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SYNTHESIS AND STRUCTURE OF 1,5-DIDEOXY-1,5-DIHALOGENO- AND 1,2:4,5-DIANHYDRO-XYLITOL DERIVATIVES*

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ABSTRACT

Eleven terminally disubstituted dihalogeno and diepoxy derivatives of xylitol have been prepared. Their structures were determined by ^{1}H-n.m.r. spectroscopy and, in one case, by X-ray diffraction.

INTRODUCTION

The cytostatic activity of some terminally disubstituted hexitol derivatives is well known, and 1,6-dibromo-1,6-dideoxygalactitol[1] and 1,2:5,6-dianhydrogalactitol[2] are in clinical use. Their acylated[3,4] and alkylated[5] derivatives have also been tested. We now report on analogues in the xylitol series.

RESULTS AND DISCUSSION

1,5-Dibromo-1,5-dideoxyxylitol (**2**) was prepared from xylitol (**1**) by reaction under pressure with hydrogen bromide. Treatment of **2** with an anion-exchange resin gave 1,2:4,5-dianhydroxylitol (**3**). The reaction of **3** with hydrogen bromide regenerated **2** and, with hydrogen iodide, 1,5-dideoxy-1,5-di-iodoxylitol (**4**) was obtained. Compound **3** was non-crystalline, but was characterised as the 3-acetate (**5**), 3-benzoate (**6**), and 3-(4-phenylbenzoate) (**7**). The structure of **7** was proved by X-ray analysis and that of **3** was supported by ^{1}H-n.m.r. data.

Treatment of **7** with hydrogen bromide gave 1,5-dibromo-1,5-dideoxy-3-(4-phenylbenzoyl)xylitol (**8**). The reaction of **3** with diazomethane in the presence of

*1,5-Dihalogeno- and 1,2:4,5-Dianhydro-xylitol Derivatives, Part I.
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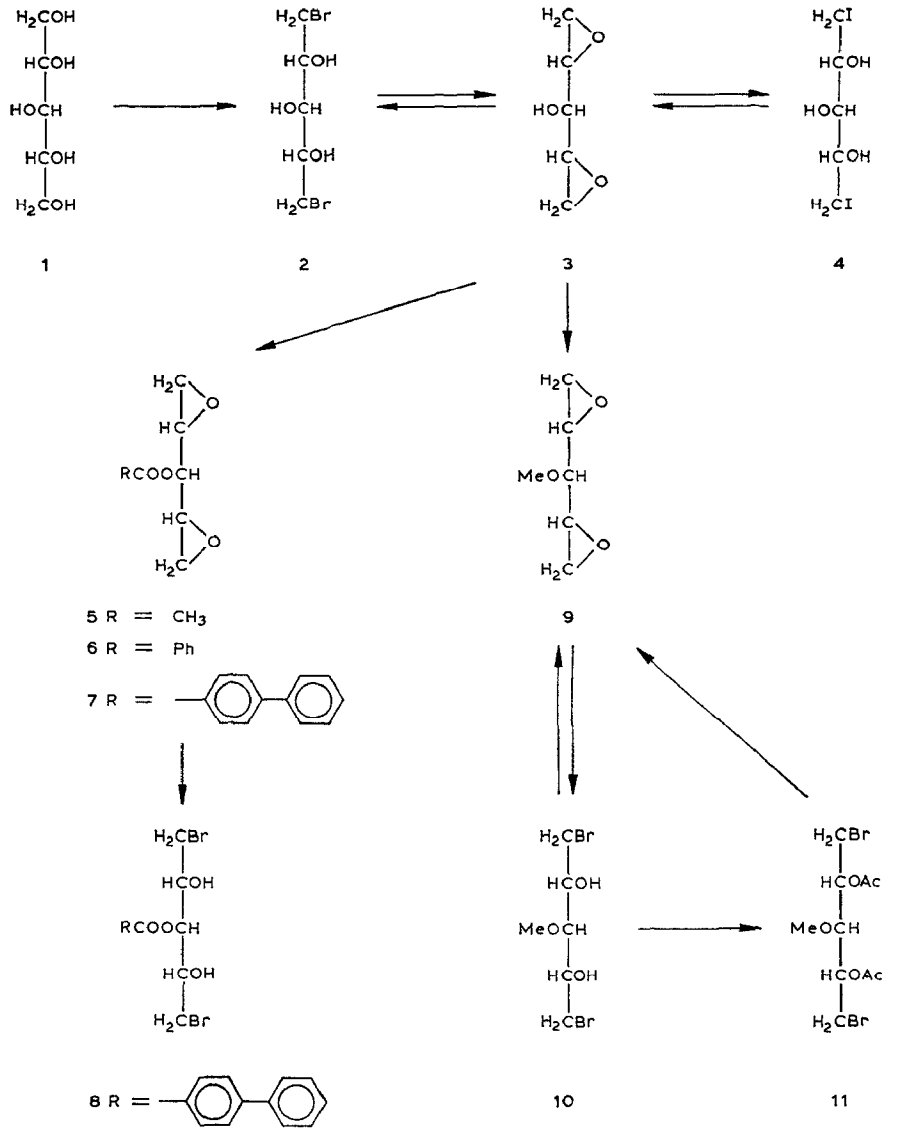

boron trifluoride etherate yielded 1,2:4,5-dianhydro-3-*O*-methylxylitol (**9**) as an oil, the structure of which was proved by ^{1}H-n.m.r. data; treatment with hydrogen bromide then gave the crystalline 1,5-dibromo derivative **10**. The conversion **10**→**9** was effected with an anion-exchange resin. The structure of the 3,5-diacetate (**11**) of **10** was proved by the ^{1}H-n.m.r. data. In the pH range 7.5–8.0, **11** was reconverted into **9**.

The crystal parameters for **7** are noted in Table I, and the conformation of the molecule is depicted in Fig. 1. Bond lengths and angles are given in Table II, and characteristic torsion angles in Table III; C-3, O-3, C-6, C-10, C-15, and C-20,

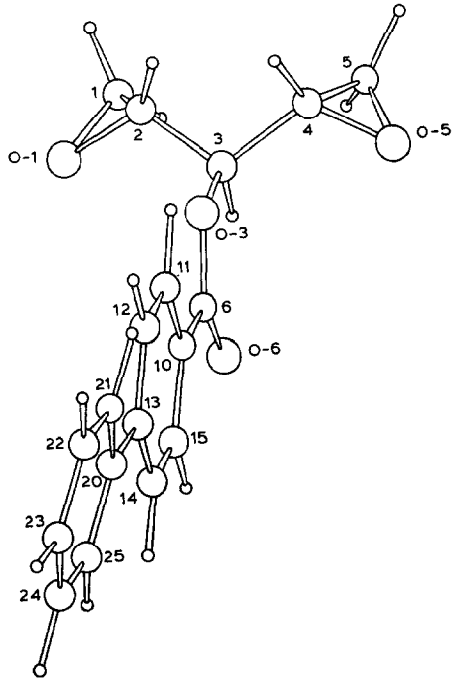

Fig. 1. Atomic numbering and molecular diagram of **7**.

within 0.06 Å, are in one plane (Table IV). This enantiotopic plane establishes the relations between corresponding atoms of the oxirane rings. The relative positions of the three-membered rings to the O-3–C-3 bond are +sc(85°) and −sc(−82°), respectively. The inclination angle between the best planes of the benzoyl group and the phenyl group (C-13, C-20–C-25) is 13°.

The symmetrical arrangement of the xylitol moiety of **7** contrasts with that found for xylitol (**1**) in the crystalline state[6] where an asymmetric, bent conformation is caused by the O-2···O-4 interaction. The distance (3.67 Å) between the terminal

TABLE I

CRYSTAL AND REFINEMENT PARAMETERS FOR COMPOUND **7**

Crystal parameters		*Refinement parameters*
Formula	$C_{18}H_{16}O_4$	Number of reflections 2095
Cell dimensions	$a = 13.709(2)$ Å	Non-zero reflections 1237
	$b = 12.467(3)$	R index
	$c = 9.144(2)$	$R = \|\|F_o\| - \|F_c\|\|/\|F_o\| = 0.050$
	$\beta = 104.06(5)°$	Weighted R index
Space group	$P2_1/c$	$R' = \|F_o^2\| - \|F_c^2\|/\|F_o^4\| = 0.051$
Molecules per unit cell	4	$w = 1.63/\sigma(F) + 0.0004\ \|F^2\|$
Linear absorbtion coefficient (μ)	0.54 cm^{-1}	

TABLE II

BOND LENGTHS AND ANGLES (E.S.D. IN PARENTHESES)

O-1–C-1	1.457(4)	O-6–C-6	1.247(5)	C-11–C-12	1.384(5)	C-15–C-10	1.411(5)
O-1–C-2	1.528(5)	C-1–C-2	1.476(5)	C-11–C-10	1.436(6)	C-21–C-22	1.396(6)
O-3–C-3	1.466(4)	C-2–C-3	1.519(5)	C-12–C-13	1.425(5)	C-21–C-20	1.456(6)
O-3–C-6	1.359(4)	C-3–C-4	1.602(7)	C-13–C-14	1.443(6)	C-22–C-23	1.433(7)
O-5–C-4	1.423(5)	C-4–C-5	1.454(6)	C-13–C-20	1.492(5)	C-23–C-24	1.428(8)
O-5–C-5	1.431(5)	C-6–C-10	1.489(5)	C-14–C-15	1.387(5)	C-24–C-25	1.396(6)
						C-25–C-20	1.443(6)

C-1–O-1–C-2	59.2(4)	O-5–C-4–C-5	59.7(5)	C-13–C-14–C-15	120.5(6)
C-3–O-3–C-6	117.1(5)	C-3–C-4–C-5	117.8(6)	C-14–C-15–C-10	119.4(6)
C-4–O-5–C-5	61.2(5)	O-4–C-5–C-4	59.1(5)	C-6–C-10–C-11	121.7(6)
O-1–C-1–C-2	62.8(4)	O-3–C-6–O-6	125.3(6)	C-6–C-10–C-15	117.6(6)
O-1–C-2–C-1	58.0(4)	O-3–C-6–C-10	111.8(5)	C-11–C-10–C-15	120.7(6)
O-1–C-2–C-3	116.5(5)	O-6–C-6–C-10	122.9(6)	C-22–C-21–C-20	120.9(7)
C-1–C-2–C-3	120.2(6)	C-12–C-11–C-10	119.9(6)	C-21–C-22–C-23	117.7(7)
O-3–C-3–C-2	107.6(5)	C-11–C-12–C-13	120.1(6)	C-22–C-23–C-24	122.6(8)
O-3–C-3–C-4	105.8(5)	C-12–C-13–C-14	119.3(6)	C-23–C-24–C-25	119.6(7)
C-2–C-3–C-4	111.2(5)	C-12–C-13–C-20	119.4(6)	C-24–C-25–C-20	119.5(7)
O-5–C-4–C-3	117.0(6)	C-14–C-13–C-20	121.2(6)	C-13–C-20–C-21	120.3(6)
				C-13–C-20–C-25	120.0(6)
				C-21–C-20–C-25	119.7(6)

TABLE III

SELECTED TORSION ANGLES (E.S.D. IN PARENTHESES)

O-3–C-3–C-2–O-1	−82.2(5)	C-4–C-3–C-2–C-1	95.7(6)
O-4–C-4–C-3–O-3	85.6(6)	C-5–O-4–C-4–C-3	108.0(5)
C-1–C-2–C-3–O-4	−148.9(7)	C-5–C-4–C-3–O-3	153.7(7)
C-2–C-3–C-4–O-4	−158.0(6)	C-5–C-4–C-3–C-2	−89.8(7)
C-3–C-2–O-1–C-1	−110.5(6)	C-6–O-3–C-3–C-2	0.1(6)
C-3–C-2–C-1–O-1	104.3(6)	C-6–O-3–C-3–C-4	121.0(6)
C-3–C-4–C-5–O-4	−106.6(7)	C-21–C-20–C-13–C-12	−11.8(6)
C-4–C-3–C-2–O-1	162.4(6)	C-25–C-20–C-13–C-14	−11.6(6)

carbon atoms in **7** is less than that (4.47 Å) in **1**. In an ideally extended pentitol, this distance would be 5.1 Å. Comparing these distances with that (5.9–6.3 Å) observed for 1,2:5,6-dianhydrogalactitol[7], it may be concluded that the respective modes of cross-linking of cellular DNA should be different.

The antitumour activity of the xylitol derivatives will be described elsewhere.

EXPERIMENTAL

General. — Melting points are uncorrected. T.l.c. was performed on Kieselgel G with *A*, benzene–methanol–1-pentanol–water–2-propanol (52:62:30:23:20); *B*,

TABLE IV

DEVIATIONS (Å) FROM THE LEAST-SQUARE PLANE DEFINED BY THE ATOMS C-3, O-3, C-6, C-10–C-15, AND C-20

C-3	0.056(4)	C-12	−0.028(4)
O-3	0.026(3)	C-13	0.004(4)
C-6	−0.044(4)	C-14	0.012(5)
C-10	−0.041(4)	C-15	0.003(4)
C-11	−0.042(4)	C-20	0.054(4)
Other atoms			
C-1	2.014(4)	C-21	−0.187(5)
C-2	1.350(4)	C-22	−0.090(5)
C-4	−1.217(5)	C-23	0.241(6)
C-5	−1.790(5)	C-24	0.451(5)
O-1	2.601(3)	C-25	0.363(5)
O-4	−2.456(4)		

benzene–ethyl acetate (95:5); *C*, benzene–ethyl acetate (1:1); and *D*, ethyl acetate; and detection with nitrobenzylpyridine + triethylamine[8] at 100°. Column chromatography was performed on Kieselgel 60 (0.063–0.125 mm).

All evaporations were performed in a rotary evaporator under diminished pressure at ⩾40° (bath).

^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a Bruker WP-80 instrument; chemical shifts are reported on the δ scale.

1,5-Dibromo-1,5-dideoxyxylitol (**2**). — A solution of xylitol (**1**, 600 g) and aqueous hydrogen bromide (1800 mL; saturated at −10°) was stored in a sealed tube for 6 h at 70–75°, and then cooled and neutralised with $NaHCO_3$. The crystalline product was collected, dried, and extracted with hot ethyl acetate. The extract was concentrated, and the residue was crystallised from dichloroethane and recrystallised from ethyl acetate, to give **2** (356 g, 32%), m.p. 104–106°, R_F 0.9 (solvent *A*).

Anal. Calc. for $C_5H_{10}Br_2O_3$: C, 21.6; H, 3.6; Br, 57.5. Found: C, 21.58; H, 3.8; Br, 57.41.

1,2:4,5-Dianhydroxylitol (**3**). — A mixture of **2** (60 g), VARION AD (HO^-) resin (1400 mL), and distilled water (1400 mL) was stirred for 10 min, filtered, and concentrated to 500 mL. The solution was added with vigorous stirring to a suspension of ethyl acetate (1200 mL) and sodium carbonate (1200 g), and then filtered, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with solvent *D*. The fractions containing **3** were combined, and concentrated, and the residue was distilled, to give **3** (21 g, 32%), b.p. 60–62°/0.3 mmHg, R_F 0.84 (solvent *A*). ^{1}H-N.m.r. data ($CDCl_3$): δ 3.74 (dt, 1 H, *H*CHOH), 3.15 (q, 2 H, C*H*OCH), 2.78 (d, 4 H, CH_2), and 2.15 (d, 1 H, O*H*); $J_{CH,OH}$ 8, J_{CH,CH_2} 3.2, $J_{CHOH,CHO}$ 3.0 Hz.

An aqueous solution of **3** (2 g) in water (2 mL) was added dropwise with vigorous stirring to conc. HBr (10 mL). The mixture was stirred for 30 min, $NaHCO_3$

was added to give pH 6, and the crystals were collected, dried, and recrystallised from ethyl acetate, to give **2** (3.75 g, 79.4%), m.p. 104–106°.

1,5-Dideoxy-1,5-di-iodoxylitol (**4**). — An aqueous solution (2 mL) of **3** (2 g) was added dropwise with vigorous stirring to conc. aqueous HI (15 mL) at −10°. After stirring for 4–5 h, the crystals were collected and washed. Compound **4** (3.1 g, 49%) had m.p. 115–118°, R_F 0.94 (solvent *A*).

Anal. Calc. for $C_5H_{10}I_2O_3$: C, 16.08; H, 2.68; I, 68.0. Found: C, 16.11; H, 2.74; I, 68.72.

An aqueous solution (53 mL) of **4** (3 g) was treated with VARION AD (HO^-) resin (53 mL) for 10 min. The mixture was then worked-up, as described above, to give **3** (0.32 g, 34.8%).

3-O-Acetyl-1,2:4,5-dianhydroxylitol (**5**). — To a solution of triethylamine (12.8 mL) and **3** (2.3 g) in benzene (50 mL) at 45° was added dropwise, during 30 min, a solution of acetyl chloride (1.42 mL) in benzene (5 mL). After stirring for 10 min, the mixture was filtered and concentrated, and the syrupy residue was eluted from a column of silica gel with solvent *B*. The fractions containing the component with R_F 0.25 were combined and concentrated, and the residue was recrystallised from ethyl acetate–hexane, to give **5** (1.76 g, 56.4%), m.p. 36–38°, R_F 0.25 (solvent *B*).

Anal. Calc. for $C_7H_{10}O_4$: C, 53.2; H, 6.34. Found: C, 51.6; H, 6.26.

1,2:4,5-Dianhydro-3-O-benzoylxylitol (**6**). — A solution of **3** (6 g) and triethylamine (8.4 mL) in benzene (120 mL) was treated with benzoyl chloride (6 mL) as described above. Column chromatography of the product and recrystallisation from hexane–ethyl acetate gave **6** (5.6 g, 49%), m.p. 39–40°, R_F 0.28 (solvent *B*).

Anal. Calc. for $C_{12}H_{12}O_4$: C, 65.5; H, 5.45. Found: C, 65.57; H, 5.41.

1,2:4,5-Dianhydro-3-O-(4-phenylbenzoyl)xylitol (**7**). — A solution of **3** (12 g) and triethylamine (14 mL) in benzene (250 mL) was treated with 4-phenylbenzoyl chloride (24 g) as described above. Column chromatography of the product and recrystallisation from ethanol gave **7** (16.7 g, 54.4%), m.p. 86–88°, R_F 0.35 (solvent *D*).

Anal. Calc. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.42; H, 5.42.

X-Ray analysis of **7**. — Suitable crystals of **7** were grown from ethanol. Intensity measurements were made with a Philips PW-1100, four-circle diffractometer with Mo-Kα radiation (λ = 0.7107 Å); 2095 independent reflections were collected using an ω–2ϑ scan.

All non-hydrogen atoms could be located from an E-map obtained by SHELX, using the automatic sign-determination routine (E_{min} = 1.4, 230 signs, 1989 triples, 121 quartets) with the best MABS figure of merit. Hydrogen atom positions were generated and were kept riding throughout the refinement; 1237 reflections [$I \geq 5\sigma(I)$] were included in the refinement; the weighting scheme was: $W = 1.626/[\sigma(F) + 0.0004\ F^2]$.

The final reliability values of the full matrix refinement are given in Table I. The co-ordinates for the non-hydrogen atoms are given in Table V, and those for the hydrogen atoms in Table VI.

1,5-Dibromo-1,5-dideoxy-3-O-(4-phenylbenzoyl)xylitol (**8**). — To stirred conc.

TABLE V

FRACTIONAL ATOMIC CO-ORDINATES($\times 10^4$) OF THE NON-HYDROGEN ATOMS FOR **7** (E.S.D. IN PARENTHESES)

O-1	1719(2)	5096(2)	−7132(3)	C-12	4236(3)	3177(3)	−685(4)
O-3	1839(2)	3597(2)	−4367(3)	C-13	4338(3)	3802(3)	601(4)
O-4	−243(2)	2389(3)	−5249(4)	C-14	3585(3)	4549(4)	611(4)
O-6	1109(2)	4788(2)	−3146(3)	C-15	2774(3)	4667(3)	−623(5)
C-1	920(3)	4618(3)	−8256(4)	C-10	2679(3)	4036(3)	−1882(4)
C-2	1489(3)	3993(3)	−7012(5)	C-21	5888(3)	2826(4)	1988(5)
C-3	1022(3)	3693(3)	−5732(4)	C-22	6748(3)	2727(4)	3164(6)
C-4	514(3)	2617(4)	−6021(4)	C-23	6955(3)	3493(5)	4284(5)
C-5	−536(3)	2563(4)	−6840(5)	C-24	6312(4)	4332(4)	4246(5)
C-6	1799(3)	4192(3)	−3182(4)	C-25	5456(3)	4433(4)	3063(5)
C-11	3425(3)	3293(3)	−1913(4)	C-20	5231(3)	3685(3)	1899(4)

TABLE VI

FRACTIONAL ATOMIC CO-ORDINATES[a] OF THE HYDROGEN ATOMS FOR **7**

	x/a	y/b	z/c
H-11	147(3)	4825(3)	−8307(4)
H-12	1009(3)	4483(3)	−9383(4)
H-21	1894(3)	3243(3)	−6937(5)
H-31	476(3)	4294(3)	−5624(4)
H-41	1196(3)	2234(4)	−6150(4)
H-51	−801(3)	1901(4)	−7594(5)
H-52	−934(3)	3284(4)	−7288(5)
H-110	3363(3)	2796(3)	−2899(4)
H-120	4810(3)	2590(3)	−717(4)
H-140	3647(3)	5046(4)	1597(4)
H-150	2200(3)	5254(3)	−592(5)
H-210	5728(3)	2230(4)	1106(5)
H-220	7251(3)	2056(4)	3197(6)
H-230	7618(3)	3419(5)	5199(5)
H-240	6471(4)	4929(4)	5129(5)
H-250	4953(3)	5104(4)	3030(5)

[a]Values are $\times 10^4$. Estimated standard deviations (in parentheses) refer to the least-significant digit.

HBr (10 mL) was added dropwise at −10° a solution of **7** (2 g) in acetone (2 mL). The mixture was stirred for 5 h at 0° and then diluted with water, and the crystals were collected and recrystallised from chloroform, to give **8** (1.5 g, 48.8%), m.p. 125–126°, R_F 0.32 (solvent *B*).

Anal. Calc. for $C_{18}H_{18}Br_2O_4$: C, 47.3; H, 3.94; Br, 34.9. Found: C, 47.02; H, 4.13; Br, 35.05.

1,2:4,5-Dianhydro-3-O-methylxylitol (**9**). — A stirred solution of **3** (2 g) in ether (150 mL) was saturated with diazomethane at room temperature. Whilst the

input of diazomethane was maintained, a few drops of BF_3-etherate solution were added. This procedure was repeated several times. When the reaction was complete, the mixture was washed with saturated, aqueous sodium hydrogencarbonate, dried (Na_2CO_3), and concentrated. Distillation of the oily residue gave **9** (1.5 g, 67%), b.p. 43°/0.2 mmHg, R_F 0.5 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$) δ 3.52 (s, 3 H, OMe), and 2.50–3.25 (m, 7 H, CH, CH_2).

Anal. Calc. for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.02; H, 7.76.

1,5-Dibromo-1,5-dideoxy-3-O-methylxylitol (**10**). — A solution of **9** (1 g) in acetone (2 mL) was added dropwise to conc. HBr at −5° with vigorous stirring. The mixture was kept at 0° for 1 h, $NaHCO_3$ was added portion-wise to give pH 5–6, and the precipitate was collected, washed with cold water, and dried. The product was extracted with dichloroethane (10 mL), the extract was filtered, and hexane was added to opalescence, to give **10** (1.2 g, 53.4%), m.p. 78–80°, R_F 0.58 (solvent *C*).

Anal. Calc. for $C_6H_{12}Br_2O_3$: C, 24.65; H, 4.1; Br, 54.79. Found: C, 25.09; H, 4.25; Br, 54.9.

An aqueous solution (65 mL) of **10** (3 g) was stirred with VARION AD (HO^-) resin (65 mL) for 20 min. The mixture was then processed as described above to give, after column chromatography, **9** (0.47 g, 35%).

2,5-Di-O-acetyl-1,5-dibromo-1,5-dideoxy-3-O-methylxylitol (**11**). — A solution of **10** (2.7 g) and triethylamine (2.48 mL) in benzene (54 mL) was treated with acetyl chloride (1.28 mL) as described above. Column chromatography of the product and recrystallisation from hexane gave **11** (2.5 g, 72%), m.p. 63–64°, R_F 0.3 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.18 (q, 2 H, *H*COAc), 4.00 (t, 1 H, *H*COMe), 3.65 (s, 3 H, OMe), 3.25–3.75 (m, 4 H, CH_2Br), and 2.18 (s, 6 H, AcO).

Anal. Calc. for $C_{10}H_{16}Br_2O_5$: C, 31.91; H, 4.25; Br, 42.55. Found: C, 31.69; H, 4.15; Br, 42.30.

An aqueous solution (85 mL) of **11** (5 g) was stirred with VARION AD (HO^-) resin (85 mL) for 30 min. The mixture was processed as described above to give, after column chromatography, **3** (0.45 g, 30%).

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