 52.82; H, 6.20.

*(1*SR,*2*RS,*7*RS,*10*RS*) - 4,4,12,12 - Tetramethyl - 3,5,11,13 - tetraoxatricyclo-*

[8.3.0.0^{2,7}]tridecan-9-one [**24**, *1,2:3,7-di-O-isopropylidene derivative of* DL-*(1,3/2,4)-4-hydroxymethyl-6-oxo-1,2,3-cyclohexanetriol*]. — Compound **17** (138 mg, 0.53 mmol) was oxidised as described above for the preparation of **11**, to give **24** (130 mg, 94.6%) as needles, m.p. 140.5–142.5° (from ethanol). ^{1}H-N.m.r. data: δ 4.30–3.64 (m, 5 H, H-2,3,4 and C*H*$_2$O), 1.55 and 1.46 (2 s, 3 and 9 H, 2 CMe$_2$).

Anal. Calc. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.65; H, 7.79.

*(1*SR,*2*RS,*7*RS,*9*SR,*10*RS*)-4,4,12,12-Tetramethyl-3,5,11,13-tetraoxatricyclo[8.3.0.0^{2,7}]tridecan-9-ol* [**25**, *2,3:4,7-di-O-isopropylidene derivative of* DL-*(1,2,4/3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — Compound **24** (113 mg, 0.44 mmol) was hydrogenated in ethanol over Raney nickel as described above for the preparation of **12**. T.l.c. (1:1 2-butanone–toluene) then indicated the formation of a new compound (R_F 0.58), together with **17** (R_F 0.53). The mixture was eluted from a column of silica gel with 1:5 2-butanone–toluene to give, first, **25** as needles (35 mg, 30.8%), m.p. 167–168° (from ethanol). ^{1}H-N.m.r. data: δ 4.32 (q, 1 H, $J_{1,2} = J_{1,6} = J_{1,6'} = 2.9$ Hz, H-1), 3.96 (t, 1 H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 3.41 (t, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 3.15 (dd, 1 H, H-2), 1.46, 1.42, and 1.39 (3 s, 3, 6, and 3 H, 2 CMe$_2$).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.76; H, 8.49.

The second fraction was **17** obtained as prisms (18 mg, 16%), m.p. 160–161° (from ethanol).

The acetate **26** of **25** was obtained (88%) as thin plates, m.p. 100–102° (from ethanol). ^{1}H-N.m.r. data: δ 5.45 (q, 1 H, $J_{1,2} = J_{1,6} = J_{1,6'} = 3$ Hz, H-1), 4.20–3.35 (m, 5 H, H-2,3,4 and C*H*$_2$O), 2.09 (s, 3 H, OAc), and 1.64–1.35 (m, 12 H, CMe$_2$).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.06; H, 7.90.

Deacetonation of **26** and acetylation of the product, followed by purification by chromatography on silica gel and recrystallisation from ethanol, gave the penta-acetate[9] **7** as prisms (36%), m.p. 110–111°.

DL-*(1,2/3,4,5)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol* (**28**). — This compound was prepared from its penta-acetate[8] **27**, as described in the preparation of **8**, and was obtained as white crystals, m.p. 166.5–168°; lit.[5] m.p. 173–174°.

*(1*SR,*2*SR,*6*SR,*7*RS,*9*SR*)-7-(Hydroxymethyl)-4,4,11,11-tetramethyl-3,5,10,12-tetraoxatricyclo[7.3.0.0^{2,6}]dodecane* [**29**, *1,2:3,4-di-O-isopropylidene derivative of* DL-*(1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — A mixture of **28** (100 mg, 0.56 mmol), *N,N*-dimethylformamide (2 mL), 2,2-dimethoxypropane (1 mL), and toluene-*p*-sulfonic acid monohydrate (5 mg) was stirred at 60° for 18 h and then processed in the usual manner, and the product was purified by chromatography on silica gel to give **28** as a syrup (82 mg, 57%). ^{1}H-N.m.r. data: δ 4.63–4.33 (m, 4 H, H-1,2,3,4), 3.85–3.55 (m, 2 H, C*H*$_2$OH), 1.43 and 1.33 (2 s, each 6 H, 2 CMe$_2$).

The acetate **30** of **29** was obtained as a syrup (86%). ^{1}H-N.m.r. data: δ 4.57–4.25 (m, 4 H, H-1,2,3,4), 4.12–3.90 (m, 2 H, C*H*$_2$OAc), 2.05 (s, 3 H, OAc), 1.42, 1.40, and 1.31 (3 s, 3, 3, and 6 H, 2 CMe$_2$).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.56; H, 7.86.

*(1*SR,*2*SR,*3*SR,*5*SR,*8*RS,*10*SR,*12*RS*)- and (1*SR,*2*SR,*3*SR,*5*SR,*8*RS,*10*SR, *12*SR*)-5,12-Diphenyl-4,6,11,13-tetraoxatricyclo[8.3.0.0^{3,8}]tridecan-2-ol* [exo- (**31**) *and* endo-*isomers* (**32**) *of the 1,2:4,7-di-*O*-benzylidene derivative of* DL-*(1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — To a solution of **28** (200 mg, 1.12 mmol) in *N,N*-dimethylformamide (2 mL) was added α,α-dimethoxytoluene (2.4 mL) and toluene-*p*-sulfonic acid monohydrate (2 mg), and the mixture was stirred at 55° for 8.5 h under slightly diminished pressure. T.l.c. (1:5 2-butanone–toluene) then revealed two major products (R_F 0.53 and 0.49). The products were isolated essentially by the procedure used for the preparation of **9**. The products were eluted from a column of silica gel with 1:20 2-butanone–toluene to give, first, **31**, obtained as needles (101 mg, 25.4%), m.p. 141–142° (from ethanol). ^{1}H-N.m.r. data: δ 7.60–7.33 (m, 10 H, 2 Ph), 6.16 and 5.50 (2 s, each 1 H, 2 PhC*H*).

Anal. Calc. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.89; H, 6.26.

Eluted second was **32**, obtained as needles (87 mg, 21.9%), m.p. 126–127°. ^{1}H-N.m.r. data: δ 7.60–7.23 (m, 10 H, 2 Ph), 5.89 and 5.37 (2 s, each 1 H, PhC*H*).

Anal. Found: C, 71.45; H, 6.34.

The acetate **33** of **31** was obtained as a syrup. ^{1}H-N.m.r. data: δ 7.56–7.16 (m, 10 H, 2 Ph), 6.16 and 5.46 (2 s, each 1 H, 2 PhC*H*), 5.11 (dd, 1 H, $J_{2,3}$ 8.4, $J_{3,4}$ 3 Hz, H-3), and 2.16 (s, 3 H, OAc).

Anal. Calc. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 70.12; H, 5.73.

The acetate **34** of **32** was a syrup. ^{1}H-N.m.r. data: δ 7.63–7.29 (m, 10 H, 2 Ph), 5.92 and 5.43 (2 s, each 1 H, 2 PhC*H*), 4.95 (dd, 1 H, $J_{2,3}$ 7.8, $J_{3,4}$ 4 Hz, H-3), and 2.10 (s, 3 H, OAc).

Anal. Found: C, 70.06; H, 5.81.

*(1*SR,*3*SR,*5*SR,*8*RS,*10*SR,*12*RS*)-5,12-Diphenyl-4,6,11,13-tetraoxatricyclo-[8.3.0.0^{3,8}]tridecan-2-one* [**35**, exo-*1,2:4,7-di-*O*-benzylidene derivative of* DL-*(1,2/4,5)-5-hydroxymethyl-3-oxo-1,2,4-cyclohexanetriol*]. — Compound **31** (32 mg, 0.09 mmol) was oxidised with ruthenium tetraoxide as described for the preparation of **11**. The product was recrystallised from ethanol to give **35** as needles (20.5 mg, 64.8%), m.p. 119–120°; ν_{max}^{KBr} 1732 cm^{-1} (C=O). ^{1}H-N.m.r. data: δ 7.60–7.30 (m, 10 H, 2 Ph), 6.11 and 5.60 (2 s, each 1 H, 2 PhC*H*), and 5.01 (d, 1 H, $J_{4,5}$ 4.7 Hz, H-4).

Anal. Calc. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.36; H, 5.83.

*(1*SR,*2*RS,*3*SR,*5*SR,*8*RS,*10*SR,*12*RS*)-5,12-Diphenyl-4,6,11,13-tetraoxatri-cyclo[8.3.0.0^{3,8}]tridecan-2-ol* [**36**, exo-*1,2:4,7-di-*O*-benzylidene derivative of* DL-*(1,2,3/4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol*]. — A mixture of **35** (85 mg, 0.24 mmol), sodium borohydride (150 mg), and methanol (10 mL) was stirred at 0–5° for 2 h. T.l.c. (1:8 2-butanone–toluene) then revealed two products (R_F 0.30 and 0.22). The mixture was concentrated and the residue was eluted from a column of silica gel with 1:10 2-butanone–toluene to give, first, **36** (47 mg, 54.7%), obtained as needles, m.p. 141–141.5° (from ethanol). ^{1}H-N.m.r. data: δ 7.53–7.20 (m, 10 H, 2 Ph), 6.26 and 5.47 (2 s, each 1 H, 2 PhC*H*).

Anal. Calc. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.92; H, 6.18.

Eluted second was **31** (22 mg, 26.2%), m.p. 141–142°.

The acetate **37** of **36** was a syrup. ^{1}H-N.m.r. data: δ 7.56–7.16 (m, 10 H, 2 Ph), 6.20 and 5.20 (2 s, each 1 H, 2 PhC*H*), 5.31 (t, 1 H, $J_{2,3} = J_{3,4} = 4.2$ Hz, H-3), 4.45 (t, 1 H, $J_{4,5}$ 4.2 Hz, H-4), and 2.14 (s, 3 H, OAc).

Anal. Calc. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.81; H, 6.13.

DL-*(1,2,3/4,5)-5-Acetoxymethyl-1,2,3,4-tetra-acetoxycyclohexane* (**38**). — A solution of **37** (118 mg, 0.30 mmol) in aqueous 90% acetic acid (10 mL) was heated at 90° for 1 h and then concentrated. The residue was acetylated, and the product was eluted from a column of silica gel with 1:8 2-butanone–toluene to give, after crystallisation from ethanol, **38** as prisms (85.6 mg, 74%), m.p. 109–110°. ^{1}H-N.m.r. data: δ 5.33–5.20 (m, 4 H, H-1,2,3,4), 2.07, 2.06, 2.05, and 2.04 (4 s, 3, 6, 3, and 3 H, 5 OAc).

Anal. Calc. for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23. Found: C, 52.79; H, 6.19.

DL-*(1,2,3/4,5)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol* (**4**). — Compound **38** (76 mg, 0.20 mmol) was *O*-deacetylated as described for the preparation of **8**. The product was recrystallised from ethanol to give **4** as prisms (32.8 mg, 98%), m.p. 139–140°.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.39; H, 7.79.

DL-*(1,2,4,5/3)-5-Acetoxymethyl-1,2,3,4-tetra-acetoxycyclohexane* (**40**). — A solution of DL-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol[14] (**39**; 91 mg, 0.52 mmol) in methanol (2 mL) was hydrogenated in the presence of 5% Pt/C (10 mg) at room temperature for 2 days, filtered, and concentrated. The residue was acetylated in the usual way and the product was eluted from a column of silica gel with 1:5 2-butanone–toluene to give **40** as a syrup (120 mg, 60%). ^{1}H-N.m.r. data: δ 5.53–4.80 (m, 4 H, H-1,2,3,4), 2.07, 2.06, 2.04, and 2.03 (4 s, 3, 3, 6, and 3 H, 5 OAc).

Anal. Calc. for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23. Found: C, 52.86; H, 6.32.

DL-*(1,2,4,5/3)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol* (**5**). — Compound **40** (67 mg) was *O*-deacetylated, as described for the preparation of **8**, to give **5** as a syrup in quantitative yield.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.44; H, 7.83.

ACKNOWLEDGMENTS

We thank Mr. Saburo Nakada for the elemental analyses, and Dr. Tatsushi Toyokuni for assistance in the preparation of **8**, **15**, and **28**.

REFERENCES

1 S. OGAWA, T. HATTORI, T. TOYOKUNI, AND T. SUAMI, *Bull. Chem. Soc. Jpn.*, 56 (1983) 2077–2081.
2 T. W MILLER, B. H. ARISON, AND G. ALBERS-SCHONBERG, *Biotechnol. Bioeng.*, 15 (1973) 1075–1080.
3 G. E. MCCASLAND, S. FURUTA, AND L. J. DURHAM, *J. Org. Chem.*, 31 (1966) 1516–1521.
4 G. E. MCCASLAND, S. FURUTA, AND L. J DURHAM, *J. Org. Chem.*, 33 (1968) 2835–2841.
5 G. E. MCCASLAND, S. FURUTA, AND L. J. DURHAM, *J. Org. Chem.*, 33 (1968) 2841–2844.

6 T. SUAMI, S. OGAWA, T. ISHIBASHI, AND I. KASAHARA, *Bull. Chem. Soc. Jpn.*, 49 (1976) 1388–1390.
7 T. SUAMI, S. OGAWA, K. NAKAMOTO, AND I. KASAHARA, *Carbohydr. Res.*, 58 (1977) 240–244.
8 S. OGAWA, M. ARA, T. KONDOH, M. SAITOH, R. MASUDA, T. TOYOKUNI, AND T. SUAMI, *Bull. Chem. Soc. Jpn.*, 53 (1980) 1121–1126.
9 S. OGAWA, T. TOYOKUNI, T. KONDOH, Y. HATTORI, Y. IWASAWA, M. SUETSUGU, AND T. SUAMI, *Bull. Chem. Soc. Jpn.*, 54 (1981) 2739–2746.
10 S. OGAWA, Y. IWASAWA, AND T. SUAMI, *Chem. Lett.*, (1984) 355–356.
11 S. NISHIMURA, *Bull. Chem. Soc. Jpn.*, 32 (1959) 61–63.
12 N. BAGGETT, K. W. BUCK, A. B. FOSTER, AND J. M. WEBBER, *J. Chem. Soc.*, (1965) 3401–3407.
13 A. LIPTÁK, J. IMRE, J. HARAGI, AND P. NÁNÁSI, *Carbohydr. Res.*, 116 (1983) 217–225, and references cited therein.
14 T. TOYOKUNI, Y. ABE, S. OGAWA, AND T. SUAMI, *Bull. Chem. Soc. Jpn.*, 56 (1983) 505–531.