Carbohydrate Research, 225 (1992) 269–378
Elsevier Science Publishers B.V., Amsterdam

Synthesis of 7-(2,4-dichlorophenyl)-D-*erythro*-3-hydroxy-5-heptanolide, 6-(2,4-dichlorophenyl)-D-*erythro*-2,4-dihydroxyhexane-1-sulfonic acid, and 6-(2,4-dichlorophenyl)-D-*erythro*-2,4-dihydroxyhexylphosphonic acid*

György Hodosi, Géza Galambos, Benjamin Podányi, and János Kuszmann†
Institute for Drug Research, P.O.B. 82, 1325 Budapest (Hungary)

(Received May 17th, 1991; accepted August 17th, 1991)

ABSTRACT

6-(2,4-Dichlorophenyl)-D-*erythro*-1,2,4-hexanetriol, synthesised from D-glucose, was partially silylated, then reacted with 2-methoxypropene to afford 1-*O*-*tert*-butyldimethylsilyl-6-(2,4-dichlorophenyl)-2,4-*O*-isopropylidene-D-*erythro*-1,2,4-hexanetriol (**17**). Desilylation of **17** gave 6-(2,4-dichlorophenyl)-2,4-*O*-isopropylidene-D-*erythro*-1,2,4-hexanetriol, which was converted into the 1-tosylate **18** and the 1-bromo derivative **19**. Reaction of **18** with potassium thiolbenzoate gave, after debenzoylation, oxidation, and deprotection, 6-(2,4-dichlorophenyl)-D-*erythro*-2,4-dihydroxyhexane-1-sulfonic acid (**4**). Reaction of **18** or **19** with triethyl phosphite gave, after deprotection, 6-(2,4-dichlorophenyl)-D-*erythro*-2,4-dihydroxyhexylphosphonic acid (**5**), and reaction of **19** with potassium cyanide gave, after subsequent hydrolysis and deprotection, 7-(2,4-dichlorophenyl)-D-*erythro*-3-hydroxy-5-heptanolide (**3**).

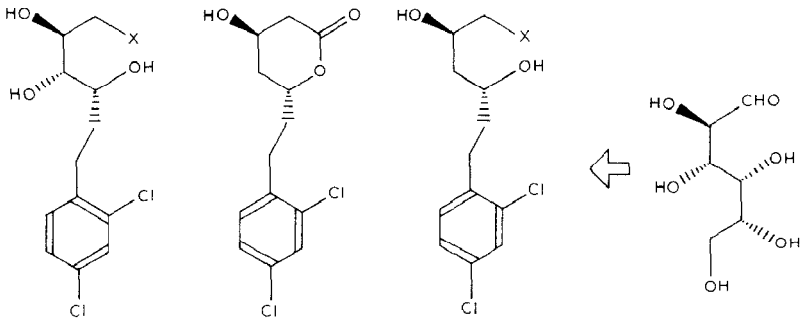
INTRODUCTION

In the preceding paper[1], the synthesis of the mevalonic acid analogue **1** was described, which differed from the model compound **3** of known biological activity[2] by an additional hydroxyl group in the lactone moiety. However, both **1** and its bioisosteric derivative **2**, in which the carboxyl group was substituted by the sulfonic acid group, were less active than the corresponding dihydroxy derivative 3**. In order to determine the possible influence of the additional hydroxyl group on the biological activity, the synthesis of analogues of **3**, which differ only in the nature of the acidic group, *i.e.* the sulfonic acid **4** and the phosphonic acid **5**, was undertaken.

The strategy of Lee[3] was applied, starting from D-glucose (**6**) and involving (*a*) removal of HO-3 by reduction, (*b*) replacement of C-5,6 by the 2,4-dichlorophenylethyl substituent, and (*c*) introduction of the new acidic group *via* a chain elongation at C-1.

* Potential Inhibitors of HMG-CoA Reductase, Part II. For Part I, see ref. 1.
† Author for correspondence.
** Despite the fact that **3** was synthesised as the optically pure D-*erythro* isomer by two different approaches[3,4], the racemate was used for the biological investigations[2].

0008-6215/92/$ 05.00



1 X = COOH
2 X = SO_3H

3

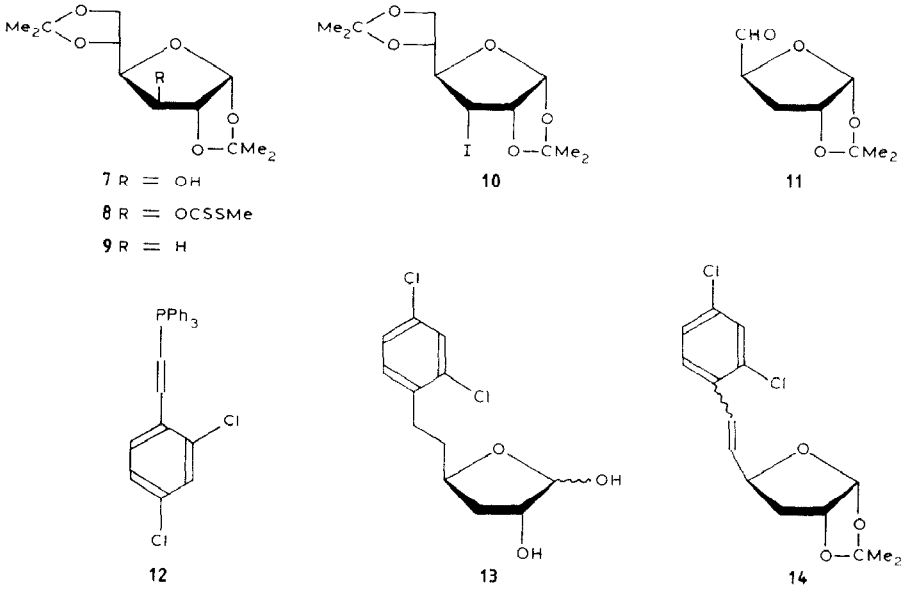
4 X = SO_3H
5 X = PO_3H_2

6

RESULTS AND DISCUSSION

The reductive elimination of HO-3 involved[3] conversion of the 1,2:5,6-di-*O*-isopropylidene derivative **7** into the 3-*O*-(*S*-methyl dithiocarbonate) **8**, followed by reduction with Bu_3SnH[5-7] to afford the 3-deoxy derivative **9** (80% from **7**). The drawbacks of this approach are the toxic reagents and the high price of Bu_3SnH. Therefore, **7** was converted[8] into the 3-deoxy-3-iodo-D-*allo* derivative **10**, using Ph_3P, I_2, and imidazole in toluene at 110°. Reduction of **10** by Bu_3SnH[6] gave 92% of **9** but, because of the drawbacks mentioned above, $NiCl_2$–$NaBH_4$ in ethanol[9,10] was used. Thus, **9** was obtained by a safe and simple procedure in an overall yield of 68% from **7**.

Partial hydrolysis of **9** and subsequent periodate oxidation[11] afforded **11**, the free aldehyde group of which was converted *via* a Wittig reaction with the 2,4-dichloroben-



7 R = OH
8 R = OCSSMe
9 R = H

10

11

12

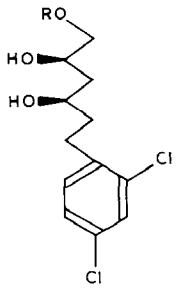
13

14

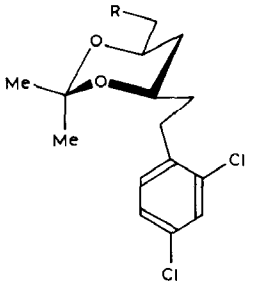
zyltriphenylphosphonium ylid **12** in 1:4 *N,N*-dimethylformamide–tetrahydrofuran into **14**. According to the n.m.r. data, **14** was a 3:1 mixture of the *Z* and *E* isomers ($J_{5,6}$ 11.4 and 16.0 Hz, respectively) which could not be resolved by column chromatography. Hydrogenation (Pd/C) of this mixture gave, after hydrolysis, the free saturated lactol **13**[3].

Borohydride reduction of **13** afforded the triol **15**, which was the key intermediate in the synthesis of the target molecules **4** and **5** (**4** was isolated as the potassium salt **29**). Since, the direct activation of HO-1 would lead[1] only to the 1,4-anhydro derivative **27**, due to rapid intramolecular cyclisation, an indirect route was used. Thus, HO-1 in **15** was protected by the ^{t}BuMe$_2$Si group (→**16**) and HO-3,5 were blocked by the isopropylidene group (→**17**). Protection by acetylation was avoided because of possible acetyl migration[1] during the removal of the ^{t}BuMe$_2$Si group. The silyl group of **17** was removed by reaction with Bu$_4$NF in tetrahydrofuran to give 95% of **26**. The primary hydroxyl group of **26** was activated either by tosylation (→**18**) or by conversion into the bromide **19** by treatment[12] with *N*-bromosuccinimide and Ph$_3$P in *N,N*-dimethylformamide. Treatment of **18** with a boiling solution of sodium iodide in acetone gave the iodide **20**.

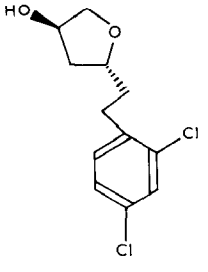
Both **18** and **19** are suitable for the introduction of acidic functions at C-1. Thus, treatment of **18** with potassium thiolbenzoate in boiling acetone afforded 85% of **22**, which was converted into thiol **23** on treatment with methanolic sodium methoxide (at



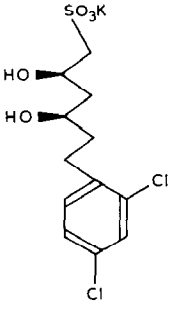
15 R = H
16 R = ^{t}BuMe$_2$Si



17 R = ^{t}BuMe$_2$SiO
18 R = OTs
19 R = Br
20 R = I
21 R = CN
22 R = SBz
23 R = SH
24 R = SO_3K
25 R = $PO(OEt)_2$
26 R = OH
28 R = $PO(OSiMe_3)_2$



27



29

least 1.1 equiv. because of the acidity of the SH group). Oxidation[13] of **23** with $KMnO_4$ in acetone afforded the potassium sulfonate **24**, which was hydrolysed with acid to give **29**.

When **18** was treated with sodium diethyl phosphonate[14,15], only the derivative **26** could be isolated. The Michaelis–Arbusov reaction[15–17] of **18** with triethyl phosphite at 150–160° afforded 58% of the diethyl phosphonate **25**. A higher yield (78%) of **25** was obtained when this reaction was applied to the bromide **19**. The ester **25** was deprotected using Me_3SiCl–NaI in *N,N*-dimethylformamide[18] to give the silylated intermediate **28**, which hydrolysed spontaneously in the presence of water to yield **5**.

In order to obtain appropriate biological data, the activites of **29**, **5**, and **3** should be compared. However, only the biological activity of racemic **3** has been reported[2]. Hence, **3** was synthesised from the bromide **19** by treatment in sequence with sodium cyanide in hexamethylphosphoric triamide at 80° to give the nitrile **21**, oxidation with H_2O_2 in dimethyl sulfoxide[19], and hydrolysis of the resulting amide. The lactone **3** ($\nu_{C=O}$ 1730 cm^{-1}) was identical with that described[3,4].

BIOLOGICAL RESULTS

The assay for the inhibition of HMG-CoA reductase was carried as described[2] for racemic **3**, but with the D-*erythro*(3*R*,5*R*) isomer. The following activities were obtained: **3** (10^{-5}M) 82% inhibition relative to that of compactin (*cf.* 80% for racemic **3**), **29** (10^{-5}M) 13.3%, **5** (10^{-4}M) 16.2%.

Thus, exchange of the carboxyl group at C-1 by a sulfonic (**29**) or phosphonic (**5**) group decreases the activity significantly.

EXPERIMENTAL

General methods. — Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure. Reactions were carried out at 20° and optical rotations were determined on 1% solutions in $CHCl_3$ at 20° unless stated otherwise.

T.l.c. was performed on Kieselgel G with EtOAc (*A*), EtOAc–hexane (*B* 3:1, *C* 2:1, *D* 1:1, *E* 1:2, *F* 1:3, *G* 1:4, *H* 1:5, *I* 1:6, and *J* 1:10), and EtOAc–EtOH (*K* 2:1, *L* 1:1, *M* 1:2, and *N* 1:3), with detection by charring with H_2SO_4. N.m.r. spectra (^1H, 250 MHz; ^{13}C, 75 MHz) were recorded on a Bruker Ac 250 spectrometer on solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise. Multiplicities of ^{13}C signals were obtained from DEPT experiments.

7-(2,4-Dichlorophenyl)-D-erythro-*3-hydroxy-5-heptanolide* (**3**). — A solution of K_2CO_3 (0.1 g) in water (0.5 mL) was added to a stirred solution of **23** (0.17 g) in Me_2SO (8 mL) at 0°, then aq. 30% H_2O_2 (0.2 mL) was added. The mixture was stirred for 2 h at 0°, then concentrated at 12 Pa. To a solution of the residue in 1:1 water–MeCN (4 mL) was added 2m HCl (1 mL), and the solution was boiled under reflux for 3 h, then concentrated. Column chromatography (solvent *A*) of the residue gave **3** (0.065 g, 46.4%), isolated as a syrup, $[\alpha]_D$ +60.2°, R_F 0.3 (solvent *A*); lit.[3] $[\alpha]_D^{20}$ +63.1°; lit.[4] $[\alpha]_D^{20}$ +59.7°. N.m.r. data: ^1H, δ 7.35 (m, 1 H, H-3′, aromatic), 7.17 (m, 2 H, H-5′,6′, aromatic), 4.70 (m, 1 H,

H-5), 4.38 (m, 1 H, H-3), 3.05–2.57 (m, 4 H, H-2a,2b,7a,7b), and 2.05–1.70 (m, 4 H, H-4a,4b,6a,6b); ^{13}C, δ 170.5 (C-1), 137.3 (C-1′, aromatic), 134.6 (C-4′, aromatic), 132.7 (C-2′, aromatic), 131.4 (C-6′, aromatic), 129.4 (C-3′, aromatic), 127.3 (C-5′, aromatic), 74.9 (C-5), 62.7 (C-3), 38.7 (C-2), 35.9 (C-4), 35.2 (C-6), and 28.7 (C-7).

Anal. Calc. for $C_{13}H_{24}Cl_2O_3$: C, 54.00; H, 4.87. Found: C, 53.95; H, 4.93.

6-(2,4-Dichlorophenyl)-D-erythro-*2,4-dihydroxyhexylphosphonic acid* (**5**). — Chlorotrimethylsilane (0.5 mL) and NaI (0.58 g) were added to a stirred solution of **25** (0.41 g) in MeCN (8 mL). The mixture was kept for 3 h at 60° (bath) to give the intermediate **28**, R_F 0.15 (solvent *A*), then cooled, filtered, washed with MeCN, and concentrated. A solution of the residue in water was neutralised with conc. NH_4OH and extracted with $CHCl_3$, and the aqueous solution was concentrated. The cations were removed from an aqueous solution of the residue with Varion KS (H^+) resin and the solution was concentrated to give **5** (0.12 g, 40.0%), isolated as a syrup, $[\alpha]_D$ + 13.6° (*c* 0.7, MeOH). N.m.r. data: ^1H (MeOD + D_2O), δ 7.41 (d, 1 H, H-3′, aromatic), 7.32 (d, 1 H, H-6′, aromatic), 7.26 (dd, 1 H, H-5′, aromatic), 4.20 (m, 1 H, H-2), 3.86 (m, 1 H, H-4), 2.95–2.65 (m, 2 H, H-6a,6b), and 2.1–1.65 (m, 6 H, H-1a,1b,3a,3b,5a,5b); $J_{3',5'}$ 1.6, $J_{5',6'}$ 8.3 Hz; ^{13}C (MeOD), δ 139.6 (C-1′, aromatic), 135.2 (C-4′, aromatic), 132.9 (C-2′, aromatic), 132.6 (C-6′, aromatic), 129.8 (C-3′, aromatic), 128.2 (C-5′, aromatic), 70.1 (C-4), 66.8 (C-2), 45.2 (C-3), 37.6 (C-5), 36.2 (C-1), and 29.7 (C-6); $^1J_{C\text{-}1,P}$ 133, $^3J_{C\text{-}3,P}$ 10.5 Hz.

Anal. Calc. for $C_{12}H_{17}Cl_2O_5P$: C, 42.00; H, 4.99. Found: C, 42.11; H, 4.97.

*3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-*D*-ribo-hexofuranose* (**9**). — (*a*) A mixture of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-iodo-D-*allo*-furanose[8] (**10**, 25 g) and Bu_3SnH (20.0 mL) in toluene (300 mL) was stirred under reflux for 40 min. The residue obtained after concentration was purified by column chromatography (solvent *D*) to give **9** (15.6 g, 96%), isolated as a syrup, $[\alpha]_D$ − 4.9° (*c* 0.5), R_F 0.55 (*D*); lit.[20] $[\alpha]_D^{18}$ − 8.6° (EtOH); lit.[5] $[\alpha]_D^{20}$ − 7.5°. N.m.r. data: ^1H, δ 5.74 (d, 1 H, H-1), 4.70 (dd, 1 H, H-2), 4.15–3.70 (m, 4 H, H-4,5,6a,6b), 2.11 (dd, 1 H, H-3a), 1.69 (ddd, 1 H, H-3b), 1.24, 1.28, 1.34, and 1.43 (4 s, each 3 H, 2 CMe_2); $J_{1,2}$ 3.6, $J_{2,3b}$ 4.6, $J_{3a,3b}$ 13.1, $J_{3a,4}$ 3.5, $J_{3b,4}$ 9.9 Hz.

(*b*) A solution of $NiCl_2 \cdot 6H_2O$ (0.041 g) in EtOH (1 mL) was added dropwise to a cooled (0–10°) and stirred mixture of **10** (1.3 g) and $NaBH_4$ (0.40 g) in EtOH (25 mL). The temperature was raised to 20–25°. The resulting black suspension was neutralised with M HCl and filtered. The filtrate was concentrated and the residue was extracted with $CHCl_3$ to give, after column chromatography (solvent *E*), **9** (0.68 g, 79.6%).

Anal. Calc. for $C_{12}H_{20}O_5$: C, 59.02; H, 8.25. Found: C, 58.96; H, 8.32.

6-(2,4-Dichlorophenyl)-D-erythro-*1,2,4-hexanetriol* (**15**). — To a stirred solution of **13**[3] (5.2 g) in EtOH (100 mL) at 0° was added $NaBH_4$ (1.4 g). After 1 h, the solution was neutralised with acetic acid and concentrated, and the residue was extracted with hot $CHCl_3$. Concentration of the extract gave **15** as a crude syrup (5.0 g, 95.6%). Column chromatography (solvent *A*) gave material with $[\alpha]_D$ + 8.3°, R_F 0.15 (solvent *A*). N.m.r. data: ^1H, δ 7.36–7.18 (m, 3 H, aromatic), 4.1–3.9 (m, 2 H, H-2,4), 3.66 (dd, 1 H, H-1a), 3.49 (dd, 1 H, H-1b), 3.0–2.7 (m, 2 H, H-6a,6b), and 1.9–1.6 (m, 4 H, H-3a,3b,5a,5b); $J_{1a,1b}$ 11.0, $J_{1a,2}$ 3.4, $J_{1b,2}$ 6.6 Hz; ^{13}C, δ 131.3 (d, C-6′, aromatic), 129.3 (d,

C-3′, aromatic), 127.2 (d, C-5′, aromatic), 72.7, 71.4 (d, C-2,4), 66.8 (t, C-1), 39.0 and 37.8 (t, C-3,5).

Anal. Calc. for $C_{12}H_{16}Cl_2O_3$: C, 51.63; H, 5.78. Found: C, 51.74; H, 5.81.

*1-O-tert-Butyldimethylsilyl-6-(2,4-dichlorophenyl)-*D-erythro-*1,2,4-hexanetriol* (**16**). — ^{t}BuMe$_2$SiCl (5.9 g) was added to a solution of **15** (10 g) in pyridine (80 mL) under N_2. After 3 h, when the reaction was completed, H_2O (1 mL) was added and the mixture was processed in the usual way to give, after column chromatography (solvent *D*), **16** (11.1 g, 78.8%), isolated as a syrup, $[\alpha]_D$ +11.2° (*c* 0.4), R_F 0.7 (solvent *A*). N.m.r. data: ^{1}H, δ 7.36 (d, 1 H, H-3′, aromatic), 7.2–7.1 (m, 2 H, H-5′,6′, aromatic), 3.96–3.84 (m, 2 H, H-2,4), 3.60 (dd, 1 H, H-1a), 3.43 (dd, 1 H, H-1b), 2.83 (m, 2 H, H-6a,6b), 1.8–1.5 (m, 4 H, H-3a,3b,5a,5b), 0.9 (s, 9 H, ^{t}Bu), and 0.1 (s, 6 H, Me$_2$Si); $J_{1a,1b}$ 9.9, $J_{1a,2}$ 3.7, $J_{1b,2}$ 7.2 Hz; ^{13}C, δ 131.4 (d, C-6′, aromatic), 129.2 (d, C-3′, aromatic), 127.0 (d, C-5′, aromatic), 72.9, 70.9 (d, C-2,4), 67.2 (t, C-1), 39.0, 37.4 (t, C-3,5), 29.0 (t, C-6), 25.9 (q, CMe$_3$), 0.01 and 5.4 (each q, Me$_2$Si).

Anal. Calc. for $C_{21}H_{34}Cl_2O_3Si$: C, 58.19; H, 7.91. Found: C, 58.24; H, 7.85.

*1-O-tert-Butyldimethylsilyl-6-(2,4-dichlorophenyl)-2,4-*O*-isopropylidene-*D-erythro-*1,2,4-hexanetriol* (**17**). — *p*-Toluenesulfonic acid (0.15 g) was added to a stirred mixture of **16** (6.5 g) and 2-methoxypropene (1.82 mL) in acetone (80 mL) under N_2. After 40 min, Et_3N (0.1 mL) was added and the solution was concentrated. Column chromatography (solvent *F*) of the residue gave **17** (6.4 g, 89.5%), isolated as a syrup, $[\alpha]_D$ +25.9°, R_F 0.8 (solvent *D*). N.m.r. data: ^{1}H, δ 7.35 (m, 1 H, H-3′, aromatic), 7.15 (m, 2 H, H-5′,6′, aromatic), 3.95–3.72 (m, 2 H, H-2,4), 3.66 (dd, 1 H, H-1a), 3.46 (dd, 1 H, H-1b), 2.92–2.66 (m, 2 H, H-6a,6b), 1.75 (m, 2 H, H-5a,5b), 1.59 (m, 1 H, H-3a), 1.42, 1.40 (2 s, each 3 H, Me$_2$C), 1.16 (m, 1 H, H-3b), 0.89 (s, 9 H, Me$_3$C), and 0.06 (s, 6 H, Me$_2$Si).

Anal. Calc. for $C_{21}H_{34}Cl_2O_3Si$: C, 58.19; H, 7.91. Found: C, 58.12; H, 8.02.

*6-(2,4-Dichlorophenyl)-2,4-*O*-isopropylidene-1-*O*-p-toluenesulfonyl-*D-erythro-*1,2,4-hexanetriol* (**18**). — To a solution of **26** (4.5 g) in pyridine (60 mL) was added tosyl chloride (4.01 g). After 7 h, the mixture was processed in the usual way. Crystallisation of the product from EtOAc–hexane gave **18** (5.4 g, 81.8%), m.p. 86–87° $[\alpha]_D$ +14.9°. N.m.r. data: ^{1}H, δ 7.79 (d, 2 H, H-3″,5″, aromatic), 7.33 (m, 3 H, H-3′,2″,6″, aromatic), 7.14 (m, 2 H, H-5′,6′, aromatic), 4.07 (m, 1 H, H-2), 4.0–3.85 (m, 2 H, H-1a,1b), 3.78 (m, 1 H, H-4), 2.75 (m, 2 H, H-6a,6b), 2.44 (s, 3 H, Ts*Me*), 1.71 (m, 2 H, H-5a,5b), 1.48 (dt, 1 H, H-3a), 1.35, 1.33 (2 s, each 3 H, Me$_2$C), and 1.17 (q, 1 H, H-3b); $J_{3a,3b}$ 12.6, $J_{3a,4}$ 2.3, $J_{2,3a}$ 2.5, $J_{3b,4}$ 11.5, $J_{2,3b}$ 11.5 Hz; ^{13}C, δ 131.2 (d, C-6′, aromatic), 129.3 (d, C-3′, aromatic), 127.1 (d, C-5′, aromatic), 77.4, 72.7 (d, C-2,4), 75.3 (t, C-1), 41.5 (t, C-3), 35.1 (t, C-5), and 29.8 (t, C-6).

Anal. Calc. for $C_{22}H_{26}Cl_2O_5S$: C, 55.81; H, 5.54. Found: C, 55.72; H, 5.63.

The tosylate **18** was unstable at room temperature and decomposed slowly to give **27**.

*1-Bromo-6-(2,4-dichlorophenyl)-2,4-*O*-isopropylidene-*D-erythro-*2,4-hexanediol* (**19**). — (*a*) Triphenylphosphine (0.9 g) was added gradually to a solution of **26** (1 g) and *N*-bromosuccinimide (0.61 g) in *N,N*-dimethylformamide (30 mL) at 0°. The mixture

was heated for 1 h at 50° (bath), then cooled, EtOAc (70 mL) was added, the mixture was washed with brine (40 mL), dried, and filtered, and the solvent was evaporated. The semicrystalline residue was extracted with ether, and the extract was filtered from Ph_3PO and concentrated. Column chromatography (solvent *F*) of the residue gave **19** (0.9 g, 75.0%), isolated as a syrup, R_F 0.80 (solvent *D*).

(*b*) Triphenylphosphine (0.74 g) was added gradually to a solution of **26** (0.6 g) and *N*-bromosuccinimide (0.5 g) in CH_2Cl_2 (10 mL) at 0°. The mixture was boiled under reflux for 40 min, then cooled, diluted with CH_2Cl_2 (50 mL), washed with aq. 5% $NaHCO_3$ (10 mL), dried, filtered, and concentrated. Column chromatography (solvent *F*) of the residue gave **19** (0.55 g, 76.6%), R_F 0.8 (solvent *D*). N.m.r. data: ^1H, δ 7.36 (m, 1 H, H-3′, aromatic), 7.15 (m, 2 H, H-5′,6′, aromatic), 4.01 (m, 1 H, H-2), 3.78 (m, 1 H, H-4), 3.36 (dd, 1 H, H-1a), 3.24 (dd, 1 H, H-1b), 2.80 (m, 2 H, H-6a,6b), 1.85–1.70 (m, 3 H, H-3a,5a,5b), 1.43 (s, 6 H, Me_2C), and 1.22 (q, 1 H, H-3b); $J_{3a,3b}$ 12.6, $J_{3b,4}$ 11.7, $J_{2,3b}$ 11.7 Hz.

Anal. Calc. for $C_{15}H_{19}BrCl_2O_2$: C, 47.15; H, 5.01. Found: C, 47.26; H, 4.98.

*6-(2,4-Dichlorophenyl)-1-iodo-2,4-*O*-isopropylidene-*D*-erythro-2,4-hexanediol* (**20**). — A solution of **18** (1.5 g) and dry NaI (2.37 g) in dry acetone (30 mL) was boiled under reflux for 3 h, then cooled, and the solvent was evaporated. A solution of the semi-crystalline residue in $CHCl_3$ (50 mL) was washed with water, saturated aq. $Na_2S_2O_3$, and water, dried, filtered, and concentrated. Column chromatography (solvent *I*) of the residue gave **20** (0.8 g, 58.8%), isolated as a syrup, R_F 0.7 (solvent *F*). N.m.r. data: ^1H, δ 7.36 (m, 1 H, H-3′, aromatic), 7.16 (m, 2 H, H-5′,6′, aromatic), 3.90–3.70 (m, 2 H, H-2,4), 3.20–3.05 (m, 2 H, H-1a,1b), 2.80 (m, 2 H, H-6a,6b), 1.85–1.70 (m, 3 H, H-3a,5a,5b), 1.44, 1.42 (2 s, each 3 H, CMe_2), and 1.15 (m, 1 H, H-3b); ^{13}C, δ 137.9 (C-1′, aromatic), 134.6 (C-4′, aromatic), 132.2 (C-2′, aromatic), 131.4 (C-6′, aromatic), 129.2 (C-3′, aromatic), 126.9 (C-5′, aromatic), 99.4 (*C*Me_2), 69.2, 67.6 (C-2,4), 36.7 (C-3), 35.6 (C-5), 29.9 (C-6), 28.4 (C-1), 19.9, and 9.4 (C*Me*$_2$).

Anal. Calc. for $C_{15}H_{19}Cl_2IO_2$: C, 40.11; H, 4.26. Found: C, 40.02; H, 4.29.

*1-Cyano-6-(2,4-dichlorophenyl)-2,4-*O*-isopropylidene-*D*-erythro-2,4-hexanediol* (**21**). — Dry NaCN (0.38 g) in hexamethylphosphoric triamide (7 mL) was heated, with stirring, under N_2 for 1 h at 60–70° (bath). A solution of **19** (0.5 g) in hexamethylphosphoric triamide (3 mL) was added and heating was continued for 3 h. The mixture was cooled, aq. 10% LiCl (30 mL) was added, the mixture was extracted with ether (3 × 20 mL), and the combined extracts were washed with aq. 10% LiCl (10 mL), dried, filtered, and concentrated. Column chromatography (solvent *F*) of the residue gave **21** (0.3 g, 67.9%), isolated as a syrup, $[\alpha]_D$ + 34.7° (*c* 0.1), R_F 0.4 (solvent *F*). N.m.r. data: ^1H, δ 7.36 (m, 1 H, H-3′, aromatic), 7.15 (m, 2 H, H-5′,6′, aromatic), 4.10 (m, 1 H, H-3), 3.80 (m, 1 H, H-5), 2.80 (m, 2 H, H-7a,7b), 2.50 (m, 2 H, H-2a,2b), 1.77 (m, 2 H, H-6a,6b), 1.65 (dt, 1 H, H-4a), 1.43 (s, 6 H, CMe_2), and 1.32 (q, 1 H, H-4b); $J_{4a,4b}$ 12.7, $J_{3,4a}$ 2.5, $J_{4a,5}$ 2.3, $J_{3,4b}$ 11.5, $J_{4b,5}$ 11.5 Hz.

Anal. Calc. for: $C_{16}H_{19}Cl_2NO_2$: C, 58.55; H, 5.83. Found: C, 58.62; H, 5.86.

*1-Benzoylthio-6-(2,4-dichlorophenyl)-2,4-*O*-isopropylidene-*D*-erythro-2,4-hexanediol* (**22**). — A solution of **18** (2 g) and potassium thiolbenzoate (1.15 g) in acetone (30

mL) was boiled under reflux for 11 h, then cooled, filtered, and concentrated. A solution of the residue in $CHCl_3$ (30 mL) was washed with aq. 5% $NaHCO_3$ (10 mL) and water (10 mL), dried, filtered, and concentrated. Column chromatography (solvent *G*) of the residue gave **22** (1.6 g, 86.0%), isolated as a syrup, R_F 0.5 (solvent *F*). N.m.r. data: ^1H, δ 7.98 (d, 2 H, H-2″,6″, aromatic), 7.58 (t, 1 H, H-4″, aromatic), 7.45 (t, 2 H, H-3″,5″, aromatic), 7.35 (m, 1 H, H-3′, aromatic), 7.14 (m, 2 H, H-5′,6′, aromatic), 4.00 (m, 1 H, H-2), 3.78 (m, 1 H, H-4), 3.25 (dd, 1 H, H-1a), 3.13 (dd, 1 H, H-1b), 2.79 (m, 2 H, H-6a,6b), 1.75 (m, 2 H, H-5a,5b), 1.66 (dt, 1 H, H-3a), 1.43, 1.41 (2 s, each 3 H, CMe_2), and 1.30 (q, 1 H, H-3b); $J_{1a,1b}$ 13.6, $J_{1a,2}$ 5.1, $J_{1b,2}$ 6.6, $J_{3a,3b}$ 13.0, $J_{2,3a}$ 3.3, $J_{3a,4}$ 3.3, $J_{3b,4}$ 12.0, $J_{2,3b}$ 12.0 Hz.

Anal. Calc. for $C_{22}H_{24}Cl_2O_3S$: C, 60.13; H, 5.51. Found: C, 60.27; H, 5.43.

*6-(2,4-Dichlorophenyl)-2,4-*O*-isopropylidene-1-mercapto-*D-erythro-*2,4-hexanediol* (**23**). — A solution of **22** (0.53 g) and methanolic 4.4M sodium methoxide (0.32 mL) in 2:1 tetrahydrofuran–MeOH (6 mL) was boiled under reflux, with stirring under N_2. After 2 h, the mixture was cooled, neutralised with acetic acid, and concentrated. A solution of the residue in $CHCl_3$ was washed with water, dried, filtered, and concentrated. Column chromatography (solvent *H*) of the residue gave **23** (0.37 g, 92.5%), isolated as a syrup, R_F 0.4 (*H*). N.m.r. data: ^1H, δ 7.35 (m, 1 H, H-3′, aromatic), 7.15 (m, 2 H, H-5′,6′, aromatic), 4.05 (m, 1 H, H-2), 3.78 (m, 1 H, H-4), 2.90–2.65 (m, 4 H, H-1a,1b,6a,6b), 1.75 (m, 2 H, H-5a,5b), 1.68 (dt, 1 H, H-3a), 1.43, 1.42 (2 s, each 3 H, CMe_2), and 1.20 (q, 1 H, H-3b); $J_{3a,3b}$ 12.8, $J_{2,3a}$ 2.4, $J_{3a,4}$ 2.4, $J_{3b,4}$ 12.0, $J_{2,3b}$ 12.0 Hz.

Anal. Calc. for $C_{15}H_{20}Cl_2O_2S$: C, 53.73; H, 6.01. Found: C, 53.81; H, 5.98.

*Potassium 6-(2,4-dichlorophenyl)-*D-erythro-*2,4-isopropylidenedioxyhexane-1-sulfonate* (**24**). — A solution of **23** (0.20 g) and $KMnO_4$ (0.60 g) in acetone (10 mL) and water (0.5 mL) was boiled under reflux for 10 h. More $KMnO_4$ (0.10 g) was added and boiling was continued for 5 h. The mixture was cooled, the residual $KMnO_4$ was decomposed with aq. H_2O_2 (30%), the brown precipitate was filtered off, and the solution was concentrated. Column chromatography (solvent *K*) of the residue gave **24** (0.14 g, 56.0%), isolated as a syrup, $[\alpha]_D$ 0° (*c* 0.1, MeOH), R_F 0.4 (solvent *K*). N.m.r. data (MeOD): ^1H, δ 7.38 (m, 1 H, H-3′, aromatic), 7.24 (m, 2 H, H-5′,6′, aromatic), 4.38 (m, 1 H, H-2), 3.86 (m, 1 H, H-4), 3.04 (dd, 1 H, H-1a), 2.86 (dd, 1 H, H-1b), 2.80 (m, 2 H, H-6a,6b), 1.99 (d, 1 H, H-3a), 1.72 (m, 2 H, H-5a,5b), 1.46, 1.35 (2 s, each 3 H, CMe_2), and 1.22 (q, 1 H, H-3b); $J_{1a,1b}$ 13.8, $J_{1a,2}$ 4.3, $J_{1b,2}$ 7.7, $J_{3a,3b}$ 12.9, $J_{3a,4}$ 2.4, $J_{2,3a}$ 2.4, $J_{3b,4}$ 11.3, $J_{2,3b}$ 11.5 Hz; ^{13}C (MeOD), δ 139.7 (C-1′, aromatic), 135.6 (C-4′, aromatic), 133.4 (C-2′, aromatic), 133.0 (C-6′, aromatic), 130.0 (C-3′, aromatic), 128.2 (C-5′, aromatic), 100.3 ($OCMe_2O$), 69.2, 67.5 (C-2,4), 58.5 (C-1), 38.3, 37.1 (C-3,5), 30.4 (C-6), 29.5, and 20.1 (CMe_2).

Anal. Calc. for $C_{15}H_{19}Cl_2KO_5S$: C, 42.75; H, 4.54; K, 9.28. Found: C, 42.83; H, 4.46; K, 9.12.

*Diethyl 6-(2,4-Dichlorophenyl)-*D-erythro-*2,4-isopropylidenedioxyhexylphosphonate* (**25**). — (*a*) A solution of **18** (0.46 g) in freshly distilled triethyl phosphite (5 mL) was boiled under reflux for 40 h under N_2. The reagent was then distilled off at 12 Pa. Column chromatography (solvent *A*) of the residue gave **25** (0.25 g, 58.1%), isolated as a

syrup, $[\alpha]_D$ ~0° (*c* 0.1, MeOH), R_F 0.3 (solvent *A*). N.m.r. data: ^{1}H, δ 7.35 (m, 1 H, H-3′, aromatic), 7.14 (m, 2 H, H-5′,6′, aromatic), 4.22 (m, 1 H, H-2), 4.11, 4.08 (2 q, 2 H, *J* 7.1 Hz, OCH_2CH_3), 3.78 (m, 1 H, H-4), 2.78 (m, 2 H, H-6a,6b), 2.15–1.70 (m, 6 H, H-1a,1b,3a,3b,5a,5b), 1.44, 1.40 (2 s, each 3 H, CMe_2), and 1.32 [t, 6 H, *J* 7.1 Hz, $(CH_3CH_2O)_2P$].

(*b*) The solution of **19** (0.5 g) in freshly distilled triethyl phosphite (5 mL) was boiled under reflux for 30 h, then processed as in (*a*) to give **25** (0.55 g, 78%).

Anal. Calc. for $C_{19}H_{29}Cl_2O_5P$: C, 51.94; H, 6.65. Found: C, 51.82; H, 6.53.

*6-(2,4-Dichlorophenyl)-2,4-*O*-isopropylidene-*D-erythro-*1,2,4-hexanetriol* (**26**). — Bu_4NF (5.0 g) was added to a solution of **17** (6.3 g) in tetrahydrofuran (100 mL). After 40 min, the solvent was evaporated. Column chromatography (solvent *D*) of the residue gave **26** (4.50 g, 95.0%), isolated as a syrup, $[\alpha]_D$ +25.9°, R_F 0.4 (solvent *D*). N.m.r. data: ^{1}H, δ 7.35 (m, 1 H, H-3′, aromatic), 7.15 (m, 2 H, H-5′,6′, aromatic), 3.96 (m, 1 H, H-2), 3.81 (m, 1 H, H-4), 3.60 (dd, 1 H, H-1a), 3.50 (dd, 1 H, H-1b), 2.9–2.65 (m, 2 H, H-6a,6b), 2.04 (b, 1 H, OH), 1.75 (m, 2 H, H-5a,5b), 1.43 (s, 6 H, CMe_2), and 1.4–1.25 (m, 2 H, H-3); $J_{1a,1b}$ 11.4, $J_{1a,2}$ 3.3, $J_{1b,2}$ 6.1 Hz.

Anal. Calc. for $C_{15}H_{20}Cl_2O_3$: C, 56.43; H, 6.32. Found: C, 56.38; H, 6.41.

*Potassium 6-(2,4-dichlorophenyl)-*D-erythro-*2,4-dihydroxyhexane-1-sulfonate* (**29**). — M HCl (2 mL) was added to a solution of **25** (0.25 g) in water (15 mL). After 15 min, the mixture was concentrated. Column chromatography (solvent *E*) of the residue gave amorphous **29** (0.9 g, 40.9%), $[\alpha]_D$ +9.6° (*c* 0.2, MeOH), R_F 0.4 (solvent *L*). N.m.r. data (MeOD): ^{1}H, δ 7.39 (d, 1 H, H-3′, aromatic), 7.30 (d, 1 H, H-6′, aromatic), 7.23 (dd, 1 H, H-5′, aromatic), 4.34 (m, 1 H, H-2), 3.87 (m, 1 H, H-4), 3.1–2.7 (m, 4 H, H-1a,1b,6a,6b), and 1.9–1.6 (m, 4 H, H-3a,3b,5a,5b).

Anal. Calc. for $C_{12}H_{15}Cl_2KO_5S$: C, 37.80; H, 3.97. Found: C, 37.92; H, 3.88.

*1,4-Anhydro-6-(2,4-dichlorophenyl)-*D-erythro-*1,2,4-hexanetriol* (**27**). — Compound **18** (7.2 g) was allowed to decompose in air at room temperature. After 24 h, column chromatography (solvent *D*) of the product gave **27** (3.18 g, 80.1%), R_F 0.25 (solvent *D*). N.m.r. data: ^{1}H, δ 7.36 (s, 1 H, H-3′, aromatic), 7.18 (s, 2 H, H-5′,6′, aromatic), 4.52 (m, 1 H, H-2), 4.15 (m, 1 H, H-4), 4.03 (dd, 1 H, H-1a), 3.72 (dd, 1 H, H-1b), 2.95–2.65 (m, 2 H, H-6a,6b), and 2.10–1.60 (m, 4 H, H-3a,3b,5a,5b); $J_{1a,1b}$ 10.0, $J_{1a,2}$ 5.0, $J_{1b,2}$ 1.0 Hz; ^{13}C, δ 138.1 (C-1′, aromatic), 134.5 (C-4′, aromatic), 132.3 (C-2′, aromatic), 131.2 (C-6′, aromatic), 129.2 (C-3′, aromatic), 127.1 (C-5′, aromatic), 77.3 (C-4), 75.2 (C-1), 72.5 (C-2), 41.6 (C-3), 35.1 (C-5), and 29.8 (C-6).

Anal. Calc. for $C_{12}H_{14}Cl_2O_2$: C, 55.19; H, 5.40. Found: C, 55.26; H, 5.57.

ACKNOWLEDGMENTS

We thank Dr. I. Perczel for measuring some of the n.m.r. spectra, and Dr. A. Máderspach and Dr. A. Jávor for the biological results.

REFERENCES

1 J. Kuszmann, and B. Podányi, *Carbohydr. Res.*, 225 (1992) 247–267.
2 G. E. Stokker, W. E. Hoffmann, A. W. Alberts, E. J. Cragoe, Jr. A. A. Deanna, J. L. Gilfillan, J. W. Huff, F. C. Novello, J. D. Prugh, R. L. Smith, and A. K. Willard, *J. Med. Chem.*, 28 (1985) 347–358.
3 T. Lee, *Tetrahedron Lett.*, 26 (1985) 4995–4996.
4 Y. Guidon, C. Yoakim, M. A. Bernstein, and H. E. Morton, *Tetrahedron Lett.*, 26 (1985) 1185.
5 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, (1975) 1574–1585.
6 H. G. Kuivila, *Synthesis*, (1970) 499–509.
7 D. H. R. Barton and R. Subramanian, *J. Chem. Soc., Perkin Trans. 1*, (1977) 1718–1723.
8 B. Samuelsson and P. J. Garegg, *J. Chem. Soc., Perkin Trans. 1*, (1980) 2866–2869.
9 R. Paul, P. Buisson, and N. Joseph, *Ind. Eng. Chem.*, 44 (1952) 1006–1010.
10 H. Paulsen and V. Sinwell, *Chem. Ber.*, 111 (1978) 879–889.
11 D. H. Muray and J. Prokop, *J. Pharm. Sci.*, 54 (1965) 1468–1473.
12 S. Hanessian, M. M. Ponpipom, and P. Lavallee, *Carbohydr. Res.*, 24 (1972) 45–56.
13 B. Flaschentraeger and G. Wannschaff, *Chem. Ber.*, 67 (1934) 1121–1123.
14 T. C. Myers, P. Seymour, and V. J. Elwood, *J. Am. Chem. Soc.*, 76 (1954) 4172–4173.
15 G. M. Kosolapoff, *J. Am. Chem. Soc.*, 67 (1945) 1180–1182.
16 A. K. Bhattacharya and G. Thyagarayan, *Chem. Rev.*, 81 (1981) 415–430.
17 R. L. Whistler and C. C. Wang, *J. Org. Chem.*, 33 (1968) 4455–4458.
18 T. Morita, Y. Okamoto, and H. Sakurai, *Tetrahedron Lett.*, (1978) 2523–2526.
19 A. R. Katritzky and L. Urogdi, *Synthesis*, (1989), 949–950.
20 M. Černy and J. Pacák, *Chem. Listy*, 49 (1955) 1848–1850.