Epoxides in Synthesis. Synthesis of the Novel 2,6-Dioxabicyclo[3.2.1]octane Units in the Citreoviridinols and the Aurovertins

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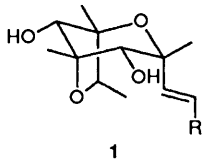
The 2,6-dioxabicyclo[3.2.1]octane ring systems, *viz.* systems **24** and **34**, present in citreoviridinol and the aurovertins, have been produced in a stereoselective manner by treatment of the corresponding 4-hydroxytetrahydrofuran epoxides **22** and **33**, respectively, with toluene-*p*-sulphonic acid. A number of related epoxy alcohol cyclisations leading to isomeric dioxabicyclooctanes are reported. These studies have led to a greater understanding of the biosynthetic pathway to the citreoviridinols and the aurovertins, and a greater appreciation of the role of epoxide intermediates in the biosynthesis apparatus.

Citreoviridinol **1**,[1] citreoviridin **2**,[2] and citreomontanin **3**[3] are members of a biogenetically connected group of polyene pyrone metabolites isolated from *Penicillium sp.* Citreoviridinol **1**, with its substituted 2,6-dioxabicyclo[3.2.1]octane ring system, is also related structurally to the aurovertins; *e.g.*, aurovertin A **4a** and aurovertin B **4b**, produced by *Calcarisporium arbuscula*.[4] In addition, citreoviridinol **1** co-occurs with isocitreoviridinols; *e.g.*, compounds **5** and **6**,[5] and the neocitreoviridinols **7** and **8** containing a 2,5-dioxabicyclo[2.2.1]heptane ring system,[6] in *Penicillium citreoviride B.*

Interest in this family of secondary metabolites stems from their interesting biological properties (*e.g.*, both citreoviridin **2** and aurovertin B **4b** are potent inhibitors of ATP synthesis and ATP hydrolysis catalysed by mitochrondrial enzyme systems) and also in the fascinating biogenetic interrelationships that exist between their members.† It seems probable that the intriguing 2,6-dioxabicyclo[3.2.1]octane ring system present in the citreoviridinols **1**, **5** and **6** and the aurovertins **4a** and **4b** is derived in Nature *via* cyclisation of a 1,2; 3,4; 5,6-triepoxide intermediate **11** produced by stepwise epoxidation of a pyrone-substituted triene precursor molecule, *viz.* system **9** (Scheme 1). Hence, in one scenario, enzyme-mediated electrophilic opening of the 3,4-epoxide ring in intermediate **11**, followed by trapping of the carbocation at C-4 by the oxygen of the adjacent 1,2-epoxide with simultaneous quenching by water at C-2, might lead to the tetrahydrofuranyl epoxide intermediate **12**. A second cyclisation, involving the tertiary OH group and the epoxide residue of **12** as shown, would then create the 2,6-dioxabicyclo-[3.2.1]octane system **14** in citreoviridinol **1** and aurovertin **4** (an alternative mode of cyclisation of intermediate **12** would of course produce the 2,5-dioxabicyclo[2.2.1]heptane ring system **15** present in the naturally occurring neocitreoviridinols **7** and **8**. The sequence leading from **9** to **14** need not occur in this stepwise fashion however, and may involve the cascade of cyclisations shown in Scheme 2 with the same overall outcome.† Finally, with the co-occurrence of citreoviridin **2** and citreoviridinol **1** in *P. citreoviride* it is also possible that citreoviridinol **1** is derived from diepoxide **10** *in vivo* by way of citreoviridin **2** (*cf.* structure **13**) and the tetrahydrofuranyl epoxide intermediate **12**. In the accompanying papers we have described total syntheses of citreomontanin **3**[7] and preaurovertin **13**; R′ = Et, R″ = H,[8] and also a formal synthesis of citreoviridin **2** *via* synthetic citreoviral **16**[9] which is a cometabolite of citreoviridin **2** in *P. citreoviride*. The syntheses of the tetrahydrofuranyl ring portions (*viz.* structure **13**) in

† For further background see earlier papers in this series (refs. 7–10) and bibliography contained therein.



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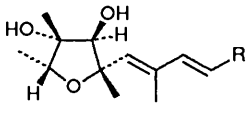

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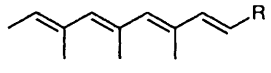

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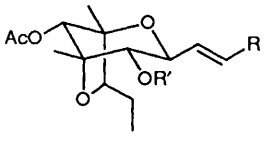
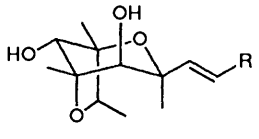


4a; R′ = Ac
b; R′ = H



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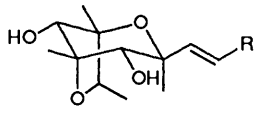

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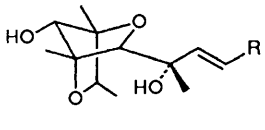

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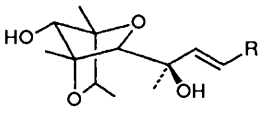

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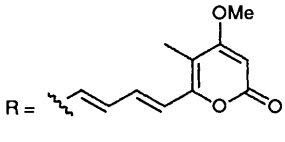
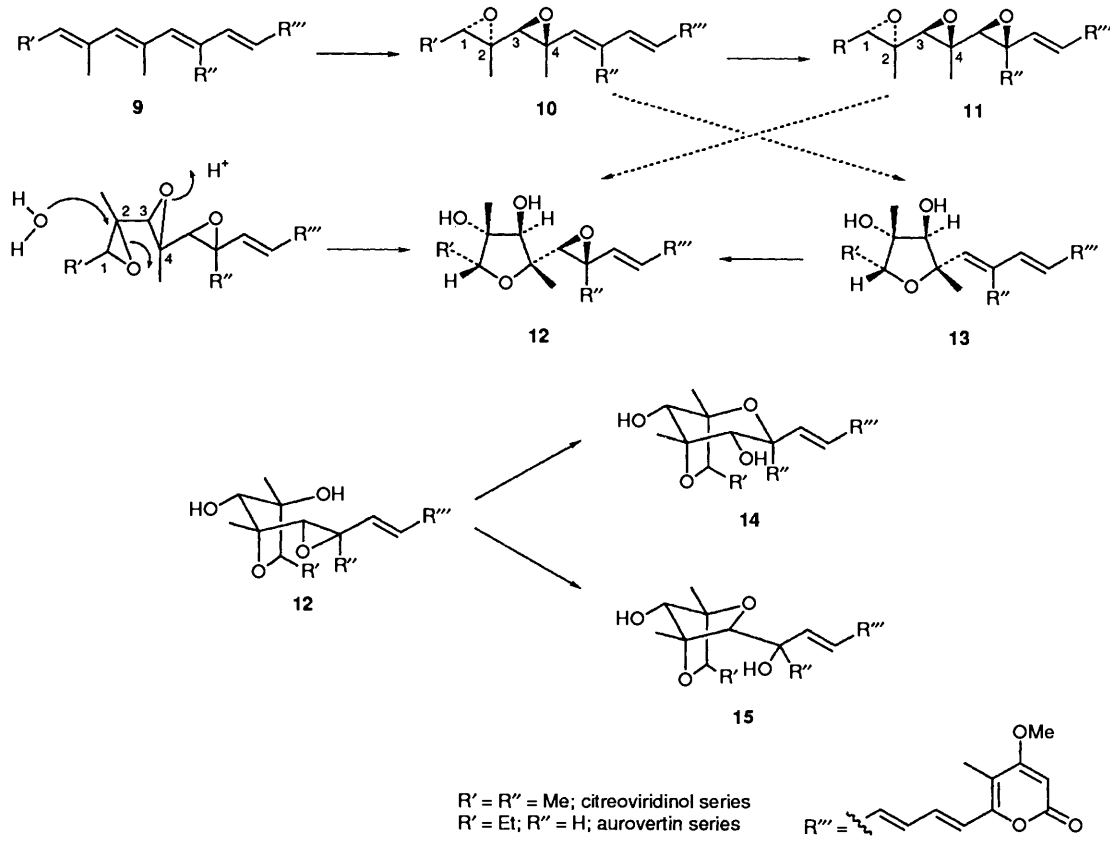
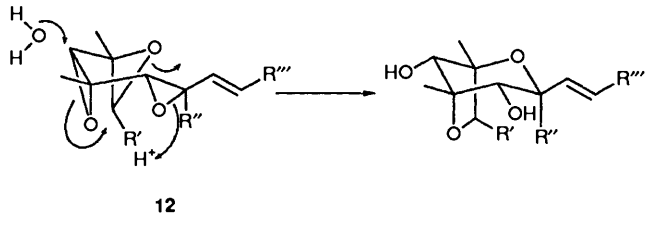




Scheme 1



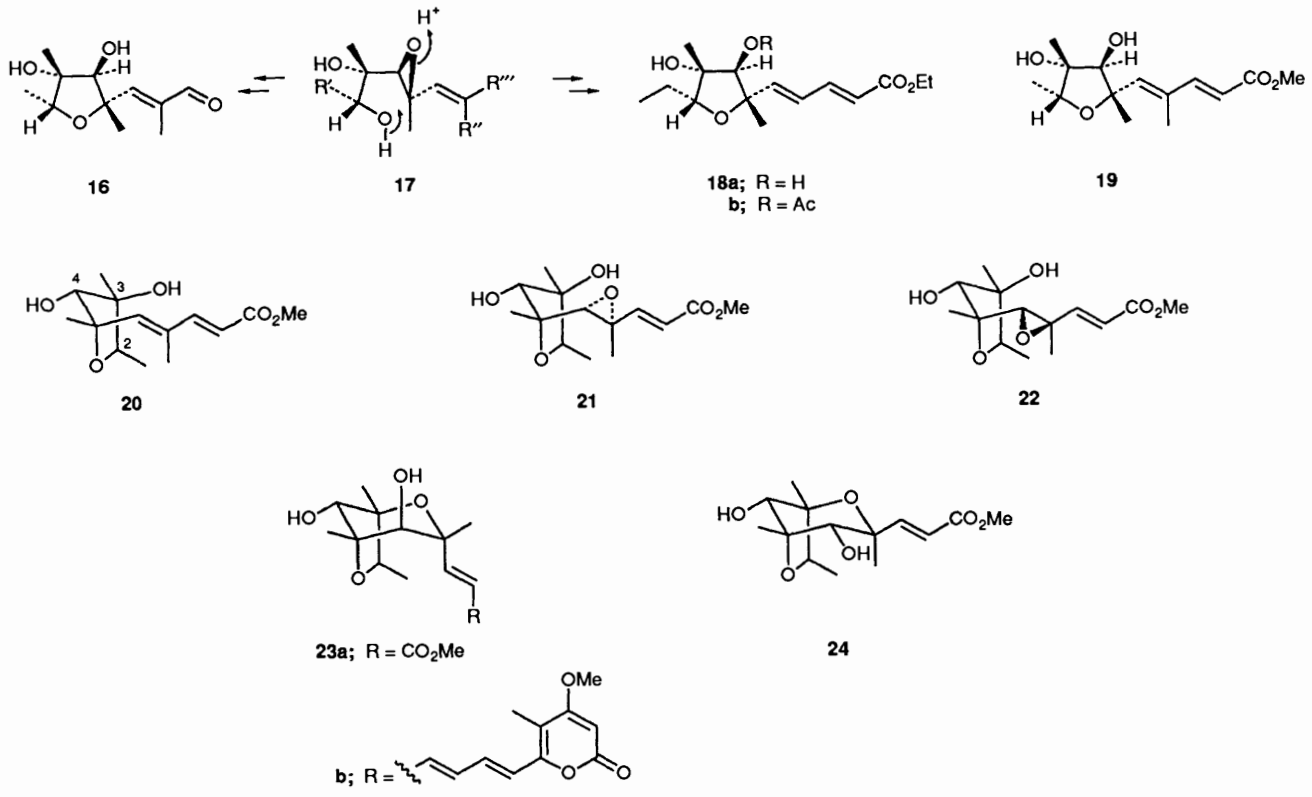
Scheme 2

preaurovertin and citreoviridin were achieved *via* the intermediate epoxy diols **17**, thereby providing some evidence for the biogenetic speculation mentioned above. In this paper we describe the elaboration of the synthetic intermediates **16** and **18** to the 2,6-dioxabicyclo[3.2.1]octane units in the citreoviridinols **1**, **5** and **6** and the aurovertins **4**.[10] Furthermore, the conversions use the key epoxide cyclisation steps **21** ⟶ **23**, **22** ⟶ **24** and **33** ⟶ **34**, thereby adding credence to the biosynthetic proposals discussed earlier.

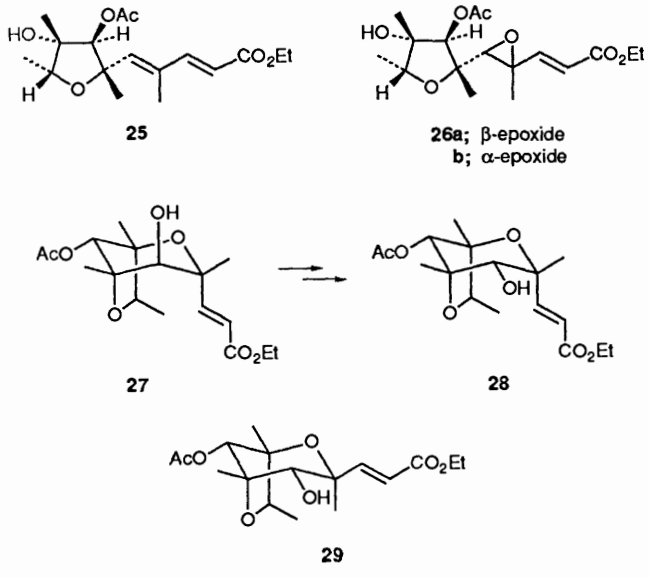
We first of all examined the synthesis of the epoxide intermediate **21**/**22** derived from our synthetic (±)-citreoviral **16**,[9] and the conversion of the epoxide into the 2,6-dioxabicyclo[3.2.1]octane ring system **23**/**24** in natural citreoviridinol **1**. At the outset of our work in 1985, only one naturally occurring citreoviridinol had been described,[1] and the full streochemistry of this metabolite was not known with certainty. On the basis of the proposed biosynthetic scheme and correlation with the aurovertins **4** we felt that the full stereochemistry of citreoviridinol would be as represented in structure **1**. Extensive work by Yamamura and co-workers over the period 1986–1990 revealed the presence of the isomeric 'isocitreoviridinols' **5**, **6** and **23b**, and also the neocitreoviridinols **7** and **8** in *P. citreoviride*.

Therefore, treatment of (±)-citreoviral **16** with methoxycarbonylmethylene(triphenyl)phosphorane first led to the *E*,*E*-dienoate **19**, which was obtained as crystals in 67% yield. Reaction between the *E*,*E*-dienoate **19** and *m*-chloroperbenzoic acid (MCPBA) next led to a clean 2:1 mixture of two monoepoxides resulting from regiospecific attack by the peracid at the more nucleophilic γ,δ-double bond in the dienoate. The two epoxides were easily separated by chromatography, and the major isomer was tentatively assigned the α-configuration **21** based on the assumption that the α-orientated 3-OH group in the substrate (see structure **20**) would direct epoxidation to the same α-face of the proximate carbon-to-carbon double bond. NMR data and subsequent chemistry showed this supposition was correct. The minor epoxide produced from dienoate **20** was therefore assigned the β-configuration **22**.

Treatment of the α-epoxide **21** with catalytic toluene-*p*-sulphonic acid (PTSA) in dry benzene at room temperature for 3 h resulted in smooth stereoselective transformation into a single 2,6-dioxabicyclo[3.2.1]octane. We were unable to detect the co-formation of the isomeric 2,5-dioxabicyclo[2.2.1]-heptane, see **15**, in the crude reaction products. The dioxabicyclooctane was assigned the relative stereochemistry **23a** on the basis of comparison of its ^{1}H NMR shift data with those of natural citreoviridinol **1** and its degradation products, and also on the basis of NOE experiments (for a summary of these data see the Experimental section). The 2,6-dioxabicyclo-[3.2.1]octane derivative **23a** correlates with natural citreoviridinol **1** except that the secondary hydroxy group in **23a** is in an axial configuration. In contemporaneous work Yamamura and co-workers[5] described the epoxidation of the acetate **25**, corresponding to diol **19**, with MCPBA which led to a 9:2 mixture of β and α epoxides **26a** and **26b**, respectively. Acid-catalysed cyclisation of β-epoxide **26a** then gave rise to the acetate **27** corresponding to diol **23a**, which could be converted in three steps into its epimer **28**. The dioxabicyclooctane **28** was then correlated with a degradation product obtained from



natural citreoviridinol **1**. The spectroscopic data for our synthetic dioxabicyclooctane **23a** were closely similar to those described by Yamamura and co-workers for compound **27**. Interestingly, in 1990, after completion of our studies, Yamamura and co-workers described the presence of epicitreoviridinol **23b** as a very minor metabolite in *P. citreoviride*.[11]

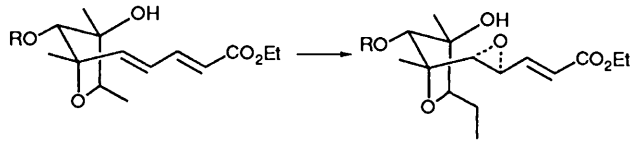


In a similar manner, treatment of the β-epoxide **22** (from **19**) with PTSA readily resulted in cyclisation to the corresponding isomeric 2,6-dioxabicyclooctane **24**, whose relative stereochemistry was established by NOE difference experiments (see the Experimental section for details). The 2,6-dioxabicyclooctane **24** correlates with natural isocitreoviridinol **5** except that the C-4 secondary hydroxy group in compound **24** is in an equatorial configuration. Subsequent to the completion of our work in this area, Yamamura and co-workers[12] isolated a new citreoviridinol from *P. citreoviride*; they have called this compound epiisocitreoviridinol (*i.e.*, compound **6**), and it has the same relative stereochemistry of groups about the dioxabicyclooctane ring system as shown in structure **24**. Furthermore these authors synthesized the same intermediate **29** by the same route employed here, *i.e.* from the tetrahydrofuranyloxirane **26b**, and they then used intermediate **29** to effect a total synthesis of epiisocitreoviridinol **6**.

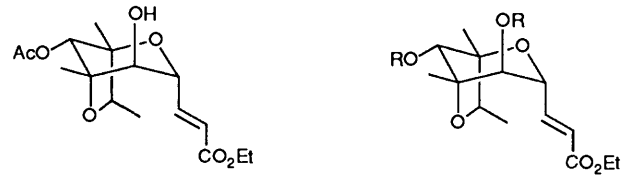
The synthetic work highlighted above therefore models the proposals for the biosynthesis of the citreoviridinols, from citreoviridin (**2**; *cf.* **13**) or from the triepoxide **11** *via* the tetrahydrofuran **12**, summarised in Scheme 1. In conjuction with Yamamura's work, and particularly the work showing that the four isomers (**1**, **5**, **6** and **23b**) of citreoviridinol are produced in Nature,[11] the present study also confirms that the introduction of the third epoxide ring [leading to triepoxide **11** or to the tetrahydrofuran **12** (Scheme 1)] in the biosynthesis of citreoviridinol is a non-stereoselective process.

Unlike the citreoviridinols produced by *P. citreoviride*, only one stereoisomer of the 2,6-dioxabicyclo[3.2.1]octane unit in the related aurovertins **4** has been reported as occurring in *C. arbuscula*.[4] With the successful synthesis of the tetrahydrofuranyl dienoate **18** and of preaurovertin (**13**; R′ = Et, R″ = H), described in the preceding paper,[8,10] we were in a position to investigate the elaboration of dienote(s) **18** to the dioxabicyclooctane unit, *viz.* compound(s) **34**, found in the aurovertins, and ultimately to investigate a total synthesis of these novel metabolites.

To our surprise, treatment of either the dienoate **18a** or the corresponding acetate **18b** with MCPBA failed to produce any epoxide products; instead starting material was recovered in essentially quantitative yield. However, the more electrophilic trifluoroperacetic acid[13] was found to react with both compounds **18a** and **18b** in a regio- and stereo-selective manner, and led to single epoxides resulting from attack at only the



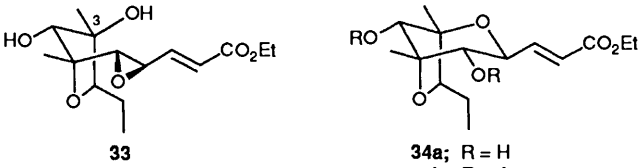
18 30a; R = H b; R = Ac



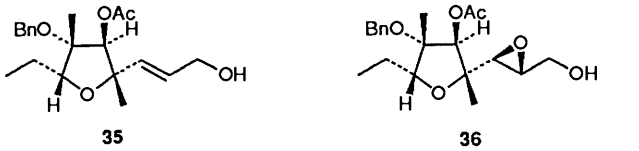
31 32a; R = H b; R = Ac

γ,δ-double bond in the dienoates. As with the citreoviridinol series described above, we felt that prior association between the peracid and the tertiary OH group in the substrates **18a** and **18b** would probably 'direct' the epoxidations, thus leading to the corresponding α-epoxides **30a** and **30b**, respectively. This supposition was indicated by the subsequent chemistry. Treatment of the epoxide obtained from compound **18b** with PTSA produced a single 2,6-dioxabicyclo[3.2.1]octane product, whose spectroscopic data showed significant differences from those reported for natural auro-vertin B **4b**. The dioxabicyclooctane product **31** correlates with aurovertin B **4b** except that both the secondary hydroxy and the acrylate groups are in the axial configuration. This relative stereochemistry can only derive from the α-epoxide **30b**. In a similar manner, reaction between the α-epoxide **30a**, derived from compound **18a** and PTSA produced the dioxabicyclooctane **32a** which could then be converted into the diacetate **32b**. Similar to **31**, the diacetate **32b** correlates with aurovertin A **4a** except that the acrylate and neighbouring acetoxy group in diacetate **32b** are both in the axial configuration.

In an attempt to counteract the 'association effect' between the reagent and the substrate in the epoxidation of compounds **18**, thereby leading to the β-epoxide **33**, we investigated the use of alternative epoxidising agents, including the sterically demanding and electrophilic 3,5-dinitroperbenzoic acid[14] and magnesium monoperoxyphthalate.[15] To our disappointment interaction between the diol-dienoate **18a** and magnesium monoperoxyphthalate produced only the α-epoxide **30a**. Reaction between substrate **18a** and the more electrophilic



33 34a; R = H b; R = Ac



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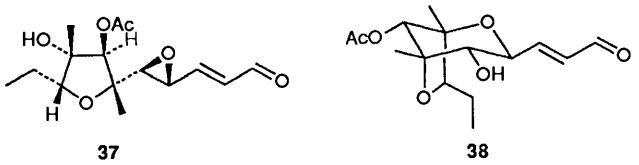

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3,5-dinitroperbenzoic acid, however, led to a 3:1 mixture of the α- and β-epoxide **30a** and **33**, from which the β-epoxide **33** could be separated and characterised. Subsequent treatment of compound **33** with PTSA gave the isomeric 2,6-dioxabicyclo-[3.2.1]octanediol **34a**, acetylation of which finally produced the corresponding diacetate **34b** which showed spectroscopic data which correlated with those of natural aurovertin A **4a**.

In contemporaneous work Yamamura and co-workers[16] employed a closely similar (biogenetically related) strategy to our own for elaboration of the dioxabicyclooctane end-group, *viz.* the propenal **38**, in aurovertin B. These authors used the allylic alcohol **35** as the precursor which, in a Sharpless epoxidation reaction, was first converted into the β-epoxide **36**. Elaboration of the derived tertiary alcohol **37** in the presence of camphorsulphonic acid then gave rise to the bicyclic enal **38** which could be used to synthesize aurovertin B **4b**.

Experimental

For general experimental details see ref. 7. Light petroleum refers to that fraction boiling in the range 40–60 °C.

(E,E)-*Methyl* 5-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2β-*yl*)-4-*methylpenta*-2,4-*dienoate* **19**.—A solution of (±)-citreoviral **16**[10] (65 mg, 0.3 mmol) and methoxycarbonylmethylene(triphenyl)phosporane (510 mg, 1.5 mmol) in chloroform (40 cm^3) was stirred at room temperature for 4 days. The mixture was adsorbed onto silica Woelm, and was then purified by chromatography on silica G with (4:1) diethyl ether–hexane as eluent. Recrystallisation from hexane–chloroform gave the E,E-*diene ester* **19** (54 mg, 67%) as crystals, m.p. 153–154 °C; λ_{max}(EtOH)/nm 270 (22 000); ν_{max}($CHCl_3$)/cm^{-1} 3560, 3420, 1700 and 1625; δ_H 1.18 (d, *J* 6.4, *Me*CH), 1.21 (Me), 1.37 (Me), 1.74 (br, OH), 1.92 (d, *J* 1.1, *Me*C=CH), 2.33 (br, OH), 3.75 (MeO), 3.82 (q, *J* 6.4, MeC*H*), 3.95 (br, C*H*OH), 5.86 (d, *J* 16, C*H*=CH), 6.15 (br, MeC=C*H*) and 7.26 (d, *J* 16, CH=C*H*); δ_C 12.2 (Me), 13.2 (Me), 17.5 (Me), 20.9 (Me), 51.6 (Me), 77.6 (CH), 80.6, 84.0, 85.7 (CH), 116.6 (CH), 132.5, 147.1 (CH), 149.8 (CH) and 167.7 (Found: M^+, 270.1476. $C_{14}H_{22}O_5$ requires M, 270.1467).

(2E,4S,5R)-*Methyl* 5-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-yl)-4,5-*epoxy*-4-*methylpent*-2-*enoate* **21** *and* (2E,4R,5S)-*Methyl* 5-(3β,4α-*Dihydroxy*-2β,4β,5α-*trimethyltetrahydrofuran*-2α-*yl*)-4,5-*epoxy*-4-*methylpent*-2-*enoate* **22**.—A solution of MCPBA (85%; 20 mg, 0.11 mmol) in dichloromethane (8 cm^3) was added to a stirred, ice-cooled solution of the unsaturated ester **19** (20 mg, 0.074 mmol) in dichloromethane (8 cm^3), and the reaction mixture was then stirred at room temperature for 23 h. Calcium hydroxide (50 mg) and sodium sulphate (50 mg) were added, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography on silica G with (3:1) diethyl ether–light petroleum as eluent to give: (i) the α-*epoxide* **21** (14 mg, 64%) as an oil; ν_{max}($CHCl_3$)/cm^{-1} 3460, 1720 and 1655; δ_H 1.13 (d, *J* 6.3, *Me*CH), 1.19 (Me), 1.31 (Me), 1.75 (Me), 2.84 (CHO), 3.65 (br, OH), 3.75 (MeO), 3.84 (q, *J* 6.3, MeC*H*), 3.98 (br, C*H*OH), 6.03 (d, *J* 16, C*H*=CH) and 6.76 (d, *J* 16, CH=C*H*) [Found: *m*/*z*, 287 and 270.1466. $C_{14}H_{22}O_6$ requires (M + H), 287 and (M − O), 270.1467]; and (ii) the β-*epoxide* **22** (7.5 mg, 35%) as an oil; ν_{max}($CHCl_3$)/cm^{-1} 3400, 1715 and 1655; δ_H 1.19 (d, *J* 6, *Me*CH), 1.21 (Me), 1.27 (Me), 1.52 (Me), 2.53 (br, 2 × OH), 3.12 (CHO), 3.74 (MeO), 3.75 (q, *J* 6, MeC*H*), 3.98 (C*H*OH), 6.01 (d, *J* 16, C*H*=CH) and 6.77 (d, *J* 16, CH=C*H*) [Found: *m*/*z*, 287 and 270.1447. $C_{12}H_{22}O_6$ requires (M + H), 287 and (M − O), 270.1467].

(E)-*Methyl* 3-[(8S)-4β,8-*Dihydroxy*-1α,3β,5α,7α-*tetramethyl*-

2,6-*dioxabicyclo*[3.2.1]*octan*-3α-*yl*)*propenoate* **23a**.—A solution of the epoxide **21** (38 mg, 0.13 mmol) and PTSA (10 mg, 0.06 mmol) in dry benzene (15 cm^3) was stirred at room temperature for 3 h. The mixture was adsorbed onto silica Woelm and purified by chromatography on silica G with (4:1) and then with (6:1) diethyl ether–hexane as eluent to give the bicyclic *bis ether* **23a** (13.5 mg, 36%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1710 and 1650; δ_H 1.17 (d, *J* 6.5, *Me*CH), 1.23 (Me), 1.34 (Me), 1.37 (Me), 1.82 (d, *J* 5, CHO*H*), 2.16 (d, *J* 5, CHO*H*), 3.74 (MeO), 3.88 (d, *J* 5, C*H*OH), 4.04 (q, *J* 6.5, MeC*H*), 4.12 (d, *J* 5, C*H*OH), 5.88 (d, *J* 15, C*H*=CH) and 7.21 (d, *J* 15, CH–C*H*) [irradiation at δ 1.17 gave NOEs at δ 4.04 (5%), 5.88 (1%) and 7.21 (1%), and irradiation at δ 3.88 gave enhancements at δ 5.88 (4%) and 7.21 (3%). Irradiation at δ 4.12 gave NOEs at δ 1.23 (1.5%), 1.34 (2%) and 1.37 (1%) and irradiation at δ 5.88 gave an enhancement at δ 3.88 (3%). Finally irradiation at δ 7.21 gave enhancements at δ 1.17 (2%) and 3.88 (2.5%)]; δ_C 13.1 (Me), 17.0 (Me), 17.1 (Me), 26.8 (Me), 51.8 (Me), 75.3 (CH), 76.3, 77.9 (CH), 79.6 (CH), 83.6, 83.7, 116.9 (CH), 155.4 (CH) and 167.7 (Found: M^+, 286.1423. $C_{14}H_{22}O_6$ requires M, 286.1416).

A solution of the diol **23a** (13 mg, 0.045 mmol) in acetic anhydride (1 cm^3)–dry pyridine (8 cm^3) was stirred under nitrogen at 50 °C for 3.5 h. The solvents were removed under reduced pressure and then at high vacuum, and the resulting residue was then purified by chromatography on silica G with (1:2) diethyl ether–hexane as eluent to give the corresponding *diacetate* (10 mg, 60%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740br and 1650; δ_H 1.13 (Me), 1.17 (Me), 1.21 (d, *J* 6.6, *Me*CH), 1.24 (Me), 2.15 (2 × AcO), 3.74 (MeO), 4.03 (q, *J* 6.6, MeC*H*), 5.28 (C*H*OAc), 5.37 (C*H*OAc), 5.98 (d, *J* 16, C*H*=CH) and 7.23 (d, *J* 16, CH=C*H*) (Found: M^+, 370.1642. $C_{18}H_{26}O_8$ requires M, 370.1628).

(E)-*Methyl* 3-{(8S)-4α,8-*Dihydroxy*-1α,3α,5α,7α-*tetramethyl*-2,6-*dioxabicyclo*[3.2.1]*octan*-3β-*yl*}*propenoate* **24**.—A solution of the epoxide **22** (15 mg, 0.053 mmol) and PTSA (7 mg, 0.04 mmol) in dry benzene (6 cm^3) was stirred at room temperature for 18 h. The mixture was adsorbed onto silica Woelm and purified by chromatography on silica G with (3:1) diethyl ether–hexane as eluent to give the bicyclic *bis-ether* **24** (5.5 mg, 37%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3470, 1710 and 1650; δ_H 1.18 (d, *J*, 6.5, *Me*CH), 1.29 (Me), 1.35 (Me), 3.30 (d, *J* 10, CHO*H*), 3.63 (d, *J* 10, C*H*OH), 3.76 (MeO), 4.06 (br, C*H*OH), 4.09 (q, *J* 6.5, MeC*H*), 6.05 (d, *J* 15, C*H*=CH), 7.06 (d, *J* 15, CH=C*H*) [irradiation at δ 1.33 gave an NOE at δ 4.09 (3%), and irradiation at δ 1.35 gave an enhancement at δ 3.63 (3%). Irradiation at δ 4.06 gave an enhancement at δ 3.63 (2.5%), whereas irradiation at δ 6.05 gave enhancements at δ 3.63 (2.5%) and 4.06 (2%). Finally irradiation at δ 7.06 gave enhancements at δ 3.63 (5.3%) and 4.06 (2%)]; δ_C 13.3 (Me), 17.3 (Me), 18.5 (Me), 25.8 (Me), 51.9 (Me), 75.4 (CH), 78.2, 79.0 (CH), 80.3 (CH), 82.7, 83.3, 119.3 (CH), 157.5 (CH) and 167.1 (Found: M^+, 286.1408. $C_{14}H_{22}O_6$ requires M, 286.1416).

A solution of the diol **24** (5 mg, 0.018 mmol) in a mixture of acetic anhydride (0.5 cm^3) and dry pyridine (4 cm^3) was stirred under nitrogen at 50 °C for 3 h. The solvents were removed under reduced pressure and then under high vacuum, and the resulting residue was then purified by chromatography on silica G with (2:1) diethyl ether–hexane as eluent to give the corresponding *diacetate* (5.5 mg, 83%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1745, 1725 and 1655; δ_H (Me), 1.24 (Me), 1.25 (d, *J* 6.5, *Me*CH), 1.30 (Me), 2.14 (AcO), 2.20 (AcO), 3.76 (MeO), 4.09 (q, *J* 6.5, MeC*H*), 5.04 (C*H*OAc), 5.05 (C*H*OAc) and 6.12 (d, *J* 15, CH=C*H*) (Found: M^+, 370.1627. $C_{18}H_{26}O_8$ requires M, 370.1628).

(2E,4S,5R)-*Ethyl* 5-(3β-*Acetoxy*-5α-*ethyl*-4α-*hydroxy*-2β,4β-*dimethyltetrahydrofuran*-2a-*yl*)-4,5-*epoxypent*-2-*enoate* **30b**.—A solution of trifluoroperacetic acid in dichloromethane was first prepared by adding trifluoroacetic anhydride (TFAA) (0.35 g, 1.66×10^{-3} mol) to aq. hydrogen peroxide (85%; 0.04 cm^3, 1.38×10^{-3} mol) in dichloromethane (5 cm^3) at 0 °C. The solution was added to a refluxing mixture of the tetrahydrofuran **18b** (90 mg, 2.76×10^{-4} mol) and disodium hydrogen phosphate (0.62 g, 4.42×10^{-3} mol) in dichloromethane (20 cm^3), and the mixture was then heated under reflux for 3 h. Water (25 cm^3) was added and the mixture was then extracted with dichloromethane (3 × 25 cm^3). The combined extracts were dried, and then concentrated under reduced pressure to leave a yellow oil. Column chromatography, using (4:1) light petroleum–diethyl ether as eluent, gave the α-*epoxide* **30b** (88 mg, 92%) as an oil; λ_{max}(EtOH)/nm 217; ν_{max}(liq. film)/cm^{-1} 3460, 1750, 1730 and 1665; δ_H 0.98 (t, *J* 7.6, CH_2*Me*), 1.13 (Me), 1.18 (Me), 1.29 (t, *J* 7, OCH_2*Me*), 2.14 (OAc), 3.16 [d, *J* 2.2, C*H*(O)CHCH=], 3.50 (t, *J* 6.1, OC*H*Et), 3.82 [ddd, *J* 0.7, 2.2 and 7.2, CH(O)C*H*CH=CH], 3.95 (OH), 4.21 (q, *J* 7, OCH_2Me), 5.09 (C*H*OAc), 6.18 (dd, *J* 0.7 and 15.7, CH=C*H*CO_2Et) and 6.68 (dd, *J* 7.2 and 15.7, C*H*=CHCO_2Et) [Found: *m*/*z*, 343.1762. $C_{17}H_{26}O_7$ requires (M + H), 343.1770].

(E)-*Ethyl* 3-{(8S)-8-*Acetoxy*-7α-*ethyl*-4β-*hydroxy*-1α,5α-*dimethyl*-2,6-*dioxabicyclo*[3.2.1]*octan*-3α-*yl*}*propenoate* **31**.—A solution of the epoxide **30b** (18 mg, 5.17×10^{-5} mol) and PTSA (5 mg, 2.87×10^{-5} mol) in dry benzene (5 cm^3) was stirred at room temperature for 3 h. The solution was then washed with saturated aq. sodium hydrogen carbonate (1 × 5 cm^3) and the organic layer was then dried, and concentrated under reduced pressure to leave an oil. Column chromatography using (2:1) light petroleum–diethyl ether as eluent to give the bicyclic *bis-ether* **31** (6 mg, 59%) as a yellow oil; λ_{max}(EtOH)/nm 215; ν_{max}(liq. film)/cm^{-1} 3450, 1740, 1720 and 1650; δ_H 1.00 (t, *J* 7.5, CH_2*Me*), 1.21 (Me), 1.26 (Me), 1.30 (t, *J* 7, OCH_2*Me*), 1.51 (m, $CHCH_2$Me), 2.16 (OAc), 3.55 (d, *J* 8.6, C*H*OH), 3.64 (t, *J* 6.3, OC*H*Et), 4.21 (q, *J* 7, OCH_2Me), 4.22 [m, =CHC*H*(O)CHOH], 5.52 (C*H*OAc), 6.12 (dd, *J* 1.6 and 15.6, CH=C*H*CO_2Et) and 7.00 (dd, *J* 4.6 and 15.6, C*H*=CHCO_2Et) [Found: *m*/*z*, 343.1788. $C_{17}H_{26}O_7$ requires (M + H), 343.1770].

(2E,4S,5R)-*Ethyl* 5-(3β,4α-*Dihydroxy*-5α-*ethyl*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)-4,5-*epoxypentenoate* **30a**.—A solution of trifluoroperacetic acid in dichloromethane was first prepared by adding TFAA (0.388 g, 1.85×10^{-3} mol) to aq. hydrogen peroxide (85%; 0.44 cm^3, 1.54×10^{-3} mol) in dichloromethane (5 cm^3) at 0 °C. The solution was added to a refluxing mixture of the tetrahydrofuran **18a** (175 mg, 6.16×10^{-4} mol) and disodium hydrogen phosphate (0.7 g, 4.93×10^{-3} mol) in dichloromethane (25 cm^3), and the mixture was then heated under reflux for 7 h. Water (25 cm^3) was added and the mixture was then extracted with dichloromethane (3 × 30 cm^3). The combined extracts were dried, and then concentrated under reduced pressure to leave a yellow oil. Column chromatography using (1:1) diethyl ether–light petroleum as eluent gave the α-epoxide (146 mg, 79%) as an oil; λ_{max}(EtOH)/nm 219; ν_{max}(liq. film)/cm^{-1} 3450, 1720 and 1655; δ_H 0.98 (t, *J* 7.5, CH_2*Me*), 1.25 (Me), 1.29 (t, *J* 7, OCH_2*Me*), 1.49 (m, $OCHCH_2$Me), 3.04 [d, *J* 2.2, C*H*(O)CHCH=], 3.51 (t, *J* 6.4, OC*H*Et), 3.84 [dd, *J* 2.1 and 7.2, CH(O)C*H*CH=], 3.93 (C*H*OH), 4.21 (q, *J* 7, OCH_2Me), 6.18 (dd, *J* 0.7 and 15, CH=C*H*CO_2Et) and 6.68 (dd, *J* 7.2 and 15.6, C*H*=CHCO_2Et); δ_C 11.2 (Me), 14.2 (Me), 17.2 (Me), 18.4 (Me), 20.4 (CH_2), 55.0 (CH), 60.8 (CH_2), 65.3 (CH), 79.3, 79.8, 83.4 (CH), 84.1 (CH), 124.7 (CH), 142.8 (CH) and 165.6 [Found: *m*/*z*, 301. $C_{16}H_{24}O_6$ requires (M + H), 301].

(E)-*Ethyl* 3-{(8S)-7α-*Ethyl*-4β,8-*dihydroxy*-1α,5α-*dimethyl*-2,6-*dioxabicyclo*[3.2.1]*octan*-3α-*yl*}*propenoate* **32a**.—A solution

of the epoxide **30a** (11 mg, 3.77 × 10^{-5} mol) and PTSA (4 mg, 2.1 × 10^{-5} mol) in dry benzene (5 cm^3) was stirred at room temperature for 4 h. The mixture was then washed with saturated aq. sodium hydrogen carbonate (1 × 5 cm^3) and the organic layer was then dried, and concentrated under reduced pressure to leave an oil. Column chromatography on Florisil, with (1:1) diethyl ether–light petroleum as eluent, gave the bicyclic *bis-ether* **32a** (7.5 mg, 66%) as an oil; λ_{max}(EtOH)/nm 218; ν_{max}(liq. film)/cm^{-1} 3400, 1700 and 1660; δ_H 0.99 (t, *J* 7.5, CH_2*Me*), 1.30 (t, *J* 7.1, OCH_2*Me*), 1.32 (Me), 1.35 (Me), 1.49 (m, $CHCH_2$Me), 2.35 (OH), 3.15 (OH), 3.54 [d, *J* 8.5, =CHCH(O)-C*H*OH], 3.68 (dd, *J* 4.6 and 7.9, OC*H*Et), 4.11 [ddd, *J* 1.4, 4.5 and 8.5, =CHC*H*(O)CHOH], 4.16 (C*H*OH), 4.21 (dq, *J* 1.7 and 7.1, OCH_2Me), 6.12 (dd, *J* 1.5 and 15.7, CH=C*H*CO_2Et) and 6.99 (dd, *J* 4.5 and 15.7, C*H*=CHCO_2Et); δ_C 11.3 (Me), 14.2 (Me), 15.4 (Me), 17.2 (Me), 21.9 (CH_2), 60.65 (CH_2), 72.6 (CH), 75.1 (CH), 79.1 (CH), 83.1, 83.4, 83.9 (CH), 120.6 (CH), 146.6 (CH) and 166.9 [Found: *m/z* 301.1668. $C_{15}H_{24}O_6$ requires (M + H), 301.1688].

(E)-*Ethyl* 3-{(8R)-4β,8-*Diacetoxy*-7α-*ethyl*-1α,5α-*dimethyl*-2,6-*dioxabicyclo*[3.2.1]*octan*-3α-*yl*}*propenoate* **32b**.—A solution of the diol **32a** (147 mg, 4.9 × 10^{-5} mol), acetic anhydride (0.5 cm^3) and pyridine (0.5 cm^3) in dichloromethane (2 cm^3) was stirred at room temperature for 24 h. The solvents were evaporated off under reduced pressure and the residue was then purified by column chromatography on Florisil, with (1:1) diethyl ether–light petroleum as eluent, to give the *diacetate* **32b** (13.4 mg, 71%) as an oil; λ_{max}(EtOH)/nm 208; ν_{max}(liq. film)/cm^{-1} 1750, 1725 and 1670; δ_H 1.11 (t, *J* 6.9, CH_2Me), 1.14 (Me), 1.29 (Me), 1.29 (t, *J* 7,1 OCH_2*Me*), 1.58 (m, $OCHCH_2$Me), 2.09 (OAc), 2.16 (OAc), 3.68 (t, *J* 5.9, OC*H*Et), 4.20 (q, *J* 7.1, OCH_2Me), 4.36 [m, =CHC*H*(O)CHOAc], 4.93 (d, *J* 7.9, OCHC*H*OAc), 5.54 (C*H*OAc), 6.02 (dd, *J* 1.4 and 15.6, CH=C*H*CO_2Et) and 6.84 (dd, *J* 5.3 and 15.6, C*H*=CHCO_2Et) [Found: *m/z*, 385.1885. $C_{19}H_{28}O_8$ requires (M + H), 385.1909].

Aurovertin A **4a**.—A solution of aurovertin B **4b** (15.4 mg, 3.35 × 10^{-5} mol), acetic anhydride (0.1 cm^3) and 4-dimethylaminopyridine (0.5 mg, 3.35 × 10^{-6} mol) in dichloromethane (5 cm^3) was stirred at room temperature for 20 h. The mixture was then evaporated under reduced pressure and the residue was then purified by column chromatography, using ethyl acetate as eluent, to give aurovertin A (12 mg, 71%) as a yellow oil; λ_{max}(EtOH)/nm 228, 245 and 345; ν_{max}(KBr disc)/cm^{-1} 1755, 1715 and 1630; δ_H 1.11 (t, *J* 7.5, CH_2*Me*), 1.14 (Me), 1.19 (Me), 1.69 (m, $OCHCH_2$Me), 1.96 (=CMe), 2.09 (Me), 2.16 (Me), 3.83 (OAc), 3.93 (dd, *J* 4.6 and 8.5, OC*H*Et), 4.35 [t, *J* 7.8, =CHC*H*(O)CHOAc], 4.81 [d, *J* 8.7, CH(O)C*H*OAc], 4.90 (C*H*OAc), 5.50 (O=CCH=), 5.73 [dd, *J* 7.2 and 14.9, CH=C*H*CH(O)CHOAc], 6.31–6.47 (m, 4 × =CH) and 7.16 [dd, *J* 10.7 and 15, C*H*=CHC(O)]; δ_C 8.9 (Me), 11.8 (Me), 15.1 (Me), 16.3 (Me), 20.0 (CH_2), 20.7 (Me), 29.7 (Me), 56.2 (Me), 74.8 (CH), 75.3 (CH), 80.6 (CH), 82.6, 83.0, 85.55 (CH), 89.0 (CH), 108.2, 119.9 (CH), 132.5 (CH), 132.5 (CH), 132.8 (CH), 135.4 (CH), 136.6 (CH), 154.2, 163.5, 169.5, 169.7 and 170.5 [Found: *m/z* 503. $C_{27}H_{34}O_9$ requires (M + H), 503].

3,5-*Dinitroperbenzoic Acid*.—80% Aq. hydrogen peroxide (5 cm^3, 0.12 mol) was added to a mixture of 3,5-dinitrobenzoic acid (8.48 g, 0.04 mol) and methanesulphonic acid (19.2 g, 0.2 mol) and the mixture was then stirred at 40 °C for 3 h. 3,5-Dinitroperbenzoic acid (8.19 g, 89%) precipitated out and was collected by filtration and dried *in vacuo*.

CAUTION: 3,5-Dinitroperbenzoic acid is potentially highly explosive.* It should be handled with extreme care, and only in small quantities.

(2E,4R,5S)-*Ethyl* 5-(5α-*Ethyl*-3β,4α-*dihydroxy*-2β,4β-*dimethyltetrahydrofuran*-2α-*yl*)*pent*-2-*enoate* **33**.—3,5-Dinitroperbenzoic acid (35%; 292 mg, 4.49 × 10^{-4} mol) was added to a solution of the tetrahydrofuran diene ester **18a** (106 mg, 3.74 × 10^{-4} mol) in dichloromethane (30 cm^3) and the mixture was then stirred at room temperature for 24 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 and filtered, and the filtrate was then concentrated under reduced pressure to leave an oil. Column chromatography on Florisil, with (3:2) light petroleum–diethyl ether as eluent, gave: (i) the β-epoxide **33** (21 mg, 19%) as an oil; λ_{max}(EtOH)/nm 218; ν_{max}-(liq. film)/cm^{-1} 3440, 1725, 1715 and 1660; δ_C (*inter alia*) 2.98 [d, *J* 2.0, C*H*(O)CHCH=], 3.44 (t, *J* 6.3, OC*H*Et), 3.61 [dd, *J* 2.0 and 7.2, CH(O)C*H*CH=], 4.21 (q, *J* 7, OCH_2Me), 6.16 (d, *J* 15.7, C*H*CO_2Et), 6.69 (dd, *J* 7.2 and 15.7, C*H*=CHCO_2Et) [Found: *m/z*, 301.1630. $C_{15}H_{24}O_8$ requires (M + H), 301.1612]; and (ii) the α-epoxide **30a** (56 mg, 48%) which showed identical spectroscopic data with those described earlier.

(E)-*Ethyl* 3-{(8S)-7α-*Ethyl*-4α,8-*dihydroxy*-1,5-*dimethyl*-2,6-*dioxabicyclo*[3.2.1]*octan*-3β-*yl*}*propenoate* **34a**.—A solution of the epoxide **33** (12.8 mg, 4.27 × 10^{-5} mol) and PTSA (4 mg, 2.1 × 10^{-5} mol) in dry benzene (5 cm^3) was stirred at room temperature for 20 h. The solution was then washed with saturated aq. sodium hydrogen carbonate (1 × 5 cm^3) and the organic layer was then dried, and concentrated under reduced pressure to leave an oil. Column chromatography on Florisil, with (1:1) diethyl ether–light petroleum as eluent, gave the bicyclic *bis-ether* **34a** (2 mg, 16%) as an oil; λ_{max}(EtOH)/nm 216; ν_{max}(liq. film)/cm^{-1} 3440, 1720, 1700 and 1660; δ_H (*inter alia*) 3.52 (1 H, d, *J* 5.6), 3.67 (2 H, m), 4.21 (q, *J* 7, OCH_2Me), 4.29 (1 H, m), 6.11 (d, *J* 15.6, CH=C*H*CO_2E) and 7.03 (dd, *J* 5.0 and 15.6, C*H*=CHCO_2Et) [Found: *m/z*, 301.1630. $C_{16}H_{24}O_6$ requires (M + H), 301.1612].

(E)-*Ethyl* 3-{(8R)-4α,8-*Diacetoxy*-7α-*ethyl*-1α,5α-*dimethyl*-2,6-*dioxabicyclo*[3.2.1]*octan*-3β-*yl*}*propenoate* **34b**.—A solution of the diol **34a** (2 mg, 6.67 × 10^{-6} mol), acetic anhydride (0.1 cm^3) and pyridine (0.1 cm^3) in dichloromethane (2 cm^3) was stirred at room temperature for 24 h. The solvents were evaporated off under reduced pressure and the residue was then purified by column chromatography on Florisil, with (1:1) diethyl ether–light petroleum as eluent, to give the diacetate **34b** (1.9 mg, 74%) as an oil; λ_{max}(EtOH)/nm 206; ν_{max}(liq. film)/cm^{-1} 1745, 1725 and 1660; δ_H (*inter alia*) 3.95 (1 H, m, 4.20 (q, *J* 7, OCH_2Me), 4.20 (1 H, m), 4.79 [d, *J* 9.0, CH(O)C*H*OAc], 4.87 (C*H*OAc), 6.08 (d, *J* 15.7, CH=C*H*CO_2Et) and 6.77 (dd, *J* 10.5 and 15.7, C*H*=CHCO_2Et) [Found: *m/z*, 385.1861. $C_{19}H_{28}O_8$ requires (M + H), 385.1862].

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References

1 M. Niwa, T. Endo, S. Ogiso, H. Furukawa and Y. Yamamura, *Chem. Lett.*, 1981, 1285.

2 N. Sakabe, T. Goto and Y. Hirata, *Tetrahedron*, 1977, **33**, 3077; B. Franck and H. P. Gehrken, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 461.
3 S. Rebuffat, D. Davoust, L. Molho and D. Molho, *Phytochemistry*, 1980, **19**, 427.
4 L. J. Mulheirn, R. B. Beechey, D. P. Leworthy and M. D. Osselton, *J. Chem. Soc., Chem. Commun.*, 1974, 874.
5 S. Nishiyama, Y. Shizuri, D. Imai, S. Yamamura, Y. Terada, M. Niwa, K. Kawai and H. Furukawa, *Tetrahedron Lett.*, 1985, **26**, 3243; S. Nishiyama, H. Toshima and S. Yamamura, *Chem. Lett.*, 1986, 1973.
6 S. Nishiyama, Y. Shizuri, S. Yamamura, Y. Terada, K. Kawai and H. Furukawa, *Tetrahedron Lett.*, 1985, **26**, 6239.
7 P. Patel and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1941.
8 J. E. Forbes and G. Pattenden, preceding paper.
9 M. C. Bowden, P. Patel and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1947; M. J. Begley, M. C. Bowden, P. Patel and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1951.
10 Preliminary communications: M. C. Bowden and G. Pattenden, *Tetrahedron Lett.*, 1985, **26**, 4797; J. E. Forbes and G. Pattenden, *Tetrahedron Lett.*, 1987, **28**, 2771.
11 S. Lai, K. Matsunaga, Y. Shizuri and Y. Yamamura, *Tetrahedron Lett.*, 1990, **31**, 5503.
12 S. Nishiyama, Y. Shizuri, H. Toshima, M. Ozaki, S. Yamamura, K. Kawai, N. Kawai and H. Furukawa, *Chem. Lett.*, 1987, 515.
13 W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, 1955, **77**, 89.
14 W. H. Rastetter, T. J. Richard and M. D. Lewis, *J. Org. Chem.*, 1978, **43**, 3163.
15 P. Brougham, M. S. Cooper, D. A. Cummeroon, H. Heaney and N. Thompson, *Synthesis*, 1987, 1015.
16 S. Nishiyama, H. Toshima, H. Kanai and S. Yamamura, *Tetrahedron Lett.*, 1986, **27**, 3643.

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