# Total Synthesis of (±)-Citreoviral, based on a Biogenetic Model, and Formal Synthesis of (±)-Citreoviridin

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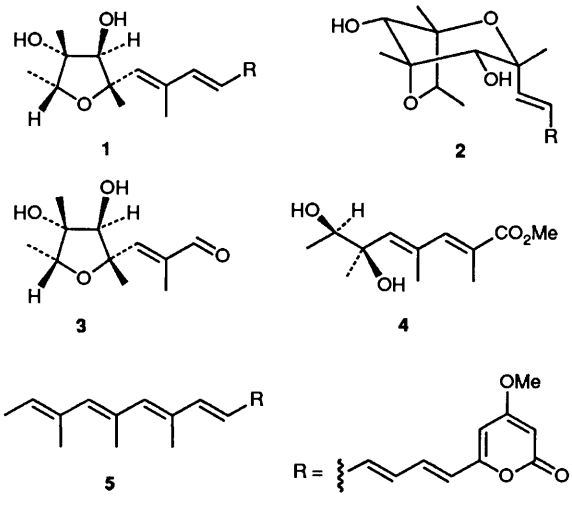
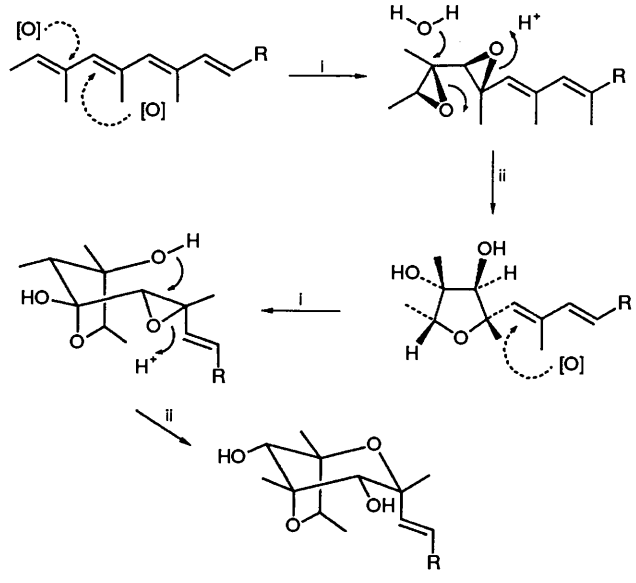
The total synthesis of (±)-citreoviral, which co-occurs with citreoviridin, citreoviridinol, and citreodiol in *Penicillium citreoviride*, is described. The synthesis is based on a biogenetic model, and has as a key feature the elaboration of the dihydroxytetrahydrofuranyl ring portion **10** by an acid-catalysed cyclisation of the central epoxy alcohol intermediate **9** which is derived in ten steps from methyl tiglate.

The polyene pyrones citreoviridin **1** and citreoviridinol **2** co-occur with the related metabolites citreoviral **3** and citreodiol **4** in *Penicillium citreoviride*.[1] Citreoviridin **1** has been shown to be a potent neurotoxic mycotoxin, acting as an inhibitor of ATP synthesis and hydrolysis catalysed by mitochondrial enzyme systems. In the previous paper we presented a total synthesis of the polyene pyrone citreomontanin **5** found in *P. pedemontanum*.[2] In the same paper we suggested that compound **5** could have a biogenetic link with citreoviridin **1** and citreoviridinol **2**, and in preliminary papers[3] and elsewhere[4] we have proposed that the dioxabicyclo[3.2.1]octane system in citreoviridinol **2** is derived in Nature *via* citreoviridin **1** by successive epoxidations of the trisubstituted double bonds associated with the terminal triene unit of citreomontamin (Scheme 1). Citreoviral **3** is most

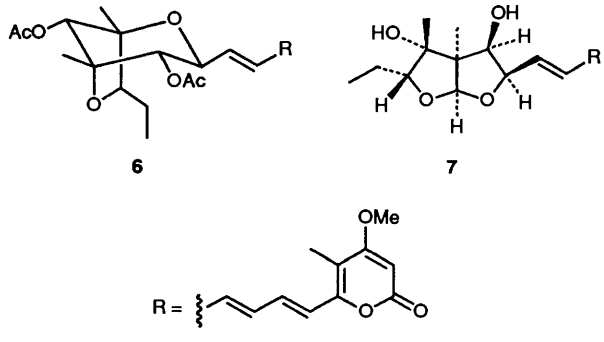



likely a catabolic oxidation product of citreoviridin **1**, whereas citreodiol **4** is almost certainly an early biosynthetic precursor of citreoviridin **1** and/or citreoviral **3**. In connection with our interests in the biogenetic interrelationships amongst the citreoviridinoids, *i.e.* **1–5**, and the related aurovertin **6**[5] and asteltoxin[6] **7** metabolites, we now describe a total synthesis of citreoviral **3** based on the biosynthetic model shown in Scheme 1.[7,8]† In the accompanying paper we describe a second conceptually distinct approach to citreoviral which starts from methyl angelate, and represents a new stereoselective approach to hydroxy-substituted tetrahydrofurans.[9]

Our biogenetically patterned synthesis of citreoviral **3** has as

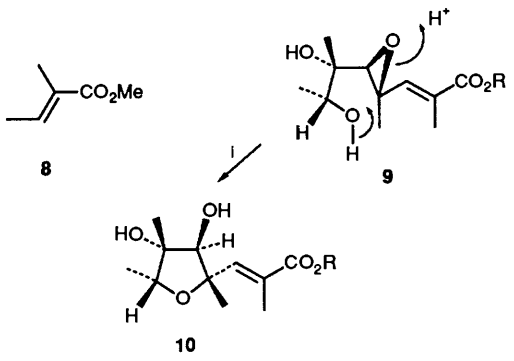



**Scheme 1** *Reactions:* i, oxidation; ii, cyclisation

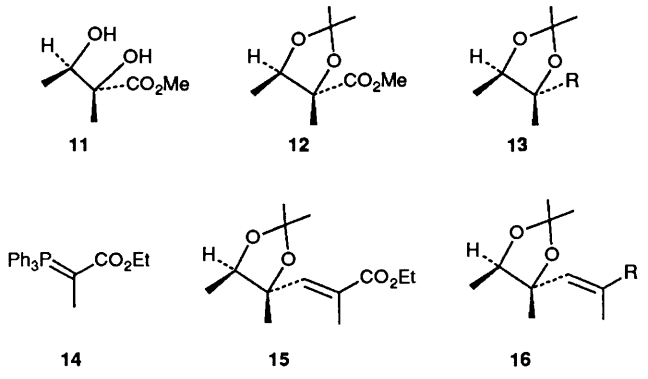



a key feature the elaboration of the tetrahydrofuran ring portion **10** by an acid-catalysed cyclisation of the central epoxy alcohol intermediate **9** derived in ten steps from (*E*)-methyl 2-methylbut-2-enoate (methyl tiglate) **8** (Scheme 2). Treatment of ester **8** with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetraoxide first led to the corresponding vicinal diol **11** which was then protected as the acetonide **12**. The acetonide **12** was next converted in two steps into the aldehyde **13b** *via* the corresponding primary alcohol **13a**, and a Wittig reaction between aldehyde **13b** and ethoxycarbonylethylidene(triphenyl)phosphorane **14** then provided the *E*-ester **15** exclusively. The *E*-geometry assigned to the newly introduced double bond in compound **15** followed conclusively

† In contemporaneous studies Yamamura and co-workers have described a closely similar route to (+)-citreoviral starting from D-glucose.[7b]



**Scheme 2** *Reagent:* i, $H_3O^+$



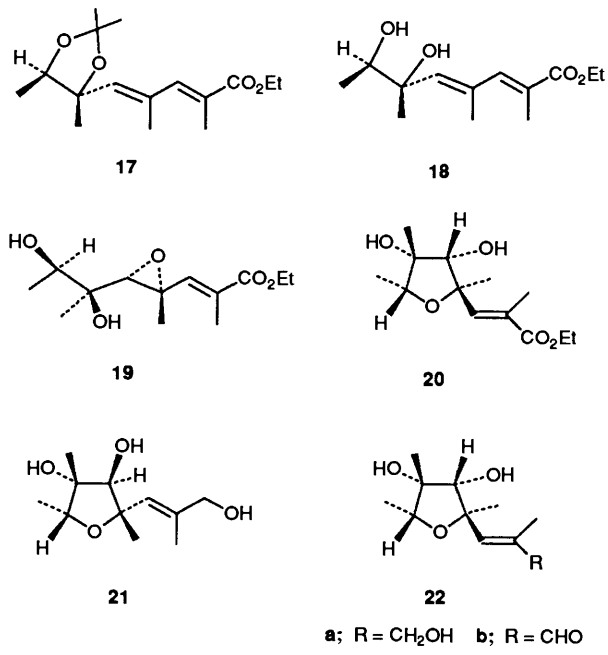
**a**; R = $CH_2OH$ **b**; R = CHO

from examination of chemical-shift data in the $^1H$ NMR spectrum.[10]

The *E,E*-dienoate **17** was next derived from the *E*-ester **15**, following successive reduction to the allylic alcohol **16a**, oxidation to the aldehyde **16b**, and a further Wittig condensation between aldehyde **16b** and ethoxycarbonylethylidene(triphenyl)phosphorane. Treatment of the acetonide **17** with Amberlyst acidic resin, at 40 °C for 40 h, then provided the diol **18** in a modest 50% yield.[11] The epoxidation of **18** with *m*-chloroperbenzoic acid (MCPBA) was found to be regiospecific and produced only the epoxide, *viz.* (**19**; *cf.* structure **9**) resulting from attack at the γδ-double bond in compound **18**. Furthermore, the epoxidation proceeded with a degree of stereospecificity, and led to a 3:2 mixture of the β- (**9**) and α-(**19**) orientated epoxides.* The epoxide mixture was not separated at this stage, but instead was treated with a catalytic amount of toluene-*p*-sulphonic acid (PTSA) in dichloromethane at room temperature for 0.5 h. Work-up then produced a mixture of the isomeric tetrahydrofurans **10**; R = Et and **20**, which were easily separated by chromatography.

Reduction of the tetrahydrofuranyl ester **10**; R = Et with diisobutylaluminium hydride (DIBAL), followed by oxidation of the resulting primary alcohol **21** with manganese dioxide, then led to (±)-citreoviral **3** as plates, which showed identical spectroscopic data with those reported for naturally derived material. In a similar manner, the isomeric tetrahydrofuranyl ester **20** was converted into the stereoisomer **22b** of natural citreoviral **3**. Since citreoviral has already been converted into citreoviridin **1**,[7,8] our synthesis of citreoviral **3** also constitutes a new formal synthesis of this tetrahydrofuranyl-substituted polyene pyrone.

* The α-orientated epoxide **19** was particularly labile, and underwent *in situ* cyclisation to the tetrahydrofuran **20** during attempted separation by chromatography; the combined yield of products **9**; R = Et and **19** was *ca.* 90%.



**a**; R = $CH_2OH$ **b**; R = CHO

## Experimental

For general experimental details see ref. 2.

(2RS,3SR)-*Methyl* 2,3-*Dihydroxy*-2-*methylbutanoate* **11**.—A solution of methyl 2-methylbutenoate **8** (31.5 g, 0.28 mol), *N*-methylmorpholine *N*-oxide (37.8 g, 0.32 mol), and osmium tetraoxide (30 mg) in a mixture of acetone (240 $cm^3$), water (120 $cm^3$), and *tert*-butyl alcohol (6 $cm^3$) was stirred at room temperature for 26 h. 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 distillation to give the diol **11** (31.7 g, 76%) as a liquid, b.p. 115–118 °C at 15 mmHg; $\nu_{max}$(liq. film)/$cm^{-1}$ 3450 and 1730; $\delta_H$ 1.22 (d, *J* 8, MeCH), 1.31 (Me), 3.83 (MeO) and 3.98 (q, *J* 8, MeC*H*) (Found: $M^+$, 148. $C_6H_{12}O_4$ requires M, 148).

(2RS,3SR)-*Methyl* 2,3-*Isopropylidenedioxy*-2-*methylbutanoate* **12**.—A solution of the diol **11** (31.3 g, 0.21 mol) and PTSA (1.5 g) in 2,2-dimethoxypropane (650 $cm^3$) was stirred at room temperature for 19 h. Evaporation under reduced pressure left a brown residue, which was purified by distillation to give the *acetonide* **12** (33.2 g, 84%) as a liquid, b.p. 78–79 °C at 15 mmHg; $\nu_{max}$(liq. film)/$cm^{-1}$ 1760 and 1735; $\delta_H$ 1.34 (d, *J* 7, *Me*CH), 1.37 (Me), 1.43 (Me), 1.50 (Me), 3.80 (MeO), 4.39 (q, *J* 7, MeC*H*) [Found: *m/z* 173. $C_9H_{16}O_4$ requires (M − $CH_3$), 173].

(2RS,3RS)-2,3-*Isopropylidenedioxy*-2-*methylbutan*-1-*ol* **13a**.—A solution of the methyl ester **12** (29.6 g, 0.16 mol) in dry diethyl ether (145 $cm^3$) was added dropwise during 0.25 h to an ice-cooled, stirred suspension of lithium aluminium hydride (6.1 g, 0.16 mol) in dry diethyl ether (145 $cm^3$), and the mixture was then heated under reflux for 17 h. Water (6 $cm^3$) was added to the cooled mixture, followed by 15% aq. sodium hydroxide (6 $cm^3$), and then water (18 $cm^3$). Evaporation of the dried ($MgSO_4$) solution under reduced pressure left a residue, which was purified by distillation to give the alcohol **13a** (23.4 g, 91%) as a liquid, b.p. 95–96 °C at 20 mmHg; $\nu_{max}$(liq. film)/$cm^{-1}$ 3450; $\delta_H$ 1.08 (Me), 1.22 (d, *J* 8, *Me*CH), 1.40 (Me), 1.48 (Me), 2.50 (OH), 3.48 (dd, *J* 8 and 16, $CH_2OH$) and 4.26 (q, *J* 8, MeC*H*).

(2RS,3SR)-2,3-*Isopropylidenedioxy*-2-*methylbutanal* **13b**.—A solution of the alcohol **13a** (10 g, 0.06 mol) in dichloromethane (80 $cm^3$) was added to an ice-cooled, stirred suspension of pyridinium chlorochromate (20 g, 0.09 mol) and Celite (20 g) in dichloromethane (300 $cm^3$), and the mixture was then stirred at room temperature for 24 h. Diethyl ether (300 $cm^3$) was added and the mixture was stirred for 10 min and then filtered through a pad of Florisil. Evaporation of the filtrate under reduced pressure left a residue, which was purified by distillation to give the *aldehyde* **13b** (6.0 g, 60%) as a pale yellow liquid, b.p. 65–70 °C at 15 mmHg; $\nu_{max}$(liq. film)/$cm^{-1}$ 2950 and 1740; $\delta_H$ 1.21 (Me), 1.25 (d, *J* 7, *Me*CH), 1.44 (Me), 1.53 (Me), 4.24 (q, *J* 7, MeC*H*) and 9.70 (CHO) [Found: *m*/*z* 143. $C_8H_{14}O_3$ requires (M − $CH_3$), 143].

(2E,4RS,5RS)-*Ethyl* 4,5-*Isopropylidenedioxy*-2,4-*dimethylhex*-2-*enoate* **15**.—A solution of the aldehyde **13b** (6 g, 38 mmol) and ethoxycarbonylethylidene(triphenyl)phosphorane **14** (16 g, 45 mmol) in dichloromethane (150 $cm^3$) was heated under reflux for 21 h. Further phosphorane (5 g) was added, and the mixture was then heated under reflux for 7 h. The cooled mixture was evaporated under reduced pressure and the residue was then triturated with light petroleum (b.p. 40–60 °C). Evaporation of the light petroleum solution under reduced pressure gave a residue, which was purified by distillation to give the E-*unsaturated ester* **15** (8 g, 87%) as a liquid, b.p. 120 °C at 10 mmHg; $\nu_{max}$(liq. film)/$cm^{-1}$ 1710 and 1660; $\delta_H$ 1.2–1.4 (m, 4 × Me), 1.49 (Me), 2.10 (d, *J* 2, MeC=CH), 4.10 (q, *J* 7, MeC*H*), 4.23 (q, *J* 8, MeC$H_2$O) and 6.66 (m, MeC=C*H*) [Found: *m*/*z*, 227. $C_{13}H_{22}O_4$ requires (M − $CH_3$), 227].

(2E,4RS,5RS)-4,5-*Isopropylidenedioxy*-2,4-*dimethylhex*-2-*en*-1-*ol* **16a**.—A solution of the ethyl ester **15** (8 g, 33 mmol) in dry diethyl ether (150 $cm^3$) was added dropwise during 0.25 h to an ice-cooled, stirred suspension of lithium hydride (1.25 g, 33 mmol) in dry diethyl ether (150 $cm^3$), and the mixture was then heated under reflux for 19 h. Water (1.3 $cm^3$) was added to the cooled mixture followed by 15% aq. sodium hydroxide (1.3 $cm^3$) and then water (3.9 $cm^3$). Evaporation of the dried ($MgSO_4$) solution left a residue, which was purified by distillation to give the *allylic alcohol* **16a** (6.2 g, 93%) as a liquid, b.p. 85 °C at 12 mmHg; $\nu_{max}$(liq. film)/$cm^{-1}$ 3350, 1460 and 1380; $\delta_H$ 1.22 (Me), 1.25 (d, *J* 6.5, *Me*CH), 1.38 (Me), 1.48 (Me), 1.89 (br, *Me*C=CH), 2.30 (br, OH), 4.01 (C$H_2$OH), 4.05 (q, *J* 6.5, MeC*H*) and 5.43 (br, MeC=C*H*) [Found: *m*/*z*, 185. $C_{11}H_{20}O_3$ requires (M − $CH_3$), 185].

(2E,4RS,5RS)-4,5-*Isopropylidenedioxy*-2,4-*dimethylhex*-2-*enal* **16b**.—A solution of the allylic alcohol **16a** (6.2 g, 31 mmol) in dichloromethane (600 $cm^3$) was stirred with activated manganese dioxide (62 g) at room temperature for 1.75 h. The mixture was filtered, and the filtrate was then evaporated under reduced pressure to give the unsaturated aldehyde **16b** (5.8 g, 94%) as an oil; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 1690 and 1640; $\delta_H$ 1.34 (d, *J* 6.5, *Me*OH), 1.32 (Me), 1.38 (Me), 1.51 (Me), 2.00 (d, *J* 1.4, *Me*C=CH), 4.16 (q, *J* 6.5, MeC*H*), 6.35 (q, *J* 1.4, MeC=C*H*) and 9.48 (CHO); which was used without further purification.

(2E,4E,6RS,7RS)-*Ethyl* 7-*Isopropylidenedioxy*-2,4,6-*trimethylocta*-2,4-*dienoate* **17**.—A solution of the aldehyde **16b** (5.8 g, 29 mmol) and ethoxycarbonylethylidene(triphenyl)-phosphorane **14** (19 g, 53 mmol) in dry benzene (600 $cm^3$) was heated under reflux for 4 h, allowed to cooled, and stored at room temperature for 12 h. The mixture was evaporated under reduced pressure, and the residue was then triturated with light petroleum (b.p. 40–60 °C). Evaporation of the light petroleum solution and purification of the residue by chromatography on Silica G with (1:8) diethyl ether–light petroleum (b.p. range 40–60 °C) as eluent, followed by distillation, gave the E,E-*diene ester* **17** (8.0 g, 95%) as a liquid, b.p. 119–120 °C at 2.5 mmHg; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 1690 and 1625; $\delta_H$ 1.24 (Me), 1.25 (d, *J* 6.4, *Me*CH), 1.31 (t, *J* 7.5, *Me*C$H_2$O), 1.38 (Me), 1.47 (Me), 1.98 (d, *J* 1.5, *Me*C=CH), 2.05 (d, *J* 1.3, *Me*C=CH), 4.05 (q, *J* 6.5, MeC*H*), 4.21 (q, *J* 7.5, MeC$H_2$O), 5.41 (m, MeC=C*H*) and 7.08 (m, MeC=C*H*); $\delta_C$ 13.8 (Me), 14.3 (2 × Me), 17.4 (Me), 22.1 (Me), 26.4 (Me), 28.7 (Me), 60.7 ($CH_2$), 78.6 (CH), 82.6, 107.4, 126.7, 134.1, 135.0 (CH), 143.3 (CH) and 168.8 [Found: C, 68.2; H, 9.4%; *m*/*z*, 267.1595. $C_{16}H_{26}O_4$ requires C, 68.1; H, 9.3%; (M − $CH_3$), 267.1596].

(2E,4E,6RS,7RS)-*Ethyl* 6,7-*Dihydroxy*-2,4,6-*trimethylocta*-2,4-*dienoate* **18**.—A solution of the acetonide **17** (9 g, 32 mmol) in methanol (400 $cm^3$)–water (200 $cm^3$) was stirred with Amberlyst IR 120 acidic resin (12 g) at 40 °C for 24 h. The methanol was removed by evaporation under reduced pressure, and the remaining aq. layer was then extracted with dichloromethane. Evaporation of the dried ($MgSO_4$), combined organic layers left a residue, which was purified by chromatography on Silica G with diethyl ether–light petroleum (b.p. 40–60 °C) (1:1, then 2:1) as eluent, followed by distillation to give the *diol* **8** (3.7 g, 51%) as a liquid, b.p. 160–161 °C at 1 mmHg; $\lambda_{max}$(EtOH)/nm 267 (11 250); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3550, 1685 and 1630; $\delta_H$ 1.18 (d, *J* 6.4, MeCH), 1.31 (Me), 1.31 (t, *J* 7, MeC$H_2$O), 1.98 (d, *J* 1.4, MeC=CH), 2.07 (d, *J* 1, MeC=CH), 3.83 (q, *J* 6.4, MeC*H*), 4.22 (q, *J* 7, MeC$H_2$O), 5.52 (m, MeC=C*H*) and 7.07 (m, MeC=C*H*); $\delta_C$ 13.9 (Me), 14.3 (Me), 17.4 (2 × Me), 22.5 (Me), 60.8 ($CH_2$), 73.5 (CH), 75.9, 126.4, 135.2, 137.6 (CH), 143.9 (CH) and 169.1 [Found: C, 64.3; H, 9.4%; *m*/*z*, 243.1577. $C_{13}H_{22}O_4$ requires C, 64.4; H, 9.2%; (M + H), 243.1596].

(E)-*Ethyl* 3-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenoate* **10**; R = Et *and* (E)-*Ethyl* 3-(3α,4α-*Dihydroxy*-2α,4β,5α-*trimethyltetrahydrofuran*-2β-*yl*)-2-*methylpropenoate* **20**.—A solution of MCPBA (85%; 365 mg, 1.8 mmol) in dichloromethane (5 $cm^3$) was added to a stirred, ice-cooled solution of the unsaturated ester **18** (300 mg, 1.2 mmol) in dichloromethane (10 $cm^3$) and the mixture was then stirred at 0 °C for 3 h. Calcium hydroxide (100 mg) and sodium sulphate (200 mg) were added, and the mixture was filtered. The filtrate was then evaporated under reduced pressure to give a 2:3 mixture of diastereoisomeric α- (**19**) and β-(**9**) epoxides (275 mg, 88%) as an oil, which was used without further purification.

A solution of the mixture of epoxides (200 mg, 0.78 mmol) and PTSA (100 mg, 0.5 mmol) in dichloromethane (15 $cm^3$) was stirred at room temperature for 0.5 h. The mixture was adsorbed onto silica Woelm, and purified by chromatography on Silica G with (2:1) diethyl ether–light petroleum (b.p. 40–60 °C) as eluent to give (i) the 'natural' *tetrahydrofuran* **10** (41 mg, 21%) as an oil; $\lambda_{max}$(EtOH)/nm 224; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3400, 1700 and 1645; $\delta_H$ 1.19 (d, *J* 6.5, *Me*CH), 1.22 (Me), 1.29 (t, *J* 7.5, *Me*C$H_2$O), 1.36 (Me), 1.97 (d, *J* 1.5, *Me*C=CH), 2.18 (br, CHO*H*), 3.82 (q, *J* 6.5, MeC*H*), 3.96 (br, C*H*OH), 4.18 (br q, *J* 7.5, MeC$H_2$O) and 6.97 (q, *J* 1.5, MeC=C*H*); $\delta_C$ 12.3 (Me), 13.5 (Me), 14.3 (Me), 17.9 (Me), 20.3 (Me), 61.0 ($CH_2$), 77.9 (CH), 80.6, 84.1, 85.3 (CH), 127.1, 147.6 (CH) and 168.8 (Found: $M^+$, 258.1466. $C_{13}H_{22}O_5$ requires M, 258.1467); and (ii) the 'isomeric' *tetrahydrofuran* **20** (65 mg, 33%) as an oil; $\lambda_{max}$(EtOH)/nm 220; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3530, 1700 and 1640; $\delta_H$ 1.22 (Me), 1.23 (d, *J* 6.5, *Me*CH), 1.29 (t, *J* 7, *Me*C$H_2$O), 1.31 (Me), 1.98 (d, *J* 1.5, *Me*C=CH), 2.96 (d, *J* 10, CHO*H*), 3.59 (q, *J* 6.5, MeC*H*), 3.85 (d, *J* 10, C*H*OH), 4.20 (br q, *J* 7, MeC$H_2$O) and 6.92 (q, *J* 1.5, MeC=C*H*); $\delta_C$ 12.6 (Me), 12.9 (Me), 14.3 (Me), 21.1 (Me), 21.7 (Me), 60.9 ($CH_2$), 77.6 (CH), 77.8, 83.1, 83.4 (CH), 128.5, 148.5 (CH) and 168.6 [Found: *m*/*z*, 259.1542. $C_{13}H_{22}O_5$ requires (M + H), 259.1546].

(E)-3-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropen*-1-*ol* **21**.—A solution of DIBAL in hexane (1 mol $dm^{-3}$; 12 $cm^3$, 12 mmol) was added dropwise to a stirred, ice-cooled solution of the ethyl ester **10**; R = Et (500 mg, 2.0 mmol) in dry dichloromethane (100 $cm^3$), and the mixture was then stirred under nitrogen at 0 °C for 1 h. Methanol (30 $cm^3$) and a little $MgSO_4$ were added, and the mixture was then stirred vigorously for 1.5 h. The mixture was filtered, and the filtrate was evaporated under reduced pressure to leave a residue, which was purified by chromatography on silica G with (25:2) chloroform–methanol as eluent to give the *allylic alcohol* **21** (260 mg, 60%) as a gum; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400; $\delta_H$ 1.16 (d, *J* 6.5, *Me*CH), 1.20 (Me), 1.32 (Me), 1.79 (d, *J* 1.2, *Me*C=CH), 2.22 (br, 3 × OH), 3.72 (q, *J* 6.5, MeC*H*), 3.92 (C*H*OH), 3.96 (br, $CH_2OH$) and 5.73 (m, MeC=C*H*); $\delta_C$ 12.5 (Me), 14.8 (Me), 18.0 (Me), 21.1 (Me), 68.4 ($CH_2$), 77.8 (CH), 81.2, 84.0, 85.7 (CH), 132.3 (CH) and 135.4 [Found: *m/z* 217, 201.1139 and 198.1234. $C_{11}H_{20}O_4$ requires (M + H), 217; (M − $CH_3$), 201.1127; (M − $H_2O$, 198.1256].

(E)-3-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-2-*methylpropenal* [(±)-Citreoviral] **3**.—A solution of the allylic alcohol **21** (50 mg, 0.23 mmol) in dichloromethane (20 $cm^3$) was stirred with activated manganese dioxide (500 mg) at room temperature for 1 h. The mixture was filtered, and the filtrate was then evaporated under reduced pressure to leave a residue, which was purified by chromatography on silica G with (6:1) diethyl ether–light petroleum (b.p. 40–60 °C) as eluent. Recrystallisation from hexane–chloroform gave (±)-citreoviral **3** (21 mg, 43%) as plates, m.p. 147–148 °C; $\lambda_{max}$(EtOH)/nm 225; $\nu_{max}(CHCl_3)/cm^{-1}$ 3560, 1685 and 1640; $\delta_H$ 1.21 (d, *J* 6.4, *Me*CH), 1.25 (Me), 1.41 (Me), 1.64 (br, OH), 1.87 (d, *J* 1.4, *Me*C=CH), 2.15 (d, *J* 5, CHO*H*), 3.88 (q, *J* 6.4, MeC*H*), 3.98 (d, *J* 5, C*H*OH), 6.69 (q, *J* 1.4, MeC=C*H*) and 9.36 (CHO); $\delta_C[(CD_3)_2CO]$ 10.1 (Me), 13.1 (Me), 19.5 (Me), 20.9 (Me), 79.5 (CH), 80.6, 85.3, 85.8 (CH), 136.4, 163.1 (CH) and 195.9 (Found: C, 61.6; H, 8.7%; $M^+$, 214.1214. Calc. for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5%; M, 214.1205).

(E)-3-(3α,4α-*Dihydroxy*-2α,4β,5α-*trimethyltetrahydrofuran*-2β-*yl*)-2-*methylpropen*-1-*ol* **22a**.—A solution of DIBAL in hexane (1 mol $dm^{-3}$; 0.72 $cm^3$, 0.72 mmol) was added dropwise to a stirred solution of the ethyl ester **20** (30 mg, 0.12 mmol) in dichloromethane (5 $cm^3$) at −75 °C, and the mixture was then stirred under nitrogen at −75 °C for 0.75 h. Methanol (2 $cm^3$) and a little $MgSO_4$ were added, and the mixture was stirred vigorously for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to leave a residue, which was purified by chromatography on Silica G using (8:1) diethyl ether–ethyl acetate as eluent to give the *allylic alcohol* **22a** (17 mg, 66%) as a gum; $\nu_{max}(CHCl_3)/cm^{-1}$ 3530 and 3410; $\delta_H$ 1.20 (d, *J* 6.3, *Me*CH), 1.21 (Me), 1.28 (Me), 1.79 (d, *J* 1, *Me*C=CH), 3.60 (q, *J* 6.3, MeC*H*), 3.84 (br, C*H*OH), 3.98 (br, $CH_2OH$), 5.65 (m, MeC=C*H*) [Found: *m/z* 201.1111 and 198.1290. $C_{11}H_{20}O_4$ requires (M − $CH_3$), 201.1127 and (M − $H_2O$), 198.1256].

(E)-3-(3α,4α-*Dihydroxy*-2α,4β,5α-*trimethyltetrahydrofuran*-2β-*yl*)-2-*methylpropenal* [(±)-*Iso* citreoviral] **22b**.—A solution of the allylic alcohol **22a** (10 mg, 0.05 mmol) in dichloromethane (5 $cm^3$) was stirred with activated manganese dioxide (100 mg) at room temperature for 3.5 h. The mixture was filtered, and the filtrate was then evaporated under reduced pressure to leave a residue, which was purified by column chromatography on Silica G with (2:1) diethyl ether–light petroleum (b.p. 40–60 °C) as eluent to give the *aldehyde* **22b** (4 mg, 40%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3540, 1685 and 1640; $\delta_H$ 1.23 (Me), 1.25 (d, *J* 6.4, *Me*CH), 1.36 (Me), 1.90 (d, J 1.3, *Me*C=CH), 2.95 (d, *J* 9.6, CHO*H*), 3.49 (br, OH), 3.62 (q, *J* 6.4, MeC*H*), 3.87 (d, *J* 9.6, C*H*OH), 6.60 (q, *J* 1.3, MeC=C*H*) and 9.38 (CHO) (Found: $M^+$, 214.1200. $C_{11}H_{18}O_4$ requires M, 214.1205).

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