Total Synthesis of Preaurovertin, Putative Biogenetic Precursor of Aurovertin. Biosynthetic Interrelationships between the Aurovertins, Citreoviridinols and Asteltoxin

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A number of complementary biomimetic approaches to the tetrahydrofuranyl portion of the dienal **13**, which was used in a synthesis of preaurovertin, are described. Epoxidation of the trienoate **31** produces largely the β-epoxide **32**, which on treatment with aqueous trifluoroacetic acid undergoes deacetalisation and concomitant cyclisation leading to compound **34**. After conversion of **34** into dienal **13**, a Wittig reaction with the ylide derived from the phosphonium salt **37** produces preaurovertin.

Preaurovertin is a putative biogenetic precursor of aurovertin found in *Calcarisporium arbuscula*. Citreoviridin produced by *Penicillium citreoviride* relates to preaurovertin, and the citreoviridinols are related structurally to aurovertin. In addition, aurovertin is related biogenetically to asteltoxin found in *Aspergillus stellatus*. These structural and biosynthetic interrelationships are considered alongside the synthetic work.

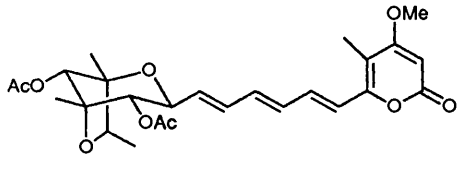
The aurovertins, exemplified by aurovertin A **1**, are a family of unusual polyenepyrone-substituted 2,6-dioxabicyclo[3.2.1]-octanes which are produced by the fungus *Calcarisporium arbuscula*.[1] They are related structurally, and show a similar biological profile, to the citreoviridinoid group of toxins (*e.g.*, citreoviridin **2**, citreoviridinol **3** and neocitreoviridinol **4** found in *Penicillium citreoviride*).[2] The aurovertins are extremely powerful inhibitors of mitochondrial ATP synthesis and hydrolysis. These properties have led to their frequent use in studies of the mechanisms of phosphate esterification and related reactions, and also in investigations of the structures of ATPase enzymes.[3] Asteltoxin **5**, which is found in *Aspergillus stellatus*, is also related structurally and biosynthetically to aurovertin A.[4] Furthermore, asteltoxin has been shown to have an inhibiting effect similar to that of compounds **1** and **2** on the activity of *E. coli* ATPase.

Although the citreoviridinols **3** and **4** co-occur with structurally related metabolites (*e.g.*, **2**), at this time no report has been made of the isolation of cometabolites related structurally to aurovertins **1** or to asteltoxin **5** from *C. arbuscula* and *A. stellatus*, respectively. It seems probable that the unusual 2,6-dioxabicyclo[3.2.1]octane ring system present in aurovertin A, and the novel bistetrahydrofuran unit in asteltoxin, are derived in Nature by cyclisation of a common 1,2; 3,4; 5,6-triepoxide intermediate, *viz.* **7**, produced by stepwise epoxidation of a pyrone-substituted triene precursor molecule, *i.e.* compound **6**.[5]

Thus, in the case of aurovertin A **1**, we can envisage an enzyme-mediated process involving electrophilic opening of the 5,6-epoxide ring in substrate **7** followed by trapping of the carbocation at C-6 by the oxygen of the adjacent 3,4-epoxide with simultaneous quenching (by water) of the incipient carbocation at C-4. This sequence might then lead to the tetrahydrofuranyl epoxide **8**, which by a second cyclisation, as shown, would create the 2,6-dioxabicyclo[3.2.1]octane ring system **9** in aurovertin (Scheme 1). The process need not occur in a stepwise fashion, of course, and may involve a cascade of cyclisations with the same overall outcome (see Scheme 2).† Whatever, it is interesting to note that the tetrahydrofuranyl epoxide **8** that is formed as a result of the first cyclisation, *viz.* **7** → **8**, is, in fact, an oxidised aurovertin analogue of citreoviridin **2**.

With asteltoxin **5** there is not such an obvious connection between the bistetrahydrofuranyl unit **11** and the triepoxide **7**. However, it is tempting to suggest that electrophilically induced (pinacol-type) rearrangement involving the 5,6-epoxide in compound **7** would lead initially to compound **10**, the branched aldehyde product of a 1,2-carbon shift. A double cyclisation involving the two remaining epoxides in compound **10** would then produce the required bistetrahydrofuran unit (Scheme 3);

† This proposition was first communicated by one of us at the Oxford Synthesis Meeting, July 1985. For biosynthetic investigations pertinent to the proposal, see ref. 5.



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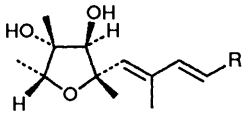

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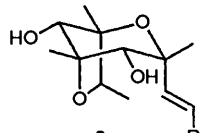

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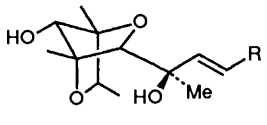

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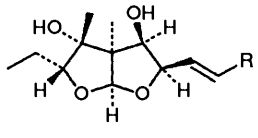

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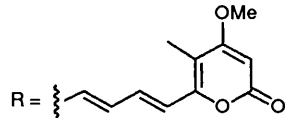
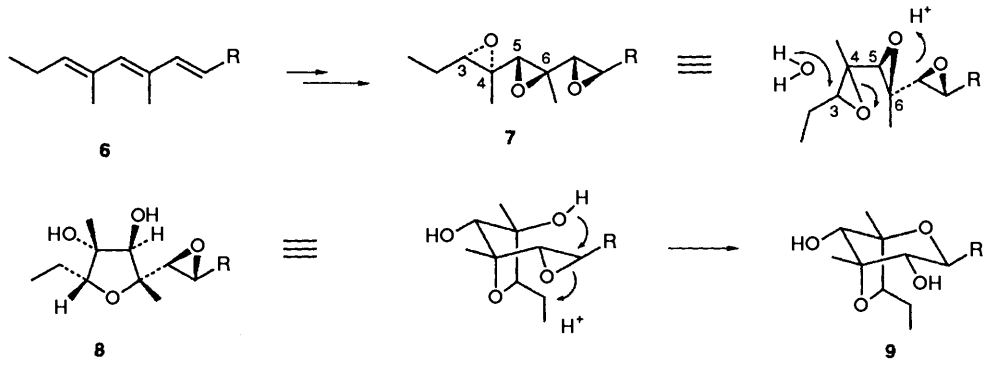
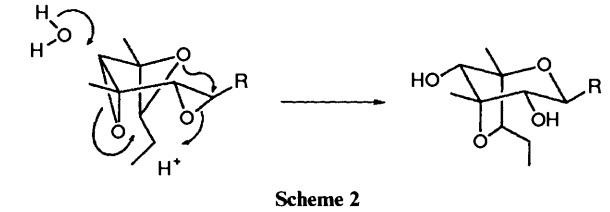
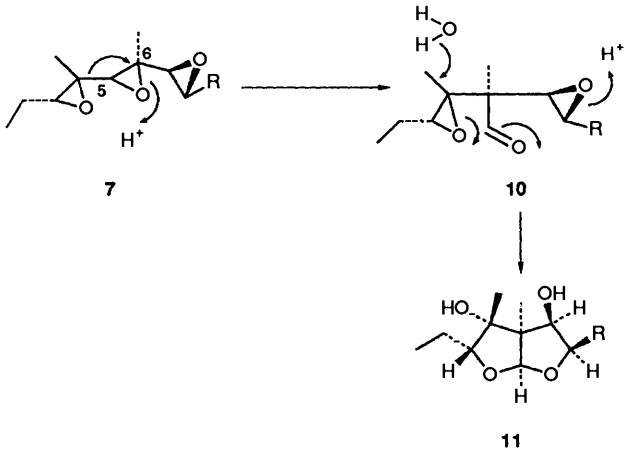




Scheme 1



Scheme 2



Scheme 3

a similar pinacol-type rearrangement has been invoked during the biosynthesis of the bistetrahydrofuran unit found in aflatoxin B_1.[6]

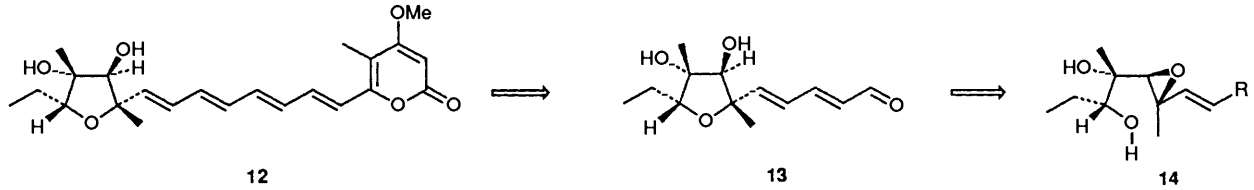
As a contribution to our understanding of: (i) the biosynthesis of aurovertin **1** and asteltoxin **5**, (ii) the involvement of epoxide intermediates and (iii) the biogenetic interrelationships between these natural products and the citreoviridinoids, *i.e.* **2–4**, we have modelled a number of possible epoxide cyclisation reactions in the laboratory.* In this paper, we demonstrate the use of epoxide intermediates in a synthesis of the tetrahydrofuran portion of the aurovertins, and describe a total synthesis of 'preaurovertin' **12**, a probable precursor of aurovertin A **1** in Nature. In the following paper we describe a synthesis of the novel 2,6-dioxabicyclo[3.2.1]octane system found in aurovertin A and in citreoviridinol **3**, which is based on the biogenetic models summarised in Schemes 1 and 2.

Our general strategy for a total synthesis of preaurovertin **12** relied on access to the tetrahydrofuranyl-substituted dienal **13**, the tetrahydrofuranyl portion of which we planned to elaborate by cyclisation of a key epoxy alcohol intermediate **14** under conditions of acid catalysis (Scheme 4). To this end a number of complementary synthetic routes towards intermediate **14** were investigated.

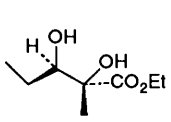
The aldehyde **16b** was first synthesized starting from (*E*)-ethyl 2-methylpent-2-enoate, following oxidation to the vicinal diol **15** by reaction with osmium tetraoxide–*N*-methylmorpholine *N*-oxide, acetonide formation, reduction to the primary alcohol **16a** with lithium aluminium hydride, and finally oxidation of the alcohol **16a** to aldehyde **16b** in the presence of pyridinium chlorochromate (PCC). A Wittig condensation between the aldehyde **16b** and ethoxycarbonylethylidene(triphenyl)phosphorane[7] next provided the *E*-unsaturated ester **17**, which by successive reduction ($LiAlH_4$) and oxidation (MnO_2) was then converted into the *E*-enal **18b**. A further Wittig reaction involving the *E*-enal **18b** and methoxycarbonylmethylene(triphenyl)phosphorane[7] eventually led to the *E,E*-dienoate **19** whose geometry followed conclusively from examination of high-field ^1H NMR data together with ^{13}C NMR shift data.[8]

Interaction between the acetonide derivative **19** and *m*-chloroperbenzoic acid (MCPBA) resulted in epoxidation of the most electron-rich, γ,δ-double bond to produce an inseparable 4:1 mixture of β and α epoxides, **20** and **21**, respectively. Treatment of this mixture of epoxides with 50% trifluoroacetic acid (TFA) at room temperature then resulted in simultaneous cleavage of the acetonide group and epoxy alcohol cyclisation, leading to a 4:1 mixture of the substituted tetrahydrofurans **22** and **23** which were easily separated by chromatography. The structures and stereochemistries of the tetrahydrofuran isomers **22** and **23** followed from comparative ^1H NMR spectral data, NOE experiments and comparison of their NMR data with those of the known citreoviridinoid analogues **24** and **25** produced in earlier work.[9] Interestingly, when the acetonide dienoate **19** was converted into the corresponding vicinal diol **26**, epoxidation was far less selective and led to a 2:1 mixture of β and α epoxides, which in turn produced a 2:1 mixture of

* For earlier related work see ref. 2.



Scheme 4



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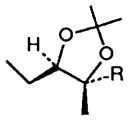

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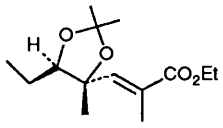

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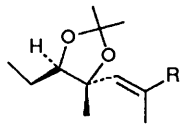

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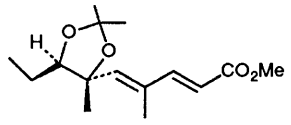

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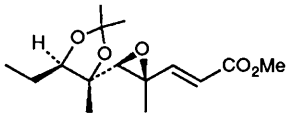
For **16,18** : **a**; R = CH_2OH **b**; R = CHO

the tetrahydrofurans **22** and **23**. Finally, a much more selective synthesis of compound **22** could be achieved starting from the primary alcohol **18a**. Epoxidation of this alcohol **18a** with MCPBA followed by oxidation to aldehyde **27**, Wittig reaction to enoate **20**, and finally acid-catalysed cyclisation led to compound **22** containing less than 8% of the isomer **23**. All this was to no avail however, since every attempt to convert the alcohol **28a** obtained from reduction of ester **22** into the corresponding aldehyde **28b** for the projected synthesis of preaurovertin (Scheme 4) met with failure.

We succeeded eventually in our objective to secure the dienal **13** by first preparing the all-*E*-trienoate **31** from reaction between the aldehyde **16b** and the phosphonate ester **30**.[10] Treatment of the trienoate **31** with one mol equiv. of MCPBA resulted in regioselective epoxidation of the most nucleophilic olefinic bond, leading to a 4:1 mixture of the β and α epoxides, **32** and **33**, respectively. The epoxides were not separated but instead the mixture was treated with aq. TFA which resulted in smooth deacetalisation and concomitant cyclisation of the resulting epoxy diol, leading to the desired tetrahydrofuranyl diene ester **34** and its isomer **35**. The structures assigned to compounds **34** and **35** followed conclusively from comparison of their NMR spectroscopic data with those of the model analogues **22** and **23**, respectively.

With the development of a stereoselective route to the 3,4-dihydroxytetrahydrofuranyl dienoate **34**, we next turned to its conversion into the dienal **13** and the reaction between compound **13** and the pyrone phosphonium salt **37**[11] produced from the known pyrone aldehyde **38** as summarised in Scheme 5. Reduction of the ester **34** with diisobutylaluminium hydride (DIBAL) first led to the corresponding primary alcohol **36**, which on oxidation with manganese dioxide was smoothly converted into the crystalline aldehyde **13**. A Wittig reaction between the ylide generated from the phosphonium salt **37** in the presence of butyllithium, and the aldehyde **13**, then led to a 3:2 mixture of *E* and *Z* stereoisomers of preaurovertin **12** which could be separated by chromatography. The major isomer was assigned the all-*E*-configuration **12** on the basis of an analysis of ^1H NMR and UV–visible absorption data, and



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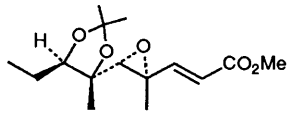

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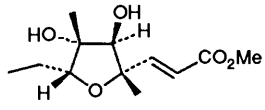

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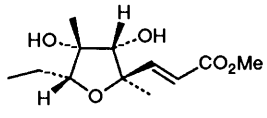

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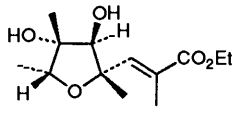

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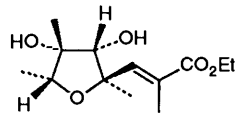

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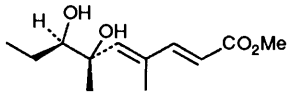

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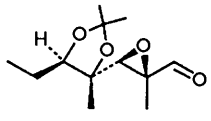

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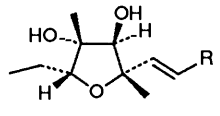
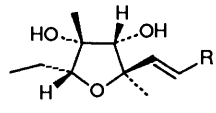
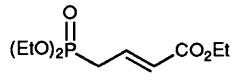




28 **a**; R = CH_2OH **b**; R = CHO 29



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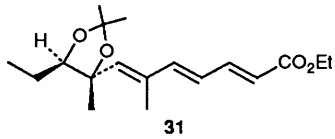

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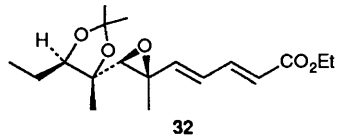

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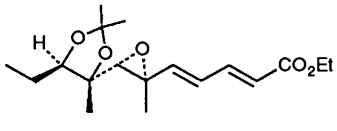

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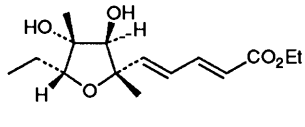

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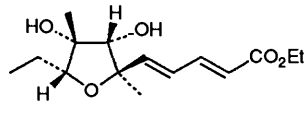

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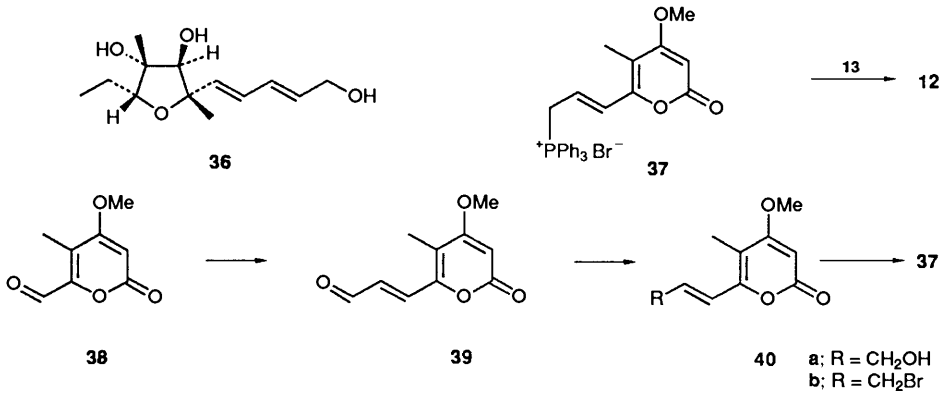
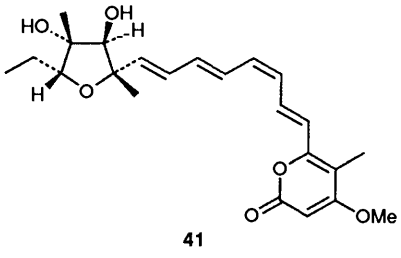


Scheme 5



comparison of these data with those of the closely related citreoviridin **2**.[12,*] The *Z*-configuration **41** was assigned to the minor isomer produced in the Wittig reaction, largely from examination of ^{1}H NMR data in conjunction with a 2D COSY spectrum.

Biological studies and biosynthetic work are now in progress to ascertain the status of preaurovertin **12** in the formation of aurovertin in *Calcarisporium arbuscula* and related micro-organisms.

Experimental

For general experimental details see ref. 13. Light petroleum refers to the fraction boiling in the range 40–60 °C.

(2RS,3SR)-*Ethyl* 2,3-*Dihydroxy*-2-*methylpentanoate* **15**.[14]—A solution of propionaldehyde (13.2 g, 0.23 mol) and 1-ethoxycarbonylethylidene(triphenyl)phosphorane (100 g, 0.27 mol) in dichloromethane (200 cm^3) was stirred at room temperature for 50 h. The mixture was evaporated under reduced pressure and the residue was then triturated with light petroleum. The light petroleum was evaporated off to leave a yellow liquid, which was purified by distillation to give (*E*)-ethyl 2-methylpent-2-enoate (23.6 g, 73%) as a liquid, b.p. 172–174 °C at 760 mmHg; λ_{max}(EtOH)/nm 217; ν_{max}(liq. film)/cm^{-1} 1715 and 1655; δ_H 1.05 (t, *J* 7, CH_2*Me*), 1.29 (t, *J* 7, OCH_2*Me*), 1.83 (d, *J* 1.4, MeC=), 2.19 (m, =CHCH_2Me), 4.19 (q, *J* 7, OCH_2Me) and 6.74 (tq, *J* 1.4 and 7, CH_3C=C*H*CH_2) (Found: M$^+$, 142.0993. Calc. for $C_8H_{14}O_2$: M, 142.0993).

A solution of (*E*)-ethyl 2-methylpent-2-enoate (23.6 g, 0.17 mol), *N*-methylmorpholine *N*-oxide (21.4 g, 0.18 mol), and osmium tetraoxide (0.1 g) in a mixture of acetone (200 cm^3), water (100 cm^3), and t-butyl alcohol (10 cm^3) was stirred at room temperature for 20 h. The acetone was removed by evaporation under reduced pressure, and the aq. residue was then extracted with ethyl acetate (3 × 100 cm^3). The combined extracts were dried, and then concentrated under reduced pressure to leave a liquid, which was purified by distillation to give the *diol* **15** (24.6 g, 84%) as a solid, b.p. 112–114 °C at 13 mmHg; m.p. 47–48 °C; ν_{max}(KBr disc)/cm^{-1} 3480 and 1730; δ_H 1.01 (t, *J* 7, CH_2*Me*), 1.30 (t, *J* 7, OCH_2*Me*), 1.33 (Me), 1.57 (m, CHCH_2Me), 3.62 [dd, *J* 3 and 9, C*H*(OH)Et] and 4.25 (q, *J* 7, OCH_2Me) [Found: C, 54.5; H, 9.1%; *m/z*, 177. $C_8H_{16}O_4$ requires C, 54.5; H, 9.1%; (*M* + H) 177].

(2RS,3RS)-2,3-*Isopropylidenedioxy*-2-*methylpentan*-1-*ol* **16a**.—A solution of ethyl 2,3-dihydroxy-2-methylpentanoate (10.3 g, 0.058 mol) and toluene-*p*-sulphonic acid (PTSA) (0.5 g) in 2,2-dimethoxypropane (250 cm^3) was stirred at room temperature for 20 h and then evaporated under reduced pressure to leave a brown liquid. Distillation gave (2RS,3RS)-*ethyl* 2,3-*isopropylidenedioxy*-2-*methylpentanoate* (12.1 g, 96%) as a liquid, b.p. 90–92 °C at 10 mmHg; ν_{max}(liq. film)/cm^{-1} 1750 and 1730; δ_H 1.03 (t, *J* 7, CH_2*Me*), 1.29 (t, *J* 7, OCH_2*Me*), 1.32 (Me), 1.40 (Me), 1.46 (Me), 1.63 (m, CHCH_2Me), 4.09 (dd, *J* 5 and 7, OC*H*Et) and 4.22 (q, *J* 7, OCH_2Me) [Found: *m/z*, 201.1127. $C_{11}H_{20}O_4$ requires (M − CH_3), 201.1127].

A solution of ethyl 2,3-isopropylidenedioxy-2-methylpentanoate (9.6 g, 0.044 mol) in dry diethyl ether (50 cm^3) was added dropwise during 0.25 h to a stirred suspension of lithium aluminium hydride (1.69 g, 0.044 mol) in dry diethyl ether (50 cm^3) maintained at 0–5 °C (ice-bath). The mixture was heated under reflux for 22 h, and then the cooled suspension was treated with water (1.6 cm^3), followed by 15% aq. sodium hydroxide (1.6 cm^3) and then with more water (4.8 cm^3). The solid was filtered off, and the filtrate was then dried and concentrated under reduced pressure to leave a liquid. Distillation gave the *alcohol* **16a** (6.8 g, 88%) as a liquid, b.p. 89–91 °C at 11 mmHg; ν_{max}(liq. film)/cm^{-1} 3460; δ_H 1.03 (t, *J* 7, CH_2*Me*), 1.05 (Me), 1.37 (Me), 1.44 (Me), 1.56 (m, CHCH_2Me), 2.66 (dd, *J* 5.5 and 7.6, CH_2O*H*), 3.47 (m, CH_2OH) and 3.93 (dd, *J* 5 and 8, OC*H*Et) [Found: *m/z*, 159.1008. $C_9H_{18}O_3$ requires (M − CH_3), 159.0995].

(2RS,3SR)-*Isopropylidenedioxy*-2-*methylpentanal* **16b**.—A solution of 2,3-isopropylidenedioxy-2-methylpentan-1-ol (12.3 g, 0.7 mol) in dichloromethane (100 cm^3) was added to a stirred suspension of PCC (22.8 g, 0.106 mol) and Celite (23 g) in dichloromethane (300 cm^3), and the mixture was then stirred at room temperature for 22 h. Evaporation under reduced pressure left a solid residue, which was taken up in diethyl ether and the mixture was filtered through a pad of Florisil. The filtrate was concentrated under reduced pressure to leave a liquid, which was purified by distillation to give the *aldehyde* **16b** (7.8 g, 65%) as a liquid, b.p. 72–74 °C at 12 mmHg; ν_{max}(liq. film)/cm^{-1} 2940, 2880 and 1735; δ_H 0.98 (t, *J* 7, CH_2*Me*), 1.18 (Me), 1.41 (Me), 1.48 (Me), 1.58 (m, CHCH_2Me), 3.94 (dd, *J* 5 and 8, OC*H*CH_2) and 9.60 (CHO) [Found: *m/z*, 157.0862. $C_9H_{16}O_3$ requires (M − CH_3), 157.0859].

* Citreoviridin was kindly supplied by Dr. R. Vleggaar, CSIR, S. Africa.

(2E,4RS,5RS)-*Ethyl* 4,5-*Isopropylidenedioxy*-2,4-*dimethylhept*-2-*enoate* **17**.—A solution of 2,3-isopropylidenedioxy-2-methylpentanal **16b** (11.5 g, 0.07 mol) and 1-ethoxycarbonylethylidene(triphenyl)phosphorane (28.7 g, 0.08 mol)[7] in dichloromethane (250 cm^3) was stirred at room temperature for 22 h. The mixture was evaporated under reduced pressure, and the residue was then triturated with light petroleum. The light petroleum was evaporated under reduced pressure to leave a liquid, which was purified by distillation to give the E-*unsaturated ester* **17** (11.7 g, 69%) as a liquid, b.p. 140–144 °C at 16 mmHg; λ_{max}(EtOH)/nm 216; ν_{max}(liq. film)/cm^{-1} 1712 and 1655; δ_H 1.06 (t, *J* 7, CH_2*Me*), 1.22 (Me), 1.29 (t, *J* 7 Hz, OCH_2CH_3), 1.35 (CH_3), 1.46 (CH_3), 1.59 (m, $CHCH_2$Me), 2.08 (d, *J* 1.4, HC=C*Me*), 3.80 (dd, *J* 5.6 and 7, OC*H*Et), 4.20 (q, *J* 7, OCH_2Me) and 6.61 (q, *J* 1.4, *H*C=CMe); δ_C 11.17 (Me), 13.08 (Me), 14.08 (Me), 21.48 (Me), 22.35 (CH_2), 26.02 (Me), 28.47 (Me), 60.56 (CH_2), 82.00, 83.73 (CH), 107.53, 129.02, 141.20 (CH) and 168.49 [Found: *m*/*z*, 241.1438. $C_{14}H_{24}O_4$ requires (M − CH_3), 241.1436].

(2E,4RS,5RS)-4,5-*Isopropylidenedioxy*-2,4-*dimethylhept*-2-*en*-1-*ol* **18a**.—A solution of (*E*)-ethyl 4,5-isopropylidenedioxy-2,4-dimethylhept-2-enoate (12.4 g, 0.05 mol) in dry diethyl ether (50 cm^3) was added dropwise during 0.3 h to a stirred suspension of lithium aluminium hydride (1.84 g, 0.05 mol) in dry diethyl ether (100 cm^3) maintained at 0–5 °C (ice-bath). The mixture was stirred at room temperature for 42 h and was then treated successively with water (2 cm^3), 15% aq. sodium hydroxide solution (2 cm^3), and again with water (6 cm^3). The solid was filtered off, and the filtrate was then dried and concentrated under reduced pressure to leave a liquid. Distillation gave the *alcohol* **18a** (10.1 g, 99%) as a liquid, b.p. 110–114 °C at 3 mmHg; ν_{max}(liq. film)/cm^{-1} 3400 and 1760; δ_H 1.03 (t, *J* 7, CH_2*Me*), 1.11 (Me), 1.36 (Me), 1.44 (Me), 1.56 (m, $CHCH_2$Me), 1.86 (d, *J* 1.3, HC=C*Me*), 2.08 (OH), 3.75 (dd, *J* 5.4 and 7.3, OC*H*Et), 3.96 (br s, CH_2OH) and 5.37 (q, *J* 1.3, C*H*=CMe) [Found: *m*/*z*, 199.1338. $C_{12}H_{22}O_3$ requires (M − CH_3), 199.1342].

(2E,4RS,5RS)-4,5-*Isopropylidenedioxy*-2,4-*dimethylhept*-2-*enal* **18b**.—A solution of (*E*)-4,5-isopropylidenedioxy-2,4-dimethylhept-2-en-1-ol (12.5 g, 0.06 mol) in dichloromethane (300 cm^3) was stirred with activated manganese dioxide (50.8 g, 0.58 mol) at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the filtrate was then evaporated under reduced pressure to leave a liquid. Distillation gave the *unsaturated aldehyde* **18b** (9.5 g, 77%) as a liquid, b.p. 134–136 °C at 18 mmHg; λ_{max}(EtOH)/nm 226; ν_{max}(liq. film)/cm^{-1} 2950, 2880, 1690 and 1640; δ_H 1.07 (t, *J* 7, CH_2*Me*), 1.29 (Me), 1.37 (Me), 1.47 (Me), 1.65 (m, $CHCH_2$Me), 1.97 (d, *J* 1.3, CH=CMe), 3.84 (dd, *J* 5 and 8, OC*H*Et), 6.27 (q, *J* 1.3, *H*C=CMe) and 9.38 (CHO) [Found: *m*/*z*, 197.1199. $C_{12}H_{20}O_3$ requires (M − CH_3), 197.1220].

(2E,4E,6RS,7RS)-*Methyl* 6,7-*Isopropylidenedioxy*-4,6-*dimethylnona*-2,4-*dienoate* **19**.—A solution of (*E*)-4,5-isopropylidenedioxy-2,4-dimethylhept-2-enal (3.8 g, 0.018 mol) and methoxycarbonylmethylene(triphenyl)phosphorane (7.2 g, 0.02 mol)[7] in dichloromethane (100 cm^3) was heated under reflux for 48 h. The dichloromethane was evaporated off under reduced pressure and the residue was then triturated with light petroleum to leave a liquid. Distillation gave the *diene ester* **19** (3.9 g, 80%) as a liquid, b.p. 140–142 °C at 13 mmHg; λ_{max}(EtOH)/nm 263; ν_{max}(liq. film)/cm^{-1} 1720 and 1625; δ_H 1.05 (t, *J* 7, CH_2*Me*), 1.23 (Me), 1.34 (Me), 1.45 (Me), 1.59 (m, $CHCH_2$Me), 2.04 (d, *J* 1.1, HC=C*Me*), 3.74 (OMe), 3.75 (dd, *J* 5.2 and 7.4, OC*H*Et), 5.77 (*H*C=CMe), 5.88 (d, *J* 15.6, HC=C*H*CO_2Me) and 7.28 (d, *J* 15.6, *H*C=C*H*CO_2Me); δ_C 11.35 (Me), 12.99 (Me), 22.15 (Me), 22.55 (CH_2), 26.34 (Me), 28.68 (Me), 51.47 (Me), 82.22, 84.34 (CH), 107.69, 116.76 (CH), 134.14, 141.94 (CH), 150.51 (CH) and 167.69 [Found: *m*/*z*, 253.1439. $C_{15}H_{24}O_4$ requires (M − CH_3), 253.1439].

(2E,4RS,5SR,6SR,7RS)- *and* (2E,4RS,5SR,6RS,7SR)-*Methyl* 4,5-*Epoxy*-6,7-*isopropylidenedioxy*-4,6-*dimethylnon*-2-*enoate* **20** *and* **21**.—A solution of MCPBA (2.5 g, 0.014 mol) in dichloromethane (25 cm^3) was added to a stirred solution of compound **19** (3.5 g, 0.01 mol) in dichloromethane (100 cm^3) and the mixture was then stirred at room temperature for 22 h. Calcium hydroxide (1 g) and sodium sulphate (2 g) were added and the mixture was then stirred at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave an oil. Column chromatography, with (2:1) light petroleum–diethyl ether as eluent, gave a mixture of diastereoisomeric epoxides (2.53 g, 68%) as an oil, λ_{max}(EtOH)/nm 218; ν_{max}(liq. film)/cm^{-1} 1720, 1655 and 1620; δ_H 1.08 (t, *J* 7, CH_2*Me*), 1.12 (Me), 1.35 (Me), 1.42 (Me), 1.49 (m, $CHCH_2$Me), 1.63 and 1.68 (each s, together OCMe), 2.61 and 2.77 (each s, together OCH), 3.74 (OMe), 4.02 (dd, *J* 4.8 and 8, OC*H*Et), 6.01 (d, *J* 15.7, CH=C*H*CO_2Me) and 6.78 (d, *J* 15.7, C*H*=CHCO_2Me) [Found: *m*/*z*, 269.1390. $C_{15}H_{24}O_5$ requires (M − CH_3), 269.1392].

(E)-*Methyl* 3-(5α-*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)*propenoate* **22** *and* (E)-*Methyl* 3-(5α-*Ethyl*-3α,4α-*dihydroxy*-2α,4β-*dimethyltetrahydrofuran*-2β-*yl*)*propenoate* **23**.—(a) *From the acetonide epoxides* **20** *and* **21**. Aq. TFA (50%; 30 cm^3) was added to a mixture of diastereoisomeric epoxides **20** and **21** (9.27 g, 9.5 × 10^{-4} mol) and the mixture was then stirred at room temperature for 3 days. The mixture was neutralised with saturated aq. sodium hydrogen carbonate and was then extracted with diethyl ether (4 × 15 cm^3). The combined extracts were dried and concentrated to leave an orange oil, which was purified by column chromatography, with (2:1) diethyl ether–light petroleum as eluent, to give (i) the 'natural' *tetrahydrofuran* **22** (0.073 g, 36%) as an oil, λ_{max}(EtOH)/nm 218; ν_{max}(liq. film)/cm^{-1} 3520, 1720 and 1655; δ_H 1.06 (t, *J* 7, CH_2*Me*), 1.24 (Me), 1.30 (Me), 1.57 (m, $CHCH_2$Me), 3.69 (dd, *J* 5.2 and 6.0, OC*H*Et), 3.74 (OMe), 3.83 (C*H*OH), 6.13 (d, *J* 15.6, HC=C*H*CO_2Me) and 7.12 (d, *J* 15.6, *H*C=CHCO_2Me). Irradiation at δ 3.83 gave nuclear Overhauser enhancements at δ 6.13 (3.4%) and at δ 7.12 (9%); δ_C 10.97 (Me), 18.51 (Me), 20.17 (Me), 20.92 (CH_2), 51.46 (Me), 81.22, 82.88, 84.17 (CH), 84.60 (CH), 117.56 (CH), 153.86 (CH) and 167.13 (Found: M^+, 244.1314. $C_{12}H_{20}O_5$ requires M, 244.1317); and (ii) the isomeric *tetrahydrofuran* **23** (0.021 g, 10%) as a solid, m.p. 78–79 °C; λ_{max}(EtOH)/nm 212; ν_{max}(KBr)/cm^{-1} 3400, 1720 and 1650; δ_H 1.08 (t, *J* 7, CH_2*Me*), 1.22 (Me), 1.28 (Me), 1.61 (m, $CHCH_2$Me), 3.39 (t, *J* 6.4, OC*H*Et), 3.75 (OMe), 3.76 (C*H*OH), 6.02 (d, *J* 15.6, HC=C*H*CO_2Me) and 6.98 (d, *J* 15.6, *H*C=CHCO_2Me); δ_C 10.67 (Me), 21.09 (CH_2), 21.31 (Me), 21.57 (Me), 51.40 (Me), 78.04, 81.45, 81.73 (CH), 83.30 (CH), 117.06 (CH), 152.47 (CH) and 167.13 [Found: *m*/*z*, 226.1189. $C_{12}H_{20}O_5$ requires (M − H_2O), 226.1174].

(b) *From the diol dienoate* **26**. A solution of MCPBA (0.13 g, 7.25 × 10^{-4} mol) in dichloromethane (10 cm^3) was added to a stirred solution of (*E*,*E*)-methyl 6,7-dihydroxy-4,6-dimethylnona-2,4-dienoate **26** (0.15 g, 6.59 × 10^{-4} mol) in dichloromethane (10 cm^3) and the mixture was then stirred at room temperature for 17 h. Calcium hydroxide (0.1 g) and sodium sulphate (0.2 g) were added, and the mixture was then stirred at room temperature for 1 h. The mixture was filtered and the filtrate was then concentrated under reduced pressure to give an oil. Column chromatography, with (2:1) diethyl ether–light

petroleum as eluent, gave a mixture of diastereoisomers of (2*E*,4*RS*,5*SR*,6*SR*,7*RS*)-methyl 4,5-epoxy-6,7-dihydroxy-4,6-dimethylnon-2-enoates (0.12 g, 75%) as an oil, λ_{max}(EtOH)/nm 219; ν_{max}(liq. film)/cm^{-1} 3460, 1710 and 1650; δ_H 1.04 (t, *J* 7, CH_2*Me*), 1.32 (Me), 1.47 (m, CHCH_2Me), 1.68 (Me), 2.25 (OH), 2.51 (OH), 2.75 and 2.91 (each s, together OCH), 3.52 (m, OC*H*Et), 3.74 (OMe), 6.01 (dd, *J* 1.1 and 15.6, HC=C*H*CO_2Me) and 6.76 (d, *J* 15.6, C*H*=CHCO_2Me) [Found: *m/z*, 226.1205. $C_{12}H_{20}O_5$ requires (M − H_2O), 226.1205].

A solution of the mixture of diastereoisomeric epoxides **20**/**21** (0.086 g, 3.5 × 10^{-4} mol) and PTSA (0.1 g, 5.3 × 10^{-4} mol) in dichloromethane (10 cm^3) was stirred at room temperature for 1 h. The mixture was adsorbed onto silica Woelm and was purified by column chromatography, with (2:1) diethyl ether–light petroleum as eluent, to give: (i) the 'natural' tetrahydrofuran **22** (0.02 g, 23%), and (ii) the isomeric tetrahydrofuran **23** (0.032 g, 36%). The tetrahydrofurans showed identical spectroscopic data with those summarised under (a).

(c) *From the acetonide epoxide* **20**. Treatment of the acetonide epoxide **20** derived from compound **27** with TFA, according to the procedure described under (a), led to a 12:1 mixture (75%) of the isomeric tetrahydrofurans **22** and **23**.

(2E,4E,6RS,7RS)-*Methyl* 6,7-*Dihydroxy*-4,6-*dimethylnona*-2,4-*dienoate* **26**.—A solution of compound **19** (0.49 g, 1.82 × 10^{-3} mol) in a mixture of methanol (100 cm^3) and water (50 cm^3) was stirred with Amberlyst IR 120 acidic resin (0.5 g) at 50 °C for 3 days. The resin was filtered off and the filtrate was then evaporated under reduced pressure to remove the methanol. The resulting aq. layer was extracted with dichloromethane (3 × 25 cm^3) and the combined extracts were then dried and concentrated to leave an oil. Column chromatography, with (1:1) diethyl ether–light petroleum as eluent, followed by crystallisation from diethyl ether–light petroleum, gave the *diol* **26** (0.23 g, 56%) as a solid, m.p. 68–71 °C; λ_{max}(EtOH)/nm 270; ν_{max}(KBr disc)/cm^{-1} 3460, 1695 and 1620; δ_H 1.00 (t, *J* 7, CH_2*Me*), 1.31 (Me), 1.52 (m, CHCH_2Me), 2.04 (d, *J* 1.1, HC=C*Me*), 2.92 (2 × OH), 3.49 (dd, *J* 3.7 and 9.2, OC*H*Et), 3.74 (OMe), 5.88 (*H*C=CMe), 5.86 (d, *J* 15.7, HC=C*H*CO_2Me) and 7.28 (d, *J* 15.7, *H*C=CHCO_2Me) [Found: *m/z*, 229.1349. $C_{12}H_{20}O_4$ requires (M + H), 229.1258].

(2RS,3SR,4RS,5SR)-2,3-*Epoxy*-4,5-*isopropylidenedioxy*-2,4-*dimethylheptanal* **27**.—A solution of MCPBA (2.7 g, 0.06 mol) in dichloromethane (25 cm^3) was added to a stirred solution of compound **18a** (2.8 g, 0.01 mol) in dichloromethane (50 cm^3) at 0 °C (ice-bath) and the mixture was then stirred at 0 °C for 2 h. Calcium hydroxide (0.5 g) and sodium sulphate (1 g) were added, and the mixture was then stirred for 1 h while attaining room temperature. The mixture was then filtered and the filtrate was then concentrated under reduced pressure to give an oil. Column chromatography, with (2:1) diethyl ether–light petroleum as eluent, gave (2RS,3SR,4SR,5RS)-2,3-epoxy-4,5-isopropylidenedioxy-2,4-dimethylheptan-1-ol (2.37 g, 97%) as a liquid, ν_{max}(liq. film)/cm^{-1} 3450; δ_H 1.08 (t, *J* 7, CH_2*Me*), 1.11 (Me), 1.34 (Me), 1.41 (Me), 1.51 (Me), 1.59 (m, CHCH_2Me), 1.81 (OH), 2.87 (OCH), 3.61 (CH_2OH) and 4.02 (dd, *J* 4.9 and 7.7, OC*H*Et) [Found: *m/z*, 215.1281. $C_{12}H_{22}O_4$ requires (M − CH_3), 215.1279].

A solution of 2,3-epoxy-4,5-isopropylidenedioxy-2,4-dimethylheptan-1-ol (0.41 g, 1.78 × 10^{-3} mol) in dichloromethane (10 cm^3) was added to a stirred suspension of PCC (0.58 g, 2.67 × 10^{-3} mol) and Celite (0.6 g) in dichloromethane (50 cm^3), and the mixture was then stirred at room temperature for 16 h. The dichloromethane was evaporated off under reduced pressure to leave a solid, which was taken up in diethyl ether and the mixture was filtered through Florisil. The filtrate was concentrated under reduced pressure to leave a sticky solid, which was purified by column chromatography, with (2:1) light petroleum–diethyl ether as eluent, to give the *aldehyde* **27** (0.31 g, 77%) as a solid, m.p. 58–59 °C (from diethyl ether–light petroleum); ν_{max}(KBr)/cm^{-1} 2940, 2880 and 1725; δ_H 1.12 (t, *J* 7, CH_2*Me*), 1.12 (Me), 1.35 (Me), 1.41 (Me), 1.53 (m, CHCH_2Me), 1.63 (Me), 2.91 (OCH), 4.09 (dd, *J* 5.0 and 7.8, OC*H*Et) and 8.86 (CHO) [Found: *m/z*, 213.1107. $C_{12}H_{20}O_4$ requires (M − CH_3), 213.1127].

(2E,4RS,5SR)-*Methyl* 4,5-*Epoxy*-6,7-*isopropylidenedioxy*-4,6-*dimethylnon*-2-*enoate* **20**.—A solution of 2,3-epoxy-4,5-isopropylidenedioxy-2,4-dimethylheptanal **27** (0.24 g, 1.04 × 10^{-3} mol) and methoxycarbonylmethylene(triphenyl)phosphorane (0.70 g, 2.08 × 10^{-3} mol) in benzene (50 cm^3) was heated to reflux for 20 h. The benzene was evaporated off under reduced pressure and the residue was then triturated with light petroleum to leave an oil. Column chromatography, with (2:1) diethyl ether–light petroleum as eluent, gave the ester **20** (0.26 g, 87%) as a liquid, λ_{max}(EtOH)/nm 218; ν_{max}(liq. film)/cm^{-1} 1725 and 1655; δ_H 1.08 (t, *J* 7, CH_2*Me*), 1.12 (Me), 1.34 (Me), 1.41 (Me), 1.60 (m, CHCH_2Me), 1.68 (Me), 2.61 (CHO), 3.74 (OMe), 4.02 (dd, *J* 4.7 and 7.9, OC*H*CH_2), 6.01 (d, *J* 15.7, CH=C*H*CO_2Me) and 6.73 (d, *J* 15.7, C*H*=CHCO_2Me); δ_C 11.11 (Me), 14.66 (Me), 19.08 (Me), 22.21 (CH_2), 25.53 (Me), 28.31 (Me), 51.31 (Me), 59.47, 66.68 (CH), 79.06, 81.89 (CH), 107.65, 120.79 (CH), 149.99 (CH) and 166.20 [Found: *m/z*, 269.1367. $C_{15}H_{24}O_5$ requires (M − CH_3), 269.1405].

(E)-3-(5α-*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)*prop*-2-*en*-1-*ol* **28a**.—A solution of DIBAL in hexanes (1 mol dm^{-3}; 3.9 cm^3, 3.87 × 10^{-3} mol) was added dropwise during 5 min to a stirred solution of the methyl ester **22** (0.19 g, 7.74 × 10^{-4} mol) in dichloromethane (50 cm^3) at 0 °C, and the mixture was then stirred at 0 °C for 1 h. Methanol (10 cm^3) and a small quantity of magnesium sulphate were added, and the mixture was then stirred for 1 h, during which time it attained room temperature. The mixture was then filtered and the filtrate was concentrated under reduced pressure to leave an oil. Column chromatography, with (2:1) diethyl ether–light petroleum as eluent, gave the *alcohol* **28a** (0.11 g, 64%) as an oil, ν_{max}(liq. film)/cm^{-1} 3450 and 1660; δ_H 1.03 (t, *J* 7.5, CH_2*Me*), 1.21 (Me), 1.24 (Me), 1.56 (m, CHCH_2Me), 2.94 (OH), 3.34 (OH), 3.62 (t, *J* 6.3, OC*H*Et), 3.77 (C*H*OH), 3.98 (OH), 4.11 (d, *J* 3.5, =CHCH_2OH), 5.89 (m, CH=C*H*CH_2OH) and 5.92 (d, *J* 15.7, C*H*=CHCH_2OH) [Found: *m/z*, 198.1251. $C_{11}H_{20}O_4$ requires (M − H_2O), 198.1251].

A similar reduction of the isomeric methyl ester **23** with DIBAL produced the *isomeric alcohol* **29a** as an oil, ν_{max}(liq. film)/cm^{-1} 3400 and 1660; δ_H 0.99 (t, *J* 7.5, CH_2*Me*), 1.16 (Me), 1.18 (Me), 1.53 (m, CHCH_2Me), 2.17 (2 × OH), 3.08 (OH), 3.35 (dd, *J* 4.7 and 8.2, OC*H*CH_2), 3.68 (C*H*OH), 4.09 (d, *J* 4.6, =CHCH_2OH), 5.70 (d, *J* 15.8, C*H*=CHCH_2OH) and 5.76 (dt, *J* 4.6 and 15.8, CH=C*H*CH_2OH) [Found: *m/z*, 198.1253. $C_{11}H_{20}O_4$ requires (M − H_2O), 198.1251].

Oxidation of the alcohol **29a** with manganese dioxide in dichloromethane then provided the *aldehyde* **29b** (30%) as an oil, ν_{max}(liq. film)/cm^{-1} 1690 and 1640; δ_H 1.08 (t, *J* 7, CH_2*Me*), 1.25 (Me), 1.33 (Me), 1.61 (m, CHCH_2Me), 1.84 (OH), 2.38 (OH), 3.40 (dd, *J* 5.2 and 7.5, OC*H*Et), 3.77 (C*H*OH), 6.23 (dd, *J* 7.8 and 15.5, HC=C*H*CHO), 6.84 (d, *J* 15.5, C*H*=CHCHO) and 9.59 (d, *J* 7.8, HC=CHC*H*O) (Found: M^+, 214.1180. $C_{11}H_{18}O_4$ requires M, 214.1156). All attempts to oxidise the alcohol **28a** to the corresponding aldehyde **28b** failed, and gave only products resulting from oxidative decomposition.

(E,E,8RS,9RS)-*Ethyl* 8,9-*Isopropylidenedioxy*-6,8-*dimethyl*-*undeca*-2,4,6-*trienoate* **31**.—A solution of triethyl phosphonocrotonate **30** (0.35 g, 1.42 × 10^{-3} mol)[10] in dry tetrahydrofuran (THF) (5 cm^3) was added during 0.2 h to a stirred suspension of sodium hydride (0.034 g, 1.42 × 10^{-3} mol) in dry THF (10 cm^3), maintained at 0–5 °C (ice-bath), and the mixture was then stirred at 0 °C for 0.5 h. A solution of the aldehyde **18b** (0.10 g, 4.72 × 10^{-4} mol) in dry THF (10 cm^3) was added dropwise during 0.2 h, and the mixture was then stirred at 0 °C for 2 h. The solvent was evaporated off under reduced pressure and the residue was then taken up in diethyl ether–water. The separated aq. layer was extracted with diethyl ether (3 × 50 cm^3), and the combined extracts were then dried and concentrated under reduced pressure to leave a yellow oil. The residue was purified by column chromatography, with (2:1) light petroleum–diethyl ether as eluent, to give the *all*-E-*triene esters* **31** (0.96 g, 66%) as a pale yellow oil, λ_{max}(EtOH)/nm 300; ν_{max}(liq. film)/cm^{-1} 3040, 1710 and 1615; δ_H 1.05 (t, *J* 7, CH_2*Me*), 1.23 (Me), 1.29 (t, *J* 7, OCH_2*Me*), 1.35 (Me), 1.46 (Me), 1.52 (m, $CHCH_2$Me), 2.04 (d, *J* 1, HC=C*Me*), 3.78 (dd, *J* 4 and 9, OC*H*Et), 4.2 (q, *J* 7, OCH_2Me), 5.58 (*H*C=CMe), 5.89 (d, *J* 15.2, MeCC*H*=CH), 6.33 (dd, *J* 11.1 and 15.2, MeCCH=C*H*CH=), 6.52 (d, *J* 15.3, CH=C*H*CO_2Et) and 7.33 (dd, *J* 11.1 and 15.3, =CHC*H*=CHCO$_2$Et); δ_C 11.40 (Me), 13.11 (Me), 14.33 (Me), 22.36 (Me), 22.49 (CH_2), 26.41 (Me), 28.70 (Me), 60.22 (CH_2), 82.19, 84.42 (CH), 107.54, 120.56 (CH), 125.18 (CH), 135.36, 138.36 (CH), 144.87 (CH), 146.29 (CH) and 167.18 [Found: *m*/*z*, 293.1733. $C_{18}H_{28}O_4$ requires (M − CH_3), 293.1753].

(E,E)-*Ethyl* 5-(5α-*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)*penta*-2,4-*dienoate* **34** *and* (E,E)-*Ethyl*-5-(5α-*Ethyl*-3α,4α-*dihydroxy*-2α,4β-*dimethyltetrahydrofuran*-2β-*yl*)-*penta*-2,4-*dienoate* **35**.—A solution of MCPBA (4.0 g, 0.023 mol) in dichloromethane (50 cm^3) was added to a stirred solution of the unsaturated ester **31** (7.2 g, 0.023 mol) in dichloromethane (300 cm^3), and the mixture was then stirred at room temperature for 18 h. Calcium hydroxide (1 g) and sodium sulphate (2 g) were added, and the mixture was then stirred at room temperature for 1 h. The mixture was filtered, and the filtrate was then concentrated under reduced pressure to give a 4:1 mixture of diastereoisomeric epoxides **32** and **33** (5.7 g, 76%) as a yellow oil, which was used without further purification.

Aq. TFA (500 cm^3) was added to the mixture of epoxides (5.60 g, 0.017 mol), and the mixture was then stirred at room temperature for 1 h, neutralised with saturated aq. sodium hydrogencarbonate and extracted with diethyl ether (4 × 100 cm^3). The combined extracts were dried, and concentrated under reduced pressure to leave an orange oil, which was purified by column chromatography, with (1:1) diethyl ether–light petroleum as eluent, to give: (i) the *'natural' tetrahydrofuran* **34** (1.14 g, 23%) as a yellow oil, λ_{max}(EtOH)/nm 265; ν_{max}(liq. film)/cm^{-1} 3430, 1690, 1635 and 1615; δ_H 1.07 (t, *J* 7, CH_2*Me*), 1.24 (Me), 1.25 (t, *J* 7, OCH_2*Me*), 1.30 (Me), 1.58 (m, $CHCH_2$Me), 3.69 (t, *J* 6.8, OC*H*Et), 3.81 (C*H*OH), 4.20 (q, *J* 7, OCH_2Me), 5.90 (d, *J* 15.4, CH=C*H*CO_2Et), 6.30 (d, *J* 15.2, MeCC*H*=CH), 6.49 (dd, *J* 10.9 and 15.2, MeCCH=C*H*CH=) and 7.26 (dd, *J* 10.9 and 15.4, =CHC*H*=CHCO$_2$Et) (Found: M^+, 284.1619. $C_{15}H_{24}O_5$ requires M, 284.1616); and (ii) the *'isomeric' tetrahydrofuran* **35** (0.29 g, 6%) as a yellow oil, λ_{max}(EtOH)/nm 265; ν_{max}(liq. film)/cm^{-1} 3430, 1690, 1637 and 1615; δ_H 1.10 (t, *J* 7, CH_2*Me*), 1.21 (Me), 1.29 (t, *J* 7, OCH_2*Me*), 1.46 (Me), 1.61 (m, $CHCH_2$Me), 3.52 (dd, *J* 5 and 8, OC*H*Et), 3.81 (C*H*OH), 4.20 (q, *J* 7, OCH_2Me), 5.90 (d, *J* 15.5, CH=C*H*CO_2Et), 6.19 [d, *J* 15.4, (O)C*H*=CH], 6.46 [dd, *J* 11.1 and 15.4, (O)CH=C*H*CH] and 7.33 (dd, *J* 11.1 and 15.5, =CHC*H*=CHCO$_2$Et) (Found: M^+, 284.1619. $C_{15}H_{24}O_5$ requires M, 284.1616).

(E,E)-5-(5α-*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)*penta*-2,4-*dien*-1-*ol* **36**.—A solution of DIBAL in hexane (1.0 mol dm^{-3}; 6.79 cm^3, 6.79 × 10^{-3} mol) was added dropwise during 10 min to a stirred solution of the ethyl ester **34** (0.39 g, 1.36 × 10^{-3} mol) in dichloromethane (50 cm^3) at 0 °C, and the mixture was then stirred at 0 °C for 1 h. Methanol (25 cm^3) and a quantity of magnesium sulphate were added, and the mixture was then stirred and allowed to warm to room temperature during 1 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure to leave a solid. Column chromatography, with (5:1) diethyl ether–light petroleum as eluent, gave the *alcohol* **36** (0.19 g, 58%) as a sticky solid, m.p. 93–94 °C (from diethyl ether–light petroleum); λ_{max}(EtOH)/nm 234; ν_{max}(KBr disc)/cm^{-1} 3400 and 1660; δ_H 1.07 (t, *J* 7, CH_2*Me*), 1.23 (Me), 1.28 (Me), 1.58 (m, $CHCH_2$Me), 1.70 (OH), 1.86 (OH), 1.99 (OH), 3.69 (dd, *J* 5.7 and 7.2, OC*H*Et), 3.78 (C*H*OH), 4.18 (d, *J* 5.2, =CHCH_2OH), 5.86 (dt, *J* 5.2 and 15.1, CH=C*H*CH_2OH), 5.90 [d, *J* 15.1, C(O)C*H*=CH], 6.25 (dd, *J* 10.5 and 15.1, CH=C*H*CH) and 6.41 (dd, *J* 10.5 and 15.1, CH=C*H*CH) [Found: *m*/*z*, 224.1398. $C_{13}H_{22}O_4$ requires (M − H_2O), 224.1384].

(E,E)-5-(5α,*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)*penta*-2,4-*dienal* **13**.—A mixture of the alcohol **36** (0.16 g, 6.69 × 10^{-4} mol) and activated manganese dioxide (0.58 g, 6.69 × 10^{-3} mol) in dichloromethane (30 cm^3) was stirred at room temperature for 1 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to leave a solid. Column chromatography, with (4:1) diethyl ether–light petroleum as eluent, gave the aldehyde **13** (0.1 g, 60%) as a solid, m.p. 116–120 °C (from diethyl ether–light petroleum); λ_{max}(EtOH)/nm 279; ν_{max}(KBr disc)/cm^{-1} 3470, 2880, 2840, 2760, 1665 and 1635; δ_H 1.08 (t, *J* 7.5, CH_2*Me*), 1.26 (Me), 1.33 (Me), 1.59 (m, $CHCH_2$Me), 3.70 (dd, *J* 5.6 and 7.3, OC*H*Et), 3.84 (C*H*OH), 6.17 (dd, *J* 7.8 and 15.2, CH=C*H*CHO), 6.44 [d, *J* 15.2, C(O)C*H*=CH], 6.62 [dd, *J* 10.6 and 15.2, C(O)CH=C*H*CH], 7.10 (dd, *J* 10.6 and 15.2, CHC*H*=CHCHO) and 9.55 (d, *J* 5.8, =CHC*H*O) (Found: M^+, 240.1349. $C_{13}H_{20}O_4$ requires M, 240.1338).

(E)-3-(4-*Methoxy*-5-*methyl*-2-*oxo*-2H-*pyran*-6-*yl*)*propenal* [*Secocitreoviridin*] **39**.—A solution of 4-methoxy-5-methyl-2-oxo-2H-pyran-6-carbaldehyde (0.02 g, 1.18 × 10^{-4} mol) and formylmethylene(triphenyl)phosphorane (0.034 g, 1.12 × 10^{-4} mol) in dry benzene (10 cm^3) was heated at reflux for 4 h. The benzene was evaporated under reduced pressure and the residue was then purified by column chromatography followed by preparative TLC (PLC), with (20:1) dichloromethane–methanol as solvent. Recrystallisation from methanol gave secocitreoviridin **39** (0.019 g, 86%) as pale yellow needles, m.p. 209–212 °C (decomp.) [lit.,[11] 207 °C (decomp.)]; λ_{max}(EtOH)/nm 238 and 335; ν_{max}(KBr disc)/cm^{-1} 1710, 1665 and 1600; δ_H 2.16 (Me), 3.94 (OMe), 5.73 (OCCH=), 6.97 (dd, *J* 7 and 15, =C*H*CHO), 7.40 [d, *J* 15, C(O)C*H*=CH] and 9.85 (d, *J* 7, =CHC*H*O) (Found: C, 61.5; H, 5.2%; M^+, 194.0592. Calc. for $C_{10}H_{10}O_4$: C, 61.9; H, 5.2%; M, 194.0580).

6-[(E)-3-*Hydroxyprop*-1-*enyl*]-4-*methoxy*-5-*methyl*-2-*pyrone* **40a**.—Sodium borohydride (0.01 g, 2.92 × 10^{-4} mol) was added in small portions to a solution of compound **39** (0.057 g, 2.92 × 10^{-4} mol) in methanol (8 cm^3)–dichloromethane (2 cm^3), and the mixture was then stirred at room temperature for 1 h. The dichloromethane was evaporated off under reduced pressure and the residue was then purified by column chromatography, with (20:1) dichloromethane–methanol as eluent, to give the *hydroxyalkenyl pyrone* **40a** (0.041 g, 71%) as a yellow solid, m.p. 158–159 °C (from dichloromethane–methanol); λ_{max}(EtOH)/nm 224 and 318; ν_{max}(KBr disc)/cm^{-1}

3360, 1720, 1650 and 1615; δ_H 1.95 (Me), 3.1 (OH), 3.84 (OMe), 4.39 (dd, *J* 1.8 and 4.3, HOCH_2CH=), 5.51 (=CHC=O), 6.57 (dt, *J* 1.9 and 15.4, C*H*=CHCH$_2$) and 6.79 (dt, *J* 4.3 and 15.4, CH=C*H*CH$_2$); δ_C 8.79 (Me), 56.26 (Me), 62.39 (CH_2), 88.80 (CH), 107.81, 117.50 (CH), 137.33 (CH), 153.78, 164.05 and 170.99 (Found: M^+, 196.0739. $C_{10}H_{12}O_4$ requires M, 196.0743).

6-[(E)-3-*Bromoprop*-1-*enyl*]-4-*methoxy*-5-*methyl*-2-*pyrone* **40b**.—A solution of 1,2-dibromotetrachloroethane (0.16 g, 4.94×10^{-4} mol) in dry dichloromethane (5 cm^3) was added during 5 min to a solution of the alcohol **40a** (0.048 g, 2.47×10^{-4} mol) and triphenylphosphine (0.13 g, 4.94×10^{-4} mol) in dichloromethane (10 cm^3) and the mixture was then stirred at room temperature for 1 h.[15] The dichloromethane was evaporated off under reduced pressure, and the residue was purified by column chromatography with diethyl ether as eluent. Recrystallisation from dichloromethane gave the *bromide* **40b** (0.054 g, 85%) as pale yellow needles, m.p. 155–157 °C; λ_{max}(EtOH)/nm 228 and 322; ν_{max}(KBr disc)/cm^{-1} 1705, 1640 and 1610; δ_H 1.98 (Me), 3.84 (OMe), 4.11 (d, *J* 7.7, =CHCH_2Br), 5.53 (=CHC=O), 6.51 (d, *J* 15.0, C*H*=CHCH$_2$) and 6.81 (dt, *J* 7.7 and 15.0, =C*H*CH$_2$Br); δ_C 8.91 (Me), 31.20 (CH_2), 56.29 (Me), 89.72 (CH), 109.35, 122.20 (CH), 132.35 (CH), 152.38, 163.19 and 170.33; (Found: M^+, 259.9875 and 257.9897. $C_{10}H_{11}{}^{81}BrO_3$ requires M, 259.9881. $C_{10}H_{11}{}^{79}BrO_3$ requires M, 257.9905).

(E)-3-4-(*Methoxy*-5-*methyl*-2-*oxo*-2H-*pyran*-6-*yl*)*prop*-2-*enyl*(*triphenyl*)*phosphonium Bromide* **37**.—A solution of 6-[(*E*)-3-bromoprop-1-enyl]-4-methoxy-5-methyl-2-pyrone **40b** (0.404 g, 7.64×10^{-4} mol) and triphenylphosphine (0.22 g, 8.41×10^{-4} mol) in dichloromethane (50 cm^3) was stirred at room temperature for 48 h. The dichloromethane was evaporated off under reduced pressure and the residue was then purified by PLC with (20:1) dichloromethane–methanol as solvent to give the phosphonium salt **37** (0.64 g, 79%) as a pale orange solid, m.p. 217–218 °C (decomp.) (from CH_2Cl_2); λ_{max}(EtOH)/nm 222 and 324; ν_{max}(KBr disc)/cm^{-1} 1715, 1645, 1610 and 1580; δ_H 1.98 (=CMe), 3.81 (OMe), 5.21 (dd, *J* 7.5 and 16.1, =CHCH_2PPh$_3$), 5.48 (=CHC=O), 6.28–6.36 (m, =CH) and 7.61–7.90 (16 H, m) [Found: M^+, 441. Calc. for $C_{28}H_{26}BrO_3P$: (M − Br), 441].

6-{(E,E,E,E)-8-[(5α-*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)]*octa*-1,3,5,7-*tetraenyl*}-4-*methoxy*-5-*methyl*-2-*pyrone* **12** *and* 6-{(E,Z,E,E)-8-[(5α,*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)]*octa*-1,3,5,7-*tetraenyl*}-4-*methoxy*-5-*methyl*-2-*pyrone* **41**.—A solution of butyllithium in hexane (1.6 mol dm^{-3}; 0.36 cm^3, 5.79×10^{-4} mol) was added dropwise during 1 min to a stirred suspension of the phosphonium bromide **40** (0.30 g, 5.79×10^{-4} mol) in dry THF (10 cm^3) at 0 °C, and the mixture was then stirred at 0 °C for 1 h. A solution of the aldehyde **13** (0.04 g, 1.81×10^{-4} mol) in dry THF (5 cm^3) was added during 5 min, and the mixture was then heated under reflux in the dark for 2 h. The THF was evaporated off under reduced pressure, and the residue was then purified by column chromatography with (97:3) dichloromethane–methanol as eluent to give a 3:2 mixture of products **12** and **41** (0.24 g, 53%) as an orange solid. Normal-phase HPLC, with (6:4) ethyl acetate–hexane then (98:2) dichloromethane–methanol as eluents, separated: (i) the *all*-E-*polyenepyrone* '*preaurovertin*' **12** (3.7 mg) as a yellow solid, λ_{max}(EtOH)/nm 228, 283, 385 and 400; ν_{max}(KBr disc)/cm^{-1} 3420, 1730, 1700 and 1630; δ_H 1.09 (t, *J* 7.5, CH_2*Me*), 1.23 (Me), 1.26 (Me), 1.60 (m, CHCH_2Me), 1.90 (OH), 1.96 (=CMe), 2.77 (OH), 3.40 (dd, *J* 4.5 and 8.3, OC*H*Et), 3.75 (d, *J* 8.9, C*H*OH), 3.83 (OMe), 5.49 (O=CCH=), 5.87 (d, *J* tetraene 14.5, 8-H), 6.26–6.39 (m, 5 × =CH), 6.51 (dd, *J* 10.4 and 14.6, =CH) and 7.20 (dd, *J* 11.2 and 14.9, tetraene 2-H) (Found: M^+, 402.2035. $C_{23}H_{30}O_6$ requires M, 402.2031); and (ii) the E,Z,E,E-*polyenepyrone* **41** (2.6 mg) as a sticky yellow solid, λ_{max}(EtOH)/nm 226, 285, 293, 387 and 405sh; ν_{max}(KBr disc)/cm^{-1} 3420, 1730, 1700 and 1630; δ_H 1.14 (t, *J* 7.4, CH_2*Me*), 1.25 (Me), 1.27 (Me), 1.59 (m, CHCH_2Me), 1.89 (OH), 1.98 (=CMe), 2.77 (OH), 3.45 (dd, *J* 5.3 and 7.7, OC*H*Et), 3.75 (d, *J* 8.6, C*H*OH), 3.84 (OMe), 5.52 (O=CCH=), 5.87 (d, *J* 14.7 tetraene, 8-H), 6.12 (t, *J* 10.9, 3-H), 6.25 (t, *J* 10.9, 4-H), 6.33 (dd, *J* 10.9 and 14.3, 6-H), 6.37 (d, *J* 14.6, 1-H), 6.42 (dd, *J* 10.9 and 14.7, 7-H), 6.87 (dd, *J* 12.2 and 14.5, 5-H) and 7.57 (dd, *J* 12.3 and 14.6, 2-H) (Found: M^+, 402.2035. $C_{23}H_{30}O_6$ requires M, 402.2031).

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References

1 L. J. Mulheirn, R. B. Beechey, D. P. Leworthy and M. D. Osselton, *J. Chem. Soc., Chem. Commun.*, 1974, 874.
2 For full bibliography, see M. C. Bowden, P. Patel and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1947.
3 See H. A. Lardy, J. L. Connelly and D. Johnson, *Biochemistry*, 1964, **3**, 1961; A. M. Robertson, R. B. Beechey, C. T. Holloway and I. G. Knight, *Biochem. J.*, 1967, **104**, 54C.
4 G. J. Kruger, P. S. Steyn, R. Vleggaar and C. J. Rabie, *J. Chem. Soc., Chem. Commun.*, 1979, 441.
5 For extensive studies of the biosynthesis of aurovertin and asteltoxin, see P. S. Steyn, R. Vleggaar and P. L. Wessels, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1298; P. S. Steyn and R. Vleggaar, *J. Chem. Soc., Chem. Commun.*, 1985, 1796 (aurovertin); P. S. Steyn and R. Vleggaar, *J. Chem. Soc., Chem. Commun.*, 1984, 977; A. E. de Jesus, P. S. Steyn and R. Vleggaar, *J. Chem. Soc., Chem. Commun.*, 1985, 1633 (asteltoxin).
6 C. P. Gorst-Allman, K. G. R. Pachler, P. S. Steyn, P. L. Wessels and D. B. Scott, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2181.
7 O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helv. Chim. Acta*, 1957, **40**, 1242.
8 D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, 1980.
9 See ref. 2 and also M. C. Bowden, Ph.D. Thesis, University of Nottingham, 1987.
10 K. Sato, S. Mizuno and H. Hirayama, *J. Org. Chem.*, 1967, **32**, 177.
11 See E. Suzuki, B. Katsuragawa and S. Inoue, *J. Chem. Res. (S)*, 1982, 224.
12 See J. E. Forbes, Ph.D. Thesis, University of Nottingham, 1988.
13 P. Patel and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1941.
14 T. M. Harris, C. M. Harris and M. P. Wachter, *Tetrahedron*, 1968, **24**, 6897.
15 E. S. Huyser and D. N. De Mott, *Chem. Ind. (London)*, 1963, 1954.

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