New Stereoselective Approach to Hydroxy-Substituted Tetrahydrofurans. Total Synthesis of (±)-Citreoviral

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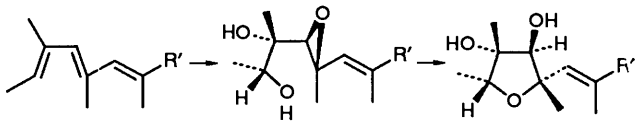
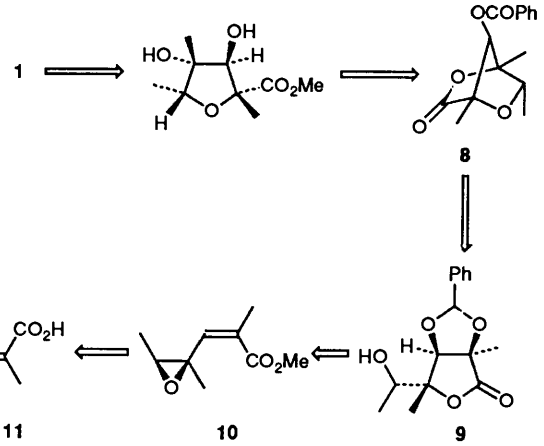
A concise total synthesis of (±)-citreoviral which illustrates a new stereoselective approach to hydroxy-substituted tetrahydrofurans is described. Key features in the synthesis are: (i) elaboration of the *Z*-unsaturated epoxy ester **10**, (ii) acid-catalysed cyclisation of ester **10** to the 4-hydroxyethyl-substituted but-2-enolide **14**, (iii) stereoselective vicinal hydroxylation of the butenolide **14** to the diol **15**, (iv) cyclic ether formation from diol **15** to the bicyclic lactone **8** *via* the benzylidene acetal **9**, (v) transesterification of bicycle **8** to the tetrahydrofuran **21** containing three of the four centres in citreoviral in the correct relative configuration. Inversion of the secondary 3-OH group in compound **21**, and elaboration of the C-2 side-chain, then completed the synthesis of (±)-citreoviral.

Citreoviral **1** together with citreoviridin **2** and the citreoviridinols **3** and **4** are complex polyene hydroxy-substituted tetrahydrofuran metabolites produced by *Penicillium citreoviride*.[1] Interest in these compounds stems from their unusual biological profile,[2] and also from the interesting biogenetic relationships that exist between them, as well as between citreomontanin **5**,[3] asteltoxin **6**[4] and the aurovertins, *viz.* **7**.[5] The synthesis of members of these families of metabolites has been the subject of considerable recent research.[6] In the previous paper we described a synthesis of (±)-citreoviral **1** which used a strategy based on a biogenetic model (Scheme 1).[7]



Scheme 1

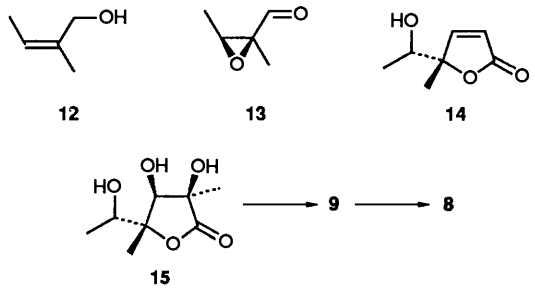
In this paper we describe a new and conceptually distinct approach to (±)-citreoviral **1**, which uses a strategy whereby three of the four stereocentres in the natural product are 'locked' in the key bicyclic lactone intermediate **8**, produced from (*Z*)-2-methylbut-2-enoic acid (angelic acid) **11** *via* the epoxy ester **10** and the substituted butyrolactone **9** (Scheme 2).[8]



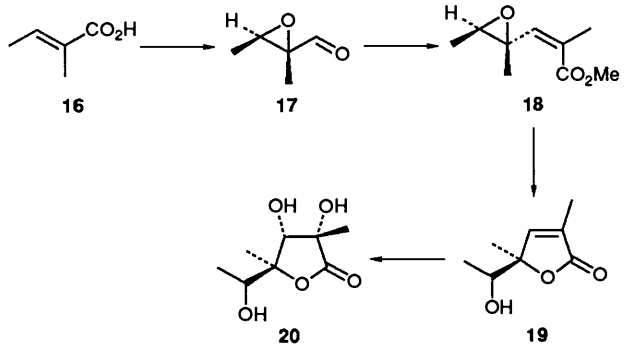
Scheme 2

Reduction of angelic acid **11** with lithium aluminium hydride, followed by epoxidation of the resulting primary alcohol **12** and oxidation with Collins' reagent first led to the epoxy aldehyde **13**. A Wadsworth–Emmons reaction between aldehyde **13** and the anion derived from triethyl 2-phosphonopropionate [methyl 2-(dimethoxyphosphoryl)propionate] next led to the *Z*-enoate **10** containing less than 10% of the corresponding *E*-isomer. The *Z*-stereochemistry assigned to product **10** followed from inspection and comparison of proton-shift data in the ^{1}H NMR spectrum, with those of model compounds.[9] Treatment of compound **10** with hot perchloric acid in 1,4-dioxane[10] then provided the butenolide **14** as an oil in 83% yield.

Reaction between the butenolide **14** and *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetraoxide[11]



resulted in stereoselective vicinal hydroxylation from the least hindered face of compound **14**, leading to the diol **15** in 60% yield. Fortunately, in model work starting with (*E*)-2-methylbut-2-enoic acid (tiglic acid) **16** instead of the less easily available angelic acid, we had carried out the aforementioned series of reactions (Scheme 3), thereby producing the isomer **19** of the

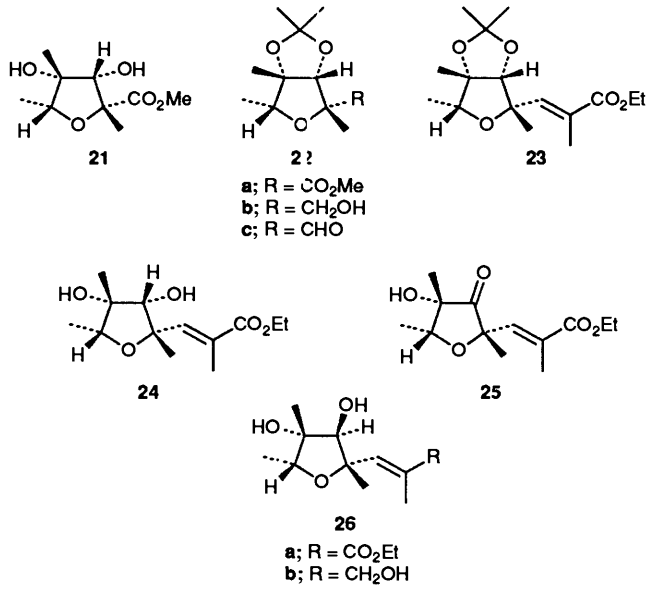


Scheme 3

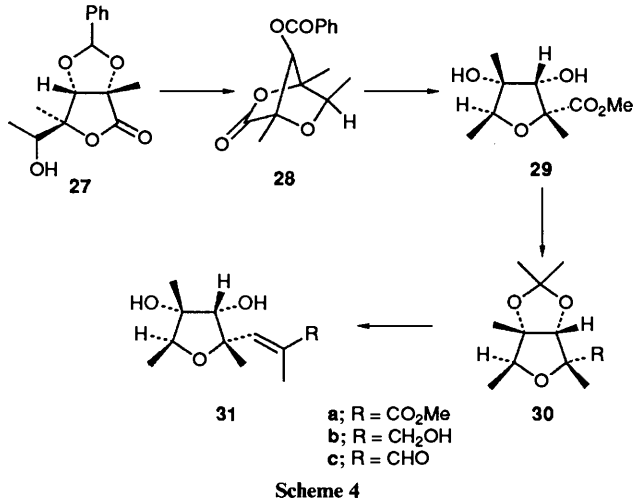
butenolide **14**. When the isomer **19** was treated with *N*-methylmorpholine *N*-oxide–osmium tetraoxide, the corresponding isomeric vicinal diol **20** was obtained as a white, crystalline solid, m.p. 130–140 °C. The structure and stereochemistry for *cis*-diol **20** followed conclusively from X-ray crystallographic analysis, demonstrating that the osmylation of the butenolide **19**, and likewise that of the isomer **14**, was controlled by the relative steric bulk of the substituents at C-4 leading to that diastereoisomer where the vicinal hydroxy groups are *anti* to the more bulky hydroxyethane residue at C-4.[12] After conversion of the triol **15** into the corresponding benzylidene acetal **9**, treatment with *N*-bromosuccinimide (NBS) in dry chloroform[13] resulted in stereoselective cyclisation to the key bicyclic lactone ether intermediate **8**, containing three of the four stereocentres of citreoviral **1** in the correct relative configuration.

Treatment of the bicyclic intermediate **8** with triethylamine in aq. methanol resulted in smooth hydrolysis and ester exchange to afford the substituted tetrahydrofuran **21**. After conversion into the corresponding acetonide **22a**, reduction with lithium aluminium hydride (to **22b**) followed by oxidation with pyridinium chlorochromate (PCC) next led to the aldehyde **22c**. A Wittig condensation between the aldehyde **22c** and ethoxycarbonylethylidene(triphenyl)phosphorane then gave an excellent yield of the *E*-unsaturated ester **23**, which could be converted into the crystalline diol **24** by treatment with Amberlyst acidic resin.

The secondary hydroxy-substituted centre in compound **24** was inverted to the correct stereochemistry, *i.e.* structure **26a**, found in natural citreoviral, following Moffatt oxidation[14] to the ketone **25** and reduction with sodium borohydride at −60 °C. The synthesis of (±)-citreoviral **1** from ester **26a** was then completed as described in the accompanying paper[7] by straightforward reduction to the corresponding primary alcohol **26b** and oxidation of the latter in the presence of



manganese dioxide. The (±)-citreoviral **1** thus obtained showed identical spectroscopic data with those reported for naturally derived material.



Scheme 4

As a corollary to this work we also converted the triol **20** with the 'incorrect' stereochemistry derived from tiglic acid, *via* a similar series of conversions (Scheme 4), into the isocitreoviral **31c**.

Experimental

For general experimental details, see ref. 15.

(*Z*)-2-*Methylbut-2-enoic Acid* (*Angelic Acid*) **11**.—A solution of (*Z*)-2-bromobut-2-ene (80 g, 0.6 mol) in dry diethyl ether (160 cm^3) was added dropwise during 0.5 h under nitrogen to an ice-cooled, stirred suspension of lithium strips (8.5 g, 1.23 mol) in dry diethyl ether (246 cm^3), and the mixture was then stirred at 0 °C for 2 h. The mixture was poured onto a slurry of solid CO_2 in dry diethyl ether (320 cm^3), and was then allowed to warm to room temperature. The mixture was acidified with 2 mol dm^{-3} hydrochloric acid, and the diethyl ether layer was then extracted with saturated aq. sodium hydrogencarbonate. The resulting aq. alkaline extract was acidified, and then extracted with diethyl ether. The combined diethyl ether layers were dried ($MgSO_4$), and then evaporated under reduced pressure to leave a pale yellow, crystalline residue. Recrystallisation from light petroleum (b.p. range 40–60 °C) gave (*Z*)-2-methylbut-2-enoic

acid (42 g, 70%) as crystals, m.p. 43–45 °C (lit.,[16] 45–46 °C); δ_H 1.91 (m, 2-Me), 2.04 (br d, *J* 7, *Me*CH=) and 6.23 (br q, *J* 7, MeC*H*=).

(Z)-2-*Methylbut*-2-*en*-1-*ol* **12**.—A solution of compound **11** (42 g, 0.42 mol) in dry diethyl ether (200 cm^3) was added dropwise during 0.3 h, under anhydrous conditions, to an ice-cooled, stirred suspension of lithium aluminium hydride (16.5 g, 0.42 mol) in dry diethyl ether (320 cm^3), and the mixture was then heated under reflux for 5 h. Water (16.5 cm^3) was added to the cooled mixture, followed by 15% aq. sodium hydroxide (16.5 cm^3) and then more water (50 cm^3). Evaporation of the dried ($MgSO_4$) solution under reduced pressure left a residue, which was purified by distillation to give the allylic alcohol **12** (20 g, 55%) as a liquid, b.p. 52–54 °C at 12 mmHg (lit.,[17] b.p. 136–136.5 °C); ν_{max}(liq. film)/cm^{-1} 3320; δ_H 1.65 (br d, *J* 7, *Me*CH=), 1.81 (m, 2-Me), 2.21 (br, CH_2OH), 4.18 (CH_2OH) and 5.42 (br q, *J* 7, MeC*H*=) (Found: M^+, 86.0741. Calc. for $C_5H_{10}O$: M, 86.0732).

(2RS,3RS)-2,3-*Epoxy*-2-*methylbutanal* **13**.—A solution of *m*-chloroperbenzoic acid (MCPBA) (90%; 45 g, 0.23 mol) in dichloromethane (340 cm^3) was added during 10 min to a stirred, ice-cooled solution of the allylic alcohol **12** (20 g, 0.23 mol) in dichloromethane (340 cm^3), and the mixture was then stirred at room temperature for 2 h. Calcium hydroxide (2 g) and sodium sulphate (3 g) were added, and the mixture was then filtered. The filtrate was evaporated under reduced pressure and the residue was then purified by distillation to give 2*RS*,3*SR*-epoxy-2-methylbutan-1-ol (14 g, 60%) as a liquid, b.p. 65–67 °C at 10 mmHg; ν_{max}(liq. film)/cm^{-1} 3400 and 1040; δ_H 1.28 (d, *J* 6, *Me*CH), 1.33 (MeCO), 2.94 (q, *J* 6, MeC*H*), 3.63 (br, CH_2OH) and 3.84 (br, OH) [Found: *m*/*z* 86.0724. $C_5H_{20}O_2$ requires (M − O), 86.0732].

Chromium trioxide (91 g, 0.9 mol) was added to a solution of dry pyridine (133 g, 1.11 mol) in dichloromethane (1850 cm^3), and the mixture was then stirred at room temperature for 0.5 h. A solution of the alcohol (from above) (14 g, 0.14 mol) in dichloromethane (130 cm^3) was added to the resulting burgundy complex, and the mixture was then stirred at room temperature for 2 h. The solvent was decanted off, and the tarry residue was then triturated with diethyl ether. The combined organic solutions were filtered through a pad of Florisil, and the filtrate was then evaporated under reduced pressure to 500 cm^3. The solution was washed with saturated aq. copper(II) sulphate (to remove pyridine), then dried (Na_2SO_4), and evaporated under reduced pressure to give the aldehyde **13** (7.6 g, 54%) as a pale yellow liquid; ν_{max}(liq. film)/cm^{-1} 1720; δ_H 1.44 (Me), 1.50 (d, *J* 6, *Me*CH), 3.23 (q, *J* 6, MeC*H*) and 9.50 (CHO); which was used without further purification.

(2Z,4RS,5SR)-*Methyl* 4,5-*Epoxy*-2,4-*dimethylhex*-2-*enoate* **10**.—A solution of trimethyl 2-phosphonopropionate (16.6 g, 84 mmol) in dry tetrahydrofuran (THF) (110 cm^3) was added during 0.25 h to a stirred, ice-cooled suspension of sodium hydride (2.1 g, 84 mmol) in dry THF (270 cm^3), and the mixture was then stirred at 0 °C for 0.5 h under nitrogen. The resulting clear solution was cooled to −70 °C, when a solution of the aldehyde **13** (7.6 g, 76 mmol) in dry THF (70 cm^3) was added dropwise during 0.5 h. The mixture was stirred at −70 °C for 2 h, and was then allowed to warm to room temperature. The solvent was removed by evaporation under reduced pressure and the residue was then taken up in diethyl ether–water. The separated aq. layer was extracted with diethyl ether, and the combined organic layers were then dried ($MgSO_4$), and evaporated under reduced pressure to leave a pale yellow oil. The residue was purified by distillation to give the *Z-unsaturated ester* **10** (10.1 g, 78%) as a liquid, b.p. 86–88 °C at 14 mmHg; ν_{max}(liq. film)/cm^{-1} 1720 and 1645; δ_H 1.12 (d, *J* 6, *Me*CH), 1.44 (Me), 1.94 (d, *J* 1, *Me*C=CH), 3.02 (q, *J* 6, MeC*H*), 3.73 (MeO) and 5.97 (m, MeC=C*H*); δ_C 15.5 (Me), 19.9 (Me), 22.5 (Me), 51.5 (Me), 61.1, 62.2 (CH), 129.9, 138.3 (CH) and 167.4 [Found: *m*/*z*, 126.0685. $C_9H_{14}O_3$ requires (M − CH_3CHO), 126.0681].

5β-[(1RS)-1-*Hydroxyethyl*]-3,5α-*dimethylfuran*-2-(5H)-*one* **14**.—A solution of the epoxy ester **10** (10 g, 59 mmol), 60% perchloric acid (10 drops), and water (0.5 cm^3) in 1,4-dioxane (280 cm^3) was heated under reflux for 0.5 h. The cooled mixture was neutralised with saturated aq. sodium hydrogen carbonate, then evaporated under reduced pressure. The residue was dissolved in chloroform, dried ($MgSO_4$), evaporated under reduced pressure, and then purified by distillation to give the *butenolide* **14** (7.6 g, 83%) as an oil, b.p. 105–106 °C at 0.2 mmHg; ν_{max}($CHCl_3$)/cm^{-1} 3370, 1740 and 1660; δ_H 1.20 (d, *J* 6, *Me*CH), 1.44 (Me), 1.92 (d, *J* 2, *Me*C=CH), 2.93 (br, OH), 3.84 (q, *J* 6, MeC*H*) and 7.12 (m, MeC=C*H*); δ_C 10.6 (Me), 17.7 (Me), 19.3 (Me), 71.5 (CH), 89.2, 130.1, 151.5 (CH) and 173.9 [Found: C, 61.0; H, 8.0%; *m*/*z*, 157.0864. $C_8H_{12}O_3$ requires C, 61.5; H, 7.8%; (M + H), 157.0864].

3α,4α-*Dihydroxy*-5β-[(1RS)-1-*hydroxyethyl*]-3β,5α-*dimethyldihydrofuran*-2(5H)-*one* **15**.—A solution of the butenolide **14** (2.68 g, 16 mmol), *N*-methylmorpholine *N*-oxide (4.2 g, 36 mmol), and osmium tetraoxide (100 mg) in a mixture of acetone (140 cm^3), water (110 cm^3), and t-butyl alcohol (10 cm^3) (these volumes chosen to fill the entire round-bottomed flask, thus avoiding loss of osmium tetraoxide from the solution by sublimation) was stirred at room temperature for 15 days. The acetone was removed by evaporation under reduced pressure, and the aq. residue was then extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure, and then purified by chromatography on silica G with diethyl ether as eluent to give the cis-*diol* **15** (1.72 g, 57%) as a gum, ν_{max}($CHCl_3$)/cm^{-1} 3290 and 1760; δ_H(CD_3OD) 1.23 (d, *J* 6.5, *Me*CH), 1.36 (Me), 1.39 (Me), 3.68 (q, *J* 6.5, MeC*H*) and 4.01 (C*H*OH); δ_C(CD_3OD) 15.8 (Me), 17.5 (Me), 22.6 (Me), 72.1 (CH), 73.6, 75.2 (CH), 90.8 and 178.2 (Found: M^+, 190.0824. $C_8H_{14}O_5$ requires M, 190.0841).

(2RS,3SR)-2,3-*Epoxy*-2-*methylbutanal* **17**.—MCPBA (90%; 11 g) in dry dichloromethane (100 cm^3) was added to an ice-cooled solution of (*E*)-2-methylbut-2-en-1-ol (5 g) in dry dichloromethane (100 cm^3). The mixture was allowed to warm to room temperature, and was then stirred at 25 °C for 2 h. The precipitated *m*-chlorobenzoic acid was removed by filtration and the filtrate was then dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Distillation of the oily residue gave 2,3-epoxy-2-methylbutan-1-ol (3.5 g, 60%) as an oil, b.p. 68–70 °C at 14 mmHg; ν_{max}(liq. film)/cm^{-1} 3400, 2950 and 1560; δ_H 1.20–1.40 (m, 2 × Me), 2.40 (OH), 3.20 (q, *J* 6, OC*H*Me) and 3.68 (br, CH_2OH).

Chromium trioxide (71 g) was added to a solution of dry pyridine in dry dichloromethane (1500 cm^3) and the mixture was then stirred at room temperature for 0.5 h. A solution of 2,3-epoxy-2-methylbutan-1-ol (11 g) in dry dichloromethane (100 cm^3) was added and the mixture was then stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the solid residue was then washed with diethyl ether. The ethereal extract was filtered through a Florosil column, washed with conc. aq. copper(II) sulphate (until all the pyridine had been removed), and was then dried (Na_2SO_4) and concentrated to give the epoxy aldehyde **17** (5.2 g, 48%) as an oil; ν_{max}(liq. film)/cm^{-1} 3000, 2850 and 1740; δ_H 1.40–1.50 (m, 2 × Me), 3.32 (q, *J* 6, OC*H*Me) and 8.96 (CHO), which was used without further purification.

Table 1 Fractional atomic co-ordinates for compound **20** with standard deviations in parentheses

Atom	*x*	*y*	*z*
O(1)	0.0265(2)	0.1395(2)	0.1920(1)
C(2)	0.1764(3)	0.1287(2)	0.1794(2)
C(3)	0.3043(3)	0.1872(2)	0.2930(2)
C(4)	0.1986(3)	0.2803(2)	0.3418(2)
C(5)	0.0270(3)	0.2190(2)	0.3017(2)
O(6)	0.1993(3)	0.0750(2)	0.0907(2)
O(7)	0.3555(2)	0.0826(2)	0.3806(2)
C(8)	0.4461(4)	0.2524(4)	0.2631(4)
O(9)	0.2577(2)	0.3004(2)	0.4721(1)
C(10)	−0.0058(4)	0.1271(3)	0.3972(3)
C(11)	−0.1098(3)	0.3210(2)	0.2523(2)
O(12)	−0.0819(2)	0.3977(2)	0.1549(2)
C(13)	−0.1239(4)	0.4145(3)	0.3528(3)

(2Z,4RS,5RS)-*Methyl Epoxy*-2,4-*dimethylhex*-2-*enoate* **18**.—A solution of trimethyl 2-phosphonopropionate (13.5 g, 68 mmol) in dry THF (135 cm^3) was added during 0.25 h, to a stirred, ice-cooled suspension of sodium hydride (1.3 g, 55 mmol) in dry THF (275 cm^3), and the mixture was then stirred at 0 °C for 0.5 h under nitrogen. The resulting clear solution was cooled to −70 °C, when a solution of the aldehyde **17** (5.5 g, 55 mmol) in dry THF (55 cm^3) was added dropwise during 0.5 h. The mixture was stirred at −70 °C for 2 h, and was then allowed to warm to room temperature. The solvent was removed by evaporation under reduced pressure, and the residue was then taken up in diethyl ether–water. The separated aq. layer was extracted with diethyl ether, and the combined organic layers were then dried ($MgSO_4$), and evaporated under reduced pressure to leave a pale yellow oil. The residue was purified by distillation to give the *Z-unsaturated ester* **18** (8 g, 86%) as a liquid, b.p. 104 °C at 28 mmHg; ν_{max}(liq. film)/cm^{-1} 1710 and 1630; δ_H 1.36 (d, *J* 6, *MeCH*), 1.40 (Me), 1.92 (d, *J* 2, *MeC*=CH), 3.00 (q, *J* 6, MeC*H*), 3.80 (MeO) and 6.18 (m, MeC=C*H*) [Found: *m/z*, 126. $C_9H_{14}O_3$ requires (M − CH_3CHO), 126].

5α-[(1R)-1-*Hydroxyethyl*]-3,5β-*dimethylfuran*-2(5H)-*one* **19**.—A solution of the epoxy ester **18** (8 g, 47 mmol), 60% perchloric acid (7 drops), and water (0.5 cm^3) in acetone (120 cm^3) was heated under reflux for 22 h. The cooled mixture was neutralised with saturated aq. sodium hydrogencarbonate, and was then evaporated under reduced pressure. The residue was dissolved in chloroform, dried ($MgSO_4$), evaporated under reduced pressure, and then purified by distillation to give the *butenolide* **19** (5.1 g, 70%) as an oil, b.p. 110–115 °C at 0.2 mmHg; ν_{max}(liq. film)/cm^{-1} 3450, 1750 and 1660; δ_H(CD_3OD) 1.18 (d, *J* 6.5, *MeCH*), 1.41 (Me), 1.87 (d, *J* 2, *MeC*=CH), 3.79 (q, *J* 6.5, MeC*H*) and 7.28 (m, MeC=C*H*) [Found: C, 61.0; H, 8.0%; *m/z*, 111. $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%; (M − CH_3CHOH), 111].

3β,4β-*Dihydroxy*-5α-[(1RS)-1-*hydroxyethyl*]-3α,5β-*dimethyldihydrofuran*-2(5H)-*one* **20**.—A solution of the butenolide **19** (4.6 g, 30 mmol), *N*-methylmorpholine *N*-oxide (9 g, 77 mmol), and osmium tetraoxide (100 mg) in a mixture of acetone (150 cm^3), water (130 cm^3), and t-butyl alcohol (10 cm^3) (these volumes chosen to fill the entire round-bottomed flask, thus avoiding loss of osmium tetraoxide from the solution by sublimation) was stirred at room temperature for 9 days. The acetone was removed by evaporation under reduced pressure, and the aq. residue was then extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure, and then purified by chromatography on silica G with (7:3) diethyl ether–light petroleum (40–60 °C) and then diethyl ether as eluent. Recrystallisation from diethyl ether gave the cis-*diol* **20** [1.3 g, 37%; 55% based on consumed starting material (3.0 g)–1.6 g recovered] as crystals, m.p. 130–140 °C; ν_{max}($CHCl_3$)/cm^{-1} 3400 and 1780; δ_H(CD_3OD) 1.20 (d, *J* 8, *MeCH*), 1.36 (Me), 1.38 (Me), 3.82 (q, *J* 8, MeC*H*) and 4.18 (*CH*OH); δ_C 18.0 (Me), 18.2 (Me), 23.3 (Me), 71.3 (CH), 73.2 (CH), 73.2, 89.8 and 176.7 (Found: C, 50.4; H, 7.5%; M^+, 190. $C_8H_{14}O_5$ requires C, 50.5; H, 7.4%; M, 190).

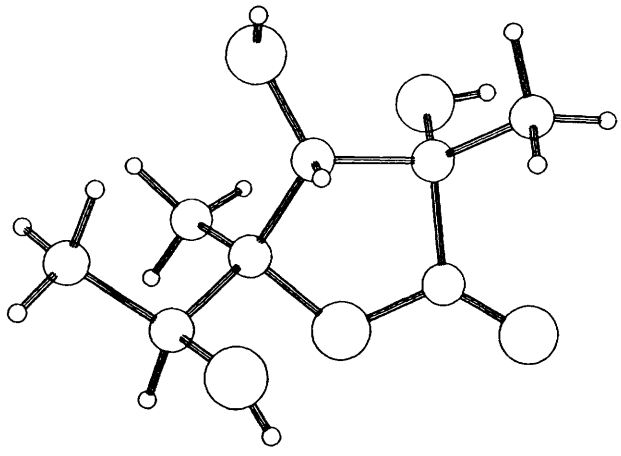


Fig. 1 X-Ray molecular structure of compound **20**

Crystallographic Analysis of the Furanone **20**.—Crystal data: $C_8H_{14}O_5$, M = 190.19. Monoclinic, *a* = 8.571(1), *b* = 10.150(2), *c* = 11.247(2) Å, β = 107.76(1)°, *V* = 931.83 $Å^3$, *Z* = 4, D_c = 1.36 g cm^{-3}, *F*(000) = 408, space group $P2_1/n$, Cu-*K*α radiation, λ = 1.541 78 Å, μ(Cu-*K*α) = 9.74 cm^{-1}.

A crystal of approximate dimensions 0.6 × 0.25 × 0.25 mm was mounted on an Enraf–Nonius CAD4 diffractometer, and 25 reflections were used to determine accurate lattice parameters. Intensity data were collected using an $\omega/2\theta$ scan for $1° < \theta < 76°$. A total of 1842 independent reflections were measured of which 1424 had $I > 3\sigma(I)$, were considered observed, and were used in the subsequent refinement. Periodic measurement of standard reflections throughout data collection demonstrated their stability. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed by using the CRYSTALS system of programs. The structure was solved by direct methods using the MULTAN program. Least-squares refinement included anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at *R* 0.0501 (R_w 0.0613). A final difference map showed no features in excess of 0.2 e $Å^{-3}$.

The refined fractional atomic co-ordinates are shown in Table 1 and the resulting molecular structure is illustrated in Fig. 1. The relative stereochemistry at each centre is clearly revealed. The lactone ring adopts the envelope conformation with the carbon atom beta to the carbonyl group 0.44 Å below the plane containing the other four atoms. The ethanol side-chain adopts the conformation in which the alcohol is *anti* to the methyl group. Three intramolecular hydrogen bonds, to three different molecules with two alcohol and one carbonyl oxygen as electron donors, control the solid-state packing in a framework arrangement. The remaining geometric data are unexceptional. Tables of thermal parameters, fractional atomic co-ordinates of hydrogen atoms, bond lengths, and bond angles have been deposited at the Cambridge Crystallographic Data Centre.*

* See section 5.6.3 of Instructions for Authors, issue 1.

3α,4α-*Benzylidenedioxy*-5β-[(1RS)-1-*hydroxyethyl*]-3β,5α-*dimethyldihydrofuran*-2(5H)-*one* **9**.—A solution of the triol **15** (1.6 g, 8.4 mmol), benzaldehyde (1.9 g, 18 mmol), and toluene-*p*-sulphonic acid (PTSA) (30 mg, 0.17 mmol) in 1,2-dichloroethane (210 cm^3) was heated under reflux beneath a column of activated 3 Å molecular sieves for 3.5 h under nitrogen. The cooled mixture was evaporated under reduced pressure, and the remaining benzaldehyde was then removed under high vacuum. Purification by chromatography on silica G with (2:1) diethyl ether–light petroleum (40–60) as eluent, followed by recrystallisation from light petroleum (40–60)–chloroform, gave the *benzylidene acetal* **9** (1.68 g, 72%) as crystals, m.p. 118–118.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3370 and 1775; δ_H 1.31 (d, *J* 6.4, *Me*CH), 1.36 (Me), 1.75 (Me), 2.44 (OH), 3.80 (q, *J* 6.4, MeC*H*), 4.57 (CHO), 5.94 (PhC*H*) and 7.32–7.53 (m, Ph); δ_C 16.7 (Me), 17.7 (Me), 18.2 (Me), 72.3 (CH), 85.0, 85.8 (CH), 87.8, 105.2 (CH), 127.0 (CH), 128.5 (CH), 129.9 (CH), 135.4 and 174.2 (Found: C, 64.6; H, 6.7%; M^+, 278.1146. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%; M, 278.1154).

(7R)-7-*Benzoyloxy*-1α,4α,6α-*trimethyl*-2,5-*dioxabicyclo*-[2.2.1]*heptan*-3-*one* **8**.—Dry, freshly recrystallised NBS (2.0 g, 11 mmol) was added, under anhydrous conditions, to a stirred solution of the benzylidene acetal **9** (1.5 g, 5.4 mmol) in dry chloroform (110 cm^3) and the mixture was then stirred at room temperature under argon for 48 h. The mixture was adsorbed onto silica Woelm, and was then purified by chromatography on silica G with (1:2) diethyl ether–light petroleum (40–60) as eluent. Recrystallisation from hexane gave the *bicyclic lactone* **8** (1.13 g, 76%) as needles, m.p. 79–80 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1795 and 1725; δ_H 1.26 (d, *J* 6.4, *Me*CH), 1.45 (Me), 1.48 (Me), 4.37 (q, *J* 6.4, MeC*H*), 5.37 (CHO) and 7.34–8.10 (m, Ph); δ_C 11.3 (Me), 12.4 (Me), 13.2 (Me), 77.5 (CH), 80.8 (CH), 81.8, 87.7, 128.5, 128.7 (CH), 130.0 (CH), 134.0 (CH), 165.2 and 172.6 (Found: C, 64.9; H, 6.0%; M^+, 276.0978. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%; M, 276.0998).

Methyl 3α,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*carboxylate* **21**.—A solution of the bicyclic lactone **8** (350 mg, 1.3 mmol) in a mixture of triethylamine (7 cm^3), methanol (35 cm^3), and water (15 drops) was stirred at room temperature for 5 h. The solvent was removed by evaporation under reduced pressure and the residue was then dissolved in dichloromethane. The dried ($MgSO_4$) solution was evaporated under reduced pressure, and the residue was then purified by chromatography on silica G with (4:1) diethyl ether–light petroleum (40–60) as eluent to give the *diol* **21** (212 mg, 80%) as needles, m.p. 89–91 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3410 and 1715; δ_H 1.20 (Me), 1.29 (d, *J* 6.3, *Me*CH), 1.53 (Me), 3.25 (d, *J* 9, CHO*H*), 3.42 (OH), 3.79 (MeO), 3.79 (d, *J* 9, C*H*OH) and 3.91 (q, *J* 6.3, MeC*H*) [Found: C, 52.9; H, 8.0%; *m*/*z*, 145.0839. $C_9H_{16}O_5$ requires C, 53.0; H, 8.0; (M − CO_2CH_3) 145.0865].

Methyl 3α,4α-*Isopropylidenedioxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*carboxylate* **22a**.—A solution of the diol **21** (210 mg, 1.0 mmol), PTSA (15 mg, 0.07 mmol), and 2,2-dimethoxypropane (1.2 cm^3) in dry acetone (15 cm^3) was stirred at room temperature under nitrogen for 48 h. The mixture was adsorbed onto silica Woelm and purified by chromatography on silica G with (1:2) diethyl ether–light petroleum (40–60) as eluent to give the *acetonide* **22a** (245 mg, 98%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 1755 and 1730; δ_H 1.31 (d, *J* 6.3, *Me*CH), 1.39 (Me), 1.43 (Me), 1.44 (Me), 1.47 (Me), 3.80 (q, *J* 6.3, MeC*H*), 3.79 (MeO) and 4.32 (CHO); δ_C 13.6 (Me), 19.5 (Me), 24.0 (Me), 27.2 (Me), 27.9 (Me), 52.1 (Me), 80.2 (CH), 85.8, 89.4, 92.9 (CH), 113.2 and 171.2 (Found: M^+, 244.1318. $C_{12}H_{20}O_5$ requires M, 244.1311).

(3α,4α-*Isopropylidenedioxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)*methanol* **22b**.—A solution of the methyl ester **22a** (320 mg, 1.3 mmol) in dry diethyl ether (25 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (100 mg, 2.6 mmol) in dry diethyl ether (25 cm^3), and the mixture was then heated under reflux for 24 h. Water (0.1 cm^3) was added to the cooled mixture, followed by 15% aq. sodium hydroxide (0.1 cm^3), and then more water (0.3 cm^3). The mixture was filtered and the filtrate was then dried, and evaporated under reduced pressure to leave a residue, which was recrystallised from hexane to give the *alcohol* **22b** (247 mg, 88%) as crystals, m.p. 77–78 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3510; δ_H 1.21 (Me), 1.21 (d, *J* 6.2, *Me*CH), 1.40 (Me), 1.47 (Me), 1.48 (Me), 2.39 (br, OH), 3.72 (CH_2OH), 3.76 (q, *J* 6.2, MeC*H*) and 4.14 (CHO); δ_C 13.8 (Me), 18.7 (Me), 24.4 (Me), 27.2 (Me), 27.3 (Me), 66.6 (CH_2), 79.8 (CH), 82.5, 90.3, 92.0 (CH) and 112.5 [Found: C, 61.3; H, 9.2%; *m*/*z*, 201.1102. $C_{11}H_{20}O_4$ requires C, 61.1; H, 9.3% (M − CH_3), 201.1127].

3α,4α-*Isopropylidenedioxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*carbaldehyde* **22c**.—A solution of the alcohol **22b** (247 mg, 1.14 mmol) in dichloromethane (50 cm^3) was added to a mixture of PCC (800 mg, 3.8 mmol), sodium acetate (310 mg, 3.8 mmol), sodium hydrogencarbonate (100 mg, 1.14 mmol), and Celite (800 mg), and the mixture was then stirred at room temperature for 20 h. Diethyl ether (40 cm^3) was added, and the mixture was stirred for 10 min and then filtered through a pad of Florosil. Evaporation of the filtrate under reduced pressure gave the *aldehyde* **22c** (207 mg, 85%) as crystals; $\nu_{max}(CHCl_3)/cm^{-1}$ 1635; δ_H 1.24 (Me), 1.34 (d, *J* 6.4, *Me*CH), 1.36 (Me), 1.47 (2 × Me), 3.86 (q, *J* 6.4, MeC*H*), 4.29 (3-H) and 9.61 (CHO) [Found: *m*/*z*, 199.0962. $C_{11}H_{18}O_4$ requires (M − CH_3), 199.0970].

(E)-*Ethyl* 3-(3α,4α-*Isopropylidenedioxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* **23**.—A solution of the aldehyde **22c** (205 mg, 1 mmol) and ethoxycarbonylethylidene(triphenyl)phosphorane (725 mg, 2 mmol) in dry benzene (25 cm^3) was heated under reflux for 22 h under nitrogen. The cooled mixture was evaporated under reduced pressure, and the residue was then triturated with light petroleum (40–60). Evaporation of the light petroleum solution left a residue, which was purified by chromatography on silica G with (1:8) diethyl ether–light petroleum (40–60) as eluent to give the E-*unsaturated ester* **23** (244 mg, 82%) as an oil; λ_{max}(EtOH)/nm 216; $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 and 1655; δ_H 1.25 (d, *J* 6, *Me*CH), 1.29 (t, *J* 7.2, *Me*CH_2O), 1.29 (Me), 1.37 (Me), 1.39 (Me), 1.46 (Me), 1.98 (d, *J* 1.2, *Me*C=CH), 3.73 (q, *J* 6, MeC*H*), 4.18 (q, *J* 7.2, MeCH_2O), 4.25 (CHO) and 6.83 (q, *J* 1.2, MeC=C*H*); δ_C 13.6 (Me), 14.0 (Me), 14.3 (Me), 21.3 (Me), 24.2 (Me), 27.3 (Me), 27.9 (Me), 60.6 (CH_2), 78.6 (CH), 84.1, 89.8, 92.8 (CH), 112.5, 128.1, 141.7 (CH) and 168.6 (Found: M^+, 298.1775. $C_{16}H_{26}O_5$ requires M, 298.1780).

(E)-*Ethyl* 3-(3α,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* **24**.—A solution of the acetonide **23** (150 mg, 0.5 mmol) in a mixture of methanol (8 cm^3) and water (8 cm^3) was stirred with Amberlyst IR 120 acidic resin (300 mg) at 60 °C for 6 days. The methanol was removed from the filtered solution by evaporation under reduced pressure, and the remaining aq. layer was then extracted with chloroform. Evaporation of the dried ($MgSO_4$), combined organic layers under reduced pressure left a residue, which was purified by chromatography on silica G with (1:1) diethyl ether–light petroleum (40–60) as eluent. Recrystallisation from light petroleum (40–60) gave the *diol* **24** (60 mg, 61%) as crystals, m.p. 70–71 °C; λ_{max}(EtOH)/nm 221; $\nu_{max}(CHCl_3)/cm^{-1}$ 3540, 3400, 1700 and 1645; δ_H 1.21 (d, *J* 6.5, *Me*CH), 1.22 (Me), 1.30

(t, *J* 7, *Me*CH_2O), 1.43 (Me), 1.76 (OH), 2.06 (d, *J* 1, *Me*C=CH), 2.77 (d, *J* 10, CHO*H*), 3.73 (d, *J* 10, C*H*OH), 3.84 (q, *J* 6.5, MeC*H*), 4.19 (q, *J* 7, MeCH_2O) and 6.91 (q, *J* 1, MeC=C*H*); δ_C 13.1 (Me), 13.7 (Me), 14.3 (Me), 20.6 (Me), 26.0 (Me), 60.9 (CH_2), 77.7, 77.8 (CH), 81.8, 85.6 (CH), 129.2, 141.7 (CH) and 168.9 (Found: C, 60.9: H, 8.9%; M^+, 258.1449. $C_{13}H_{22}O_5$ requires C, 60.5; H, 8.6%; M, 258.1468).

(E)-*Ethyl* 3-(4α-*Hydroxy*-2β,4β,5α-*trimethyl*-3-*oxotetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* **25**.—A solution of the diol **24** (50 mg, 0.19 mmol), dry dimethyl sulphoxide (315 mg, 4 mmol), dicyclohexylcarbodiimide (400 mg, 2 mmol), pyridine (3 drops), and trifluoroacetic acid (4 drops) in dry benzene (15 cm^3) was stirred under nitrogen at room temperature for 5.5 h. Ethyl acetate (10 cm^3) was added, the mixture was filtered, and then the filtrate was washed with water. The dried ($MgSO_4$) organic solution was evaporated under reduced pressure, and the residue was then purified by chromatography on silica G with (1:2) diethyl ether–light petroleum (40–60) as eluent to give the *keto* **25** (27.5 mg, 57%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 3560, 3350, 1765, 1700 and 1650; δ_H 1.28 (t, *J* 7.2, *Me*CH_2O), 1.30 (d, *J* 6.4, *Me*CH), 1.33 (Me), 1.41 (Me), 2.10 (d, *J* 1.6, *Me*C=CH), 2.32 (OH), 4.04 (q, *J* 6.4, MeC*H*), 4.18 (q, *J* 7.2, MeCH_2O) and 6.73 (q, *J* 1.6, MeC=C*H*); δ_C 13.4 (Me), 13.6 (Me), 14.2 (Me), 20.3 (Me), 22.6 (Me), 61.0 (CH_2), 74.4, 78.5 (CH), 81.1, 130.8, 139.2 (CH), 168.2 and 215.5; [Found: *m*/*z*, 211.0964. $C_{13}H_{20}O_5$ requires (M − CH_3CH_2O), 211.0970].

(E)-*Ethyl* 3-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* **26a**.—A solution of the ketone **25** (25 mg, 0.1 mmol) in dry THF (6 cm^3) was added to a stirred suspension of sodium borohydride (15 mg, 0.4 mmol) in dry THF (6 cm^3) at −60 °C. The mixture was stirred at −60 °C under nitrogen for 1 h, and then allowed to warm to room temperature during 1 h. The mixture was adsorbed onto silica Woelm and was then purified by chromatography on silica G with (2:1) diethyl ether–light petroleum (40–60) as eluent to give the *diol* (11 mg, 44%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3560, 3420, 1700 and 1645; δ_H 1.19 (d, *J* 6.5, *Me*CH), 1.22 (Me), 1.29 (t, *J* 7.5, *Me*CH_2O), 1.36 (Me), 1.97 (d, *J* 1.5, *Me*C=CH), 3.82 (q, *J* 6.5, MeC*H*), 3.96 (br, C*H*OH), 4.18 (br q, *J* 7.5, MeCH_2O) and 6.97 (q, *J* 1.5, MeC=C*H*); δ_C 12.2 (Me), 13.5 (Me), 14.3 (Me), 17.4 (Me), 20.2 (Me), 60.9 (CH_2), 77.6 (CH), 80.5, 84.0, 85.3 (CH), 127.6, 146.9 (CH) and 168.4 (Found: M^+, 258.1461. $C_{13}H_{22}O_5$ requires M, 258.1467).

3β,4β-*Benzylidenedioxy*-5α-[(1R)-1-*hydroxyethyl*]-3α,5β-*dimethyldihydrofuran*-2(5H)-*one* **27**.—A stirred solution of the triol **20** (200 mg, 1.05 mmol), benzaldehyde (225 mg, 2.1 mmol), and PTSA (2 mg, 0.01 mmol) in 1,2-dichloroethane (20 cm^3) was heated under reflux beneath a column of activated 3 Å molecular sieves for 2.5 h. The cooled mixture was evaporated under reduced pressure, and the remaining benzaldehyde was then removed under high vacuum. Recrystallisation of the residue from light petroleum (40–60)–chloroform gave the *benzylidene acetal* **27** (278 mg, 95%) as needles, m.p. 157–158 °C; ν_{max}(KBr)/cm^{-1} 3450 and 1760; δ_H 1.29 (d, *J* 7, *Me*CH), 1.38 (Me), 1.78 (Me), 2.80 (OH), 4.00 (q, *J* 7, MeC*H*), 4.67 (CHO), 6.03 (PhC*H*) and 7.40–7.62 (m, Ph); δ_C 17.6 (Me), 18.0 (Me), 18.2 (Me), 71.6 (CH), 83.1 (CH), 85.5, 88.3, 105.1 (CH), 127.5 (CH), 128.8 (CH), 130.2 (CH), 136.6 and 173.5 (Found: C, 64.7; H, 6.5%; M^+, 278.1137. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5% M, 278.1154).

(7R)-7-*Benzoyloxy*-1α,4α,6β-*trimethyl*-2,5-*dioxabicyclo*-[2.2.1]*heptan*-3-*one* **28**.—Dry, freshly recrystallised NBS (990 mg, 5.6 mmol) was added, under anhydrous conditions, to a stirred solution of the benzylidene acetal **27** (770 mg, 2.8 mmol) in dry chloroform (40 cm^3), and the mixture was then stirred at room temperature under nitrogen for 48 h, adsorbed onto silica Woelm, and then purified by chromatography on silica G with (1:2) diethyl ether–light petroleum (40–60) as eluent. Recrystallisation from diethyl ether–hexane gave the *bicyclic lactone* **28** (550 mg, 72%) as needles, m.p. 118–119 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 and 1730; δ_H 1.39 (d, *J* 7, *Me*CH), 1.46 (Me), 1.51 (Me), 4.06 (q, *J* 7, MeC*H*), 5.34 (CHO) and 7.45–8.06 (m, Ph); δ_C 11.4 (Me), 12.6 (Me), 18.2 (Me), 78.8 (CH), 79.7 (CH), 81.5, 89.8, 128.7 (CH), 130.0 (CH), 134.1 (CH), 165.4 and 172.3 (Found: C, 65.2; H, 6.0%; M^+, 276.1063. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%; M, 276.0997).

Note: 4β-Benzoyloxy-3β-hydroxy-5α-[(1R)-1-hydroxyethyl]-3α,5β-dimethyldihydrofuran-2(5*H*)-one was obtained from the benzylidene acetal **27** under conditions when the chloroform was not scrupulously dry. Recrystallisation from diethyl ether–hexane gave the *diol* (75 mg, 59%) as crystals, m.p. 138–141 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3550, 1790 and 1730; δ_H 1.20 (d, *J* 6.5, *Me*CH), 1.62 (Me), 1.68 (Me), 3.50 (br, 2 × OH), 4.02 (q, *J* 6.5, MeC*H*), 5.70 (CHO) and 7.41–8.25 (m, Ph); $\delta_C(CD_3OD)$ 15.8 (Me), 18.1 (Me), 24.0 (Me), 71.9 (CH), 74.8 (CH), 80.0, 81.2, 129.6 (CH), 130.8 (CH), 134.6, 166.9 and 177.9 [Found: C, 61.0; H, 6.3%; *m*/*z*, 276.0987. $C_{15}H_{18}O_6$ requires C, 61.2; H, 6.2%; (M − H_2O), 276.0997].

Crystallographic Analysis of the Bicyclic Lactone Ether **28**.—Crystal data: $C_{15}H_{16}O_5$, M = 276.28. Monoclinic, *a* = 10.329(1), *b* = 17.931(2), *c* = 7.791(1) Å, β = 101.09(1)°, *V* = 1415.98 $Å^3$, *Z* = 4, D_c = 1.30 g cm^{-3}, *F*(000) = 584. Space group $P2_1/c$, Cu-*K*α radiation, λ = 1.541 78 Å, μ(Cu-*K*α) = 8.23 cm^{-1}.

A crystal of approximate dimensions 0.55 × 0.25 × 0.05 mm was mounted on an Enraf–Nonius CAD4 diffractometer and 25 reflections were used to determine accurate lattice parameters. Intensity data were collected using a $\omega/2\theta$ scan for $1° < \theta < 76°$. A total of 2935 independent reflections were measured of which 1291 had $I > 3\sigma(I)$, were considered observed, and were used in the subsequent refinement. Periodic measurement of standard reflections throughout data collection demonstrated their stability. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed by using the CRYSTALS system of programs. The structure was solved by direct methods using the MULTAN program. Least-squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at *R* 0.0540 (R_w 0.0770). A final difference map showed no features in excess of 0.2 e $Å^{-3}$.

The refined fractional atomic co-ordinates are shown in Table 2 and the resulting molecular structure is illustrated in Fig. 2. Tables of thermal parameters, fractional atomic co-ordinates of hydrogen atoms, bond lengths, and bond angles have been deposited at the Cambridge Crystallographic Data Centre.*

Methyl 3α,4α-*Dihydroxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*carboxylate* **29**.—A solution of the bicyclic lactone **28** (500 mg, 1.8 mmol) in a mixture of triethylamine (7 cm^3), methanol (35 cm^3), and water (7 cm^3) was stirred at room temperature for 2 h. The triethylamine and methanol were removed by evaporation under reduced pressure, and the aq. residue was then extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$), combined organic layers left a residue, which was then purified by chromatography on silica G with (4:1) diethyl

* See section 5.6.3 of Instructions for Authors, issue 1.

Table 2 Fractional atomic co-ordinates for compound **28** with standard deviations in parentheses

Atom	*x*	*y*	*z*
O(1)	0.9126(3)	0.0839(2)	0.5217(5)
C(2)	0.8535(5)	0.0447(4)	0.3627(7)
C(3)	0.7063(5)	0.0543(3)	0.3583(7)
C(4)	0.7059(5)	0.1326(3)	0.4352(7)
C(5)	0.8051(5)	0.1129(3)	0.5977(7)
C(6)	0.7402(5)	0.0428(3)	0.6524(8)
O(7)	0.6798(3)	0.0084(2)	0.5045(5)
C(8)	0.9086(8)	0.0763(5)	0.2104(10)
C(9)	0.6106(7)	0.0331(4)	0.1959(9)
C(10)	0.8568(6)	0.1675(4)	0.7395(9)
O(11)	0.7414(5)	0.0173(2)	0.7970(6)
O(12)	0.5779(3)	0.1507(2)	0.4653(5)
C(13)	0.5517(5)	0.2241(3)	0.4849(7)
O(14)	0.6327(4)	0.2715(2)	0.4785(6)
C(15)	0.4167(4)	0.2372(3)	0.5169(6)
C(16)	0.3302(5)	0.1795(3)	0.5308(8)
C(17)	0.2060(6)	0.1954(4)	0.5569(9)
C(18)	0.1670(6)	0.2674(4)	0.5711(9)
C(19)	0.2502(6)	0.3249(4)	0.5544(9)
C(20)	0.3746(6)	0.3095(3)	0.5274(8)

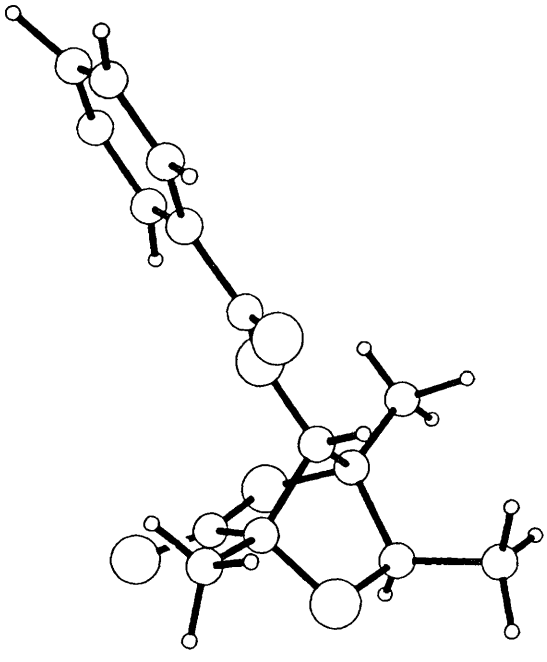


Fig. 2 X-Ray molecular structure of compound **28**

ether–light petroleum (40–60) as eluent. Recrystallisation from diethyl ether–light petroleum (40–60) gave the *diol* **29** (321 mg, 88%) as needles, m.p. 91–92 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1705; δ_H 1.21 (d, *J* 6.5, *Me*CH), 1.23 (Me), 1.55 (Me), 1.79 (br, OH), 2.76 (br, OH), 3.61 (br, C*H*OH), 3.79 (MeO) and 4.11 (q, *J* 6.5, MeC*H*); δ_C 17.0 (Me), 20.6 (Me), 24.0 (Me), 52.5 (Me), 77.6, 82.0 (CH), 82.3, 83.4 (CH) and 175.5 [Found: C, 53.1; H, 8.0%; *m/z*, 186.0855. $C_9H_{16}O_5$ requires C, 52.9; H, 7.9%; (M − H_2O), 186.0892].

Methyl 3α,4α-*Isopropylidenedioxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*carboxylate* **30a**.—A solution of the diol **29** (600 mg, 3 mmol), PTSA (30 mg, 0.15 mmol), and 2,2-dimethoxypropane (1.5 cm³) in dry acetone (75 cm³) was stirred at room temperature for 21 h. The mixture was adsorbed onto silica Woelm, and was then purified by chromatography on silica G with (1:2) diethyl ether–light petroleum (40–60) as eluent. Recrystallisation from light petroleum (40–60) gave the *acetonide* **30a** (630 mg, 86%) as clear crystals, m.p. 65–66 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; δ_H 1.19 (d, *J* 6.5, *Me*CH), 1.35 (2 × Me), 1.44 (Me), 1.53 (Me), 3.76 (MeO), 4.15 (CHO) and 4.27 (q, *J* 6.5, MeC*H*) (Found: C, 58.8; H, 8.4%; M^+, 244.1304. $C_{12}H_{20}O_5$ requires C, 59.0; H, 8.3%; M, 244.1310).

(3α,4α-*Isopropylidenedioxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*yl*)*methanol* **30b**.—A solution of the methyl ester **30a** (630 mg, 2.6 mmol) in dry diethyl ether (30 cm³) was added dropwise, under anhydrous conditions, to a stirred suspension of lithium aluminium hydride (185 mg, 4.8 mmol) in dry diethyl ether (30 cm³), and the mixture was then heated under reflux for 22 h. Water (0.2 cm³) was added to the cooled mixture followed by 15% aq. sodium hydroxide (0.2 cm³) and then further water (0.6 cm³). Evaporation of the dried ($MgSO_4$), filtered solution under reduced pressure left a residue, which was recrystallised from diethyl ether to give the *alcohol* **30b** (476 mg, 85%) as crystals, m.p. 51–52 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3570; δ_H 1.14 (d, *J* 6.5, *Me*CH), 1.33 (Me), 1.37 (Me), 1.39 (Me), 1.54 (Me), 2.33 (OH), 3.74 (dd, *J* 18, 10, CH_2OH), 4.06 (q, *J* 6.5, MeC*H*) and 4.15 (CHO) [Found: C, 60.7; H, 9.6%; *m/z*, 201.1111. $C_{11}H_{20}O_4$ requires C, 61.1; H, 9.3%; (M − CH_3), 201.1127].

3α,4α-*Isopropylidenedioxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*carbaldehyde* **30c**.—A solution of the alcohol **30b** (410 mg, 1.9 mmol) in dichloromethane (40 cm³) was added to a mixture of PCC (1.34 g, 6.3 mmol), sodium acetate (515 mg, 6.3 mmol), sodium hydrogencarbonate (185 mg, 2.1 mmol), and Celite (1.34 g) in dichloromethane (40 cm³), and the mixture was then stirred at room temperature for 19 h. Diethyl ether (80 cm³) was added, and the mixture was stirred for 10 min and then filtered through a pad of Florisil. Evaporation of the solution under reduced pressure gave a residue, which was then dissolved in diethyl ether and the solution was filtered through a pad of Florisil. Evaporation under reduced pressure gave the aldehyde **30c** (376 mg, 90%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; δ_H 1.23 (d, *J* 6.5, *Me*CH), 1.34 (Me), 1.36 (Me), 1.38 (Me), 1.46 (Me), 4.20 (q, *J* 6.5, MeC*H*), 4.22 (CHO) and 9.65 (CHO), which was used without further purification.

(E)-*Ethyl* 3-(3α,4α-*Dihydroxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* **31a**; *Et Ester*.—A solution of the aldehyde **30c** (367 mg, 1.72 mmol) and ethoxycarbonylethylidene(triphenyl)phosphorane (1.26 g, 3.48 mmol) in dry benzene (30 cm³) was heated under reflux for 22 h under argon. The cooled mixture was evaporated under reduced pressure, and the residue was then triturated with light petroleum (40–60). Evaporation of the light petroleum solution under reduced pressure left a residue, which was purified by chromatography on silica G with (1:8) diethyl ether–light petroleum (40–60) as eluent to give (E)-*ethyl* 3-(3α,4α-*isopropylidenedioxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* (370 mg, 72%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 and 1650; δ_H 1.15 (d, *J* 6.5, *Me*CH), 1.30 (t, *J* 7.5, *Me*CH_2O), 1.37 (2 × Me), 1.40 (Me), 1.44 (Me), 2.00 (d, *J* 1.4, *Me*C=CH), 3.85 (q, *J* 6.5, MeC*H*), 4.13 (CHO), 4.20 (br q, *J* 7.5, MeCH_2O) and 6.94 (q, *J* 1.4, MeC=C*H*); δ_C 13.2 (Me), 14.1 (Me), 14.3 (Me), 19.5 (Me), 26.3 (Me), 27.2 (Me), 28.2 (Me), 60.6 (CH_2), 80.0 (CH), 82.6, 88.6, 93.6 (CH), 114.4, 128.1 (CH), 142.3 (CH) and 168.6 (Found: M^+, 298.1747. $C_{16}H_{26}O_5$ requires M, 298.1780).

A solution of the acetonide (from above) (400 mg, 1.34 mmol) in methanol (25 cm³)–water (25 cm³) was stirred with Amberlyst IR 120 acidic resin (500 mg) at 60 °C for 3 days. The methanol was removed by evaporation under reduced pressure, and the remaining aq. layer was then extracted with chloroform. Evaporation of the dried ($MgSO_4$), combined organic layers left a residue, which was purified by chromatography on silica G with (2:1) diethyl ether–light petroleum (40–60) as eluent to

give the *title diol* (333 mg, 96%) as an oil, λ_{max}(EtOH)/nm 218; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1700 and 1645; δ_H 1.19 (d, *J* 6.5, *Me*CH), 1.22 (Me), 1.30 (t, *J* 7, *Me*CH_2O), 1.41 (Me), 2.05 (d, *J* 1.3, *Me*C=CH), 3.44 (C*H*OH), 3.49 (br, OH), 3.74 (q, *J* 6.5, MeC*H*), 4.18 (q, *J* 7, MeCH_2O) and 6.95 (q, *J* 1.3, MeC=C*H*); δ_C 12.8 (Me), 14.3 (Me), 16.2 (Me), 21.9 (Me), 25.8 (Me), 61.1 (CH_2), 76.9, 80.7 (CH), 82.1, 84.0 (CH), 128.6, 141.0 (CH) and 169.2 [Found: *m/z*, 259.1547. $C_{13}H_{22}O_5$ requires (M + H), 259.1546].

(E)-3-(3α,4α-*Dihydroxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylprop*-2-*en*-1-*ol* **31b**.—A solution of the ethyl ester corresponding to structure **31a** (100 mg, 0.39 mmol) in dry diethyl ether (10 cm^3) was added dropwise, under anhydrous conditions, to an ice-cooled, stirred suspension of lithium aluminium hydride (32 mg, 0.8 mmol) in dry diethyl ether (10 cm^3), and the mixture was then heated under reflux for 20 h. Water (35 mm^3) was added to the cooled mixture, followed by 15% aq. sodium hydroxide (35 mm^3) and then more water (105 mm^3). Evaporation of the dried ($MgSO_4$) solution left a residue, which was purified by chromatography on silica G with (23:2) chloroform–methanol as eluent. Recrystallisation from light petroleum (40–60)–chloroform gave the *allylic alcohol* **31b** (43 mg, 51%) as crystals, m.p. 103–103.5 °C; ν_{max}($CHCl_3$)/cm^{-1} 3380; δ_H 1.19 (d, *J* 6.5, *Me*CH), 1.21 (Me), 1.40 (Me), 1.83 (br, *Me*C=CH), 3.18, 3.36 (br, C*H*OH plus 3 × OH), 3.74 (q, *J* 6.5, MeC*H*), 3.97 (CH_2OH) and 5.63 (br, MeC=C*H*); δ_C 14.4 (Me), 16.0 (Me), 21.8 (Me), 26.6 (Me), 68.6 (CH_2), 77.4, 80.1 (CH), 81.7, 83.9 (CH), 123.6 (CH) and 137.2 [Found: C, 61.4; H, 9.5%; *m/z*, 217. $C_{11}H_{20}O_4$ requires C, 61.1; H, 9.3%; (M + H) 217].

(E)-3-(3α,4α-*Dihydroxy*-2β,4β,5β-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylprop*-2-*enal* **31c**.—A solution of the allylic alcohol **31b** (12 mg, 0.055 mmol) in dichloromethane (5 cm^3) was stirred with activated manganese dioxide (120 mg) at room temperature for 0.5 h. Evaporation of the filtered solution under reduced pressure left a residue, which was purified by preparative TLC on silica G with diethyl ether as solvent to give the unsaturated *aldehyde* **31a** (2.6 mg, 22%) as an oil, λ_{max}(EtOH)/nm 227; ν_{max}($CHCl_3$)/cm^{-1} 3360, 1680 and 1635; δ_H 1.22 (d, *J* 6.5, *Me*CH), 1.28 (Me), 1.47 (Me), 1.95 (d, *J* 1.3, *Me*C=CH), 3.54 (C*H*OH), 3.75 (q, *J* 6.5, MeC*H*), 6.68 (q, *J* 1.3, MeC=C*H*) and 9.42 (CHO) [Found: *m/z*, 215.1312. $C_{11}H_{18}O_4$ requires (M + H), 215.1283].

Acknowledgements

We thank Drs. W. P. Jackson and G. Kneen (Wellcome Research Laboratories) for their interest in this work. We also thank the SERC and Wellcome Research Laboratories for financial support (CASE SERC awards to M. C. B. and P. P.).

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Paper 1/00153A
Received 11*th January* 1991
Accepted 4*th March* 1991