Formal Total Syntheses of (−)-Isoavenaciolide and (−)-Ethisolide from L-Quebrachitol

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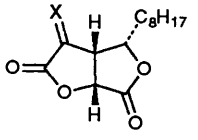
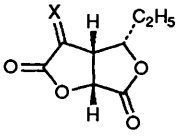
The stereoselective conversions of the naturally occurring optically active cyclitol, L-quebrachitol **5**, into the known synthetic intermediates, **3** and **4**, for preparations of structurally interesting bislactones, (−)-isoavenaciolide **1** and (−)-ethisolide **2**, respectively, are described. These bislactones, **3** and **4**, were synthesized from the common intermediate **19**, which was prepared by periodate oxidation of the bicyclic cyclitol derivative **17**.

Naturally occurring aldohexoses and pentoses have established their value as a 'chiral pool' for syntheses of optically active natural products.[1] However, cyclitols have not been used so widely as a starting material for the synthesis of natural products in spite of their abundance in Nature.[2] L-Quebrachitol **5** is an optically active cyclitol and readily available from the serum of the rubber tree,[3,4] and there have been several reports of its use in the synthesis of optically active natural products.[5] In this article, we report the stereoselective conversions of L-quebrachitol **5** into the known synthetic intermediates **3** and **4** for preparations of (−)-isoavenaciolide **1** and (−)-ethisolide **2**, and the usefulness of **5** as a chiral starting material for the synthesis of natural products.[6]



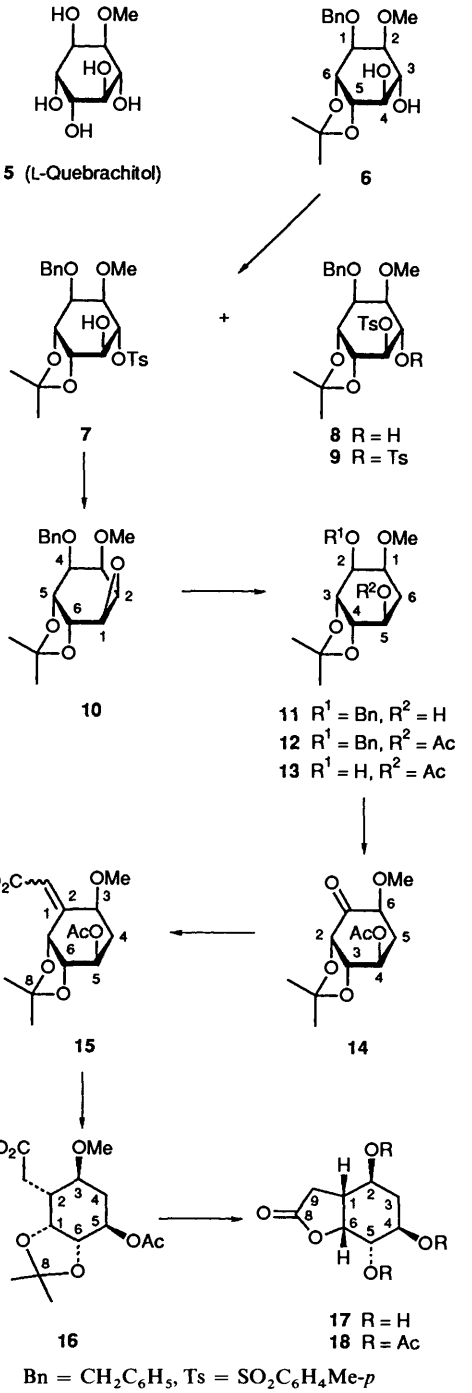
1 X = CH_2[(−)-Isoavenaciolide]
3 X = H_2



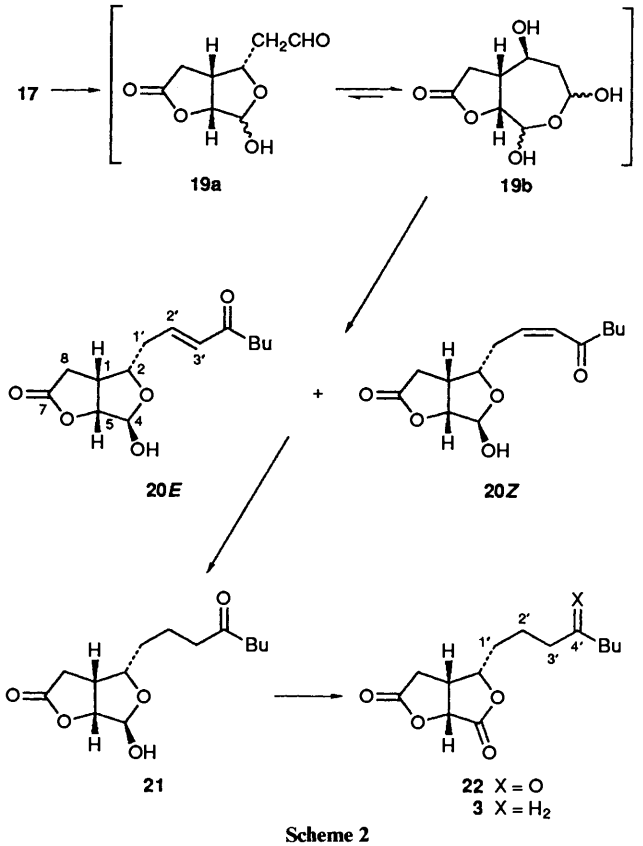
2 X = CH_2[(−)-Ethisolide]
4 X = H_2

The mould metabolites (−)-isoavenaciolide **1** and (−)-ethisolide **2** are structurally interesting bislactones and **1** has been reported to possess antifungal and antibacterial activities.[7] Isoavenaciolide has been synthesized in racemic form,[8] and as its natural enantiomer from D-glucose,[9] D-ribose,[10,11] and a non-carbohydrate precursor,[12] and ethisolide has been synthesized in racemic form[8d,13] and in optically active form from D-ribose.[11] Since bislactones, **3** and **4**, have been known as synthetic intermediates for preparations of **1**[8a,b,9–12] and **2**,[11] respectively, we tried to prepare compound **3** and **4** starting from L-quebrachitol **5**. Retrosynthetically, both the target molecules, **3** and **4**, were envisioned to be derived from the same aldehyde **19**, and **19** would be prepared from bicyclic cyclitol derivative **17** by oxidative cleavage of its cyclohexane ring. Therefore, attempts were first made to convert **5** into the bicyclic derivative **17**.

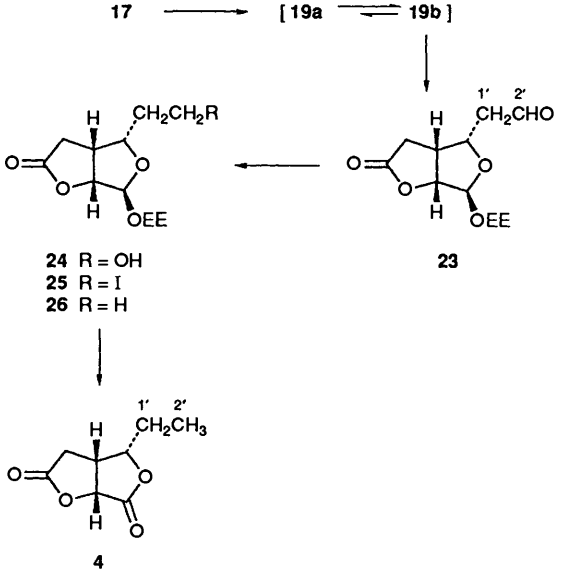
The known diol **6**,[4] prepared from **5** in three steps in 77% overall yield, was treated with 1.1 mol equiv. of toluene-*p*-sulfonyl chloride in pyridine at 50 °C to give a mixture of the two mono(toluene-*p*-sulfonates) **7** and **8** and the bis(toluene-*p*-sulfonate) **9** in 34, 32 and 19% yields, respectively (Scheme 1). The structures of compounds **7** and **8** were established from their ^{1}H NMR spectra with spin–spin decoupling experiments. In compound **7**, a proton attached to the tosyloxy group-bearing carbon (3-H) was observed at δ 4.61 as dd ($J_{2,3}$ 5.1, $J_{3,4}$ 6.2 Hz), whereas 4-H was observed at δ 3.78 as ddd ($J_{4,5}$ 7.0, $J_{4,OH}$ 5.1 Hz). In compound **8**, 3-H was observed at δ 4.06 as ddd



Scheme 1 Bn = $CH_2C_6H_5$, Ts = $SO_2C_6H_4Me$-*p*



Scheme 2



Scheme 3 EE = CH(OEt)Me

($J_{2,3}$ 5.1, $J_{3,4}$ 7.0, $J_{3,OH}$ 1.8 Hz), and 4-H was observed at δ 4.31 as dd ($J_{4,5}$ 8.4 Hz). These spectral data strongly support the assigned structures of compounds **7** and **8**, respectively. Base treatment of compound **7** cleanly afforded the epoxide **10** in 97% yield, which was then reduced with lithium aluminium hydride, followed by acetylation to give a single acetate **12** in 74% yield from **10**. In the ^{1}H NMR spectrum of compound **12**, the signal attributed to 5-H appeared at δ 4.88 as ddd (J 5.9, 7.8 and 10.7 Hz). Spin–spin decoupling experiments revealed that there is no coupling between the signal at δ 4.88 and 1-H, indicating that the acetoxy group is located at C-5 and the observed large coupling constants (7.8 and 10.7 Hz) of 5-H suggest that this proton is axially orientated, supporting the assigned structure of compound **12**. This regioselective ring opening of the epoxide **10** might be due to the presence of a *cis*-*O*-isopropylidene group at C-5 and -6, which would not have allowed the approach of the reagent to C-1.[14] Catalytic hydrogenation of **12** afforded the alcohol **13** in 97% yield. Oxidation of **13** with pyridinium chlorochromate (PCC) afforded the somewhat unstable ketone **14**. Without purification, **14** was submitted to Wittig alkenation with $Ph_3P{=}CHCO_2Et$ in toluene to afford the alkene **15** in 84% yield from **13** as an inseparable mixture (6:1) of *E* and *Z* (or *Z* and *E*) isomers. Hydrogenation of the double bond in **15** with Raney-Ni (T-4)[15] in ethanol proceeded highly stereoselectively and gave **16** and its 2-epimer in a ratio of 35:1 (96% yield). ^{1}H NMR analysis of compound **16** with the spin–spin decoupling technique showed that $J_{1,2}$ is 4 Hz and $J_{2,3}$ is 10 Hz, respectively, indicating that the ethoxycarbonylmethyl group in **16** has an equatorial orientation. Treatment of **16** with boron tribromide in CH_2Cl_2 at room temperature overnight caused deprotection of *O*-methyl, *O*-acetyl and ketal groups, as well as simultaneous lactonisation, to give the γ-lactone **17**, which was isolated as its tri-*O*-acetate **18** in 76% yield from **16**. Acid hydrolysis of **18** regenerated **17**, quantitatively.

Periodate oxidation of **17** proceeded smoothly to afford the hemiacetal aldehyde **19a**, which existed predominantly as its hydrate form **19b**. Since attempted purification of this compound using silica gel chromatography caused degradation, this was submitted to the next reaction without isolation. Thus, treatment of an equilibrium mixture of **19a** and **19b** with stabilised Wittig reagent [$Ph_3P{=}CHC(O)Bu$,[16] 2 mol equiv.] in acetonitrile at room temperature gave the hemiacetal **20*E*** and **20*Z*** in 71% combined yield from **17** in a ratio of 5:1. Using other solvents [tetrahydrofuran (THF), dimethoxyethane, methanol, THF–CH_2Cl_2 (1:5), and THF–toluene (1:5)] or adding catalytic amounts of acids [benzoic acid or pyridinium toluene-*p*-sulfonate(PPTS)] lowered the yields of **20**. The anomeric proton (4-H) in compound **20*E*** was observed at δ 5.47 as a doublet (J 1.5 Hz) and that of compound **20*Z*** appeared at δ 6.54 as a doublet (J 1.0 Hz) in their ^{1}H NMR spectra. This fact implied that the anomeric configurations in **20*E*** and **20*Z*** were specific and assumed to be β-OH, judging from their small coupling constants.[11,17] Saturation of the double bond in both **20*E*** and **20*Z*** gave the single product **21**, quantitatively. In this compound, again the anomeric configuration was specific and assumed to be β-OH (4-H, δ 5.44, d, J 2 Hz). Oxidation of **21** with PCC afforded the bislactone **22** in 68% yield. Finally, reduction of the ketone carbonyl group in **22** was successfully achieved by a modified Clemmensen reaction[18] to give the known precursor of (−)-isoavenaciolide **3** in 81% yield. The physical and spectral properties of the synthetic compound were in good accord with those of an authentic sample.[12]

Having achieved the synthesis of the precursor of (−)-isoavenaciolide, we then turned our attention to the formal total synthesis of (−)-ethisolide **2**. Treatment of the equilibrium mixture of **19a** and **19b** with ethyl vinyl ether in the presence of PPTS at room temperature afforded the acetal-aldehyde **23**. Compound **23** was an inseparable diastereoisomeric mixture of two compounds arising from the presence of the ethoxyethyl (OEE) group, and the anomeric configurations of both diastereoisomers were assigned as β-OEE, judging from the ^{1}H NMR spectrum ($J_{4,5}$ 0 Hz for both diastereoisomers). Without further purification, the aldehyde function of compound **23** was reduced with sodium borohydride to afford the primary alcohol **24** in 26% overall yield from **17**. Iodination and subsequent hydrogenolysis afforded **26** in 65% yield. Jones oxidation of **26** gave the known synthetic intermediate for (−)-ethisolide **4** in 56% yield. The physical and spectral properties of **4** were in

good accord with those of the authentic compound, reported by Wee.[11]

In summary, the formal total syntheses of (−)-isoavenaciolide and (−)-ethisolide starting from L-quebrachitol **5** have been achieved. This synthetic study revealed that L-quebrachitol should be a useful starting material for the synthesis of optically active, highly oxygenated natural products.

Experimental

M.p.s were determined on a Mitamura-riken micro hot stage and are uncorrected. ^{1}H NMR spectra were measured with a JEOL JNM EX-90 (90 MHz) and a JEOL JNM-GSX 270 (270 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in $CDCl_3$, unless otherwise noted: *J* values are given in Hz. ^{13}C NMR spectra were taken on a JEOL JNM-GSX 270 (67 MHz) spectrometer with $^{13}CDCl_3$ as internal standard (δ_C 77.0) for solutions in $CDCl_3$. High resolution mass spectra were measured by a JEOL JMS-DX-302 spectrometer with EI mode (70 eV). Optical rotations were measured with a JASCO DIP-370 instrument. IR spectra were taken with a JASCO IR-810 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure.

1L-1-O-*Benzyl*-5,6-O-*isopropylidene*-2-O-*methyl*-3-O-*tosyl*-chiro-*inositol* **7**, 1L-1-O-*Benzyl*-5,6-O-*isopropylidene*-2-O-*methyl*-4-O-*tosyl*-chiro-*inositol* **8** *and* 1L-1-O-*Benzyl*-5,6-O-*isopropylidene*-2-O-*methyl*-3,4-*di*-O-*tosyl*-chiro-*inositol* **9**.—To a stirred solution of 1L-1-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-methyl-*chiro*-inositol **6**[4] (10.8 g, 33.3 mmol) in pyridine (50 cm^3) was added toluene-*p*-sulfonyl chloride (6.98 g, 36.6 mmol) and the resulting mixture was heated at 50 °C for 4 days. To this mixture was added water (50 cm^3) at 0 °C and the products were extracted with EtOAc (2 × 100 cm^3) and the extract was washed successively with aq. HCl (1 mol dm^{-3}; 100 cm^3), saturated aq. sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3), then dried. Evaporation of the solvent left an oil, which was chromatographed on a column of silica gel (160 g) with EtOAc–PhMe (1 : 10) as eluent, to give, first, compound **9** (3.96 g, 19%) as a syrup (Found: C, 58.5; H, 5.5. $C_{31}H_{36}O_{10}S_2$ requires C, 58.85; H, 5.7%); $[\alpha]_D^{24}$ −46 (*c* 1.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1175 (SO_2); δ_H(270 MHz; $CDCl_3$) 1.22 and 1.34 (each 3 H, 2 s, CMe_2), 2.42 and 2.45 (each 3 H, 2 s, 2 PhMe), 3.27 (3 H, s, OMe), 3.73 (1 H, dd, *J* 4.4, 2.2, 1-H), 3.84 (1 H, dd, *J* 5.4, 2.2, 2-H), 4.23 (1 H, dd, *J* 6.9, 8.3, 4-H), 4.33 (1 H, dd, *J* 5.4, 6.9, 3-H), 4.62 (1 H, d, *J* 12.2, ArC*H*), 4.64 (1 H, dd, *J* 7.3, 8.3, 5-H), 4.69 (1 H, d, *J* 12.2, ArC*H*), 4.80 (1 H, dd, *J* 4.4, 7.3, 6-H), 7.26–7.35 (9 H, m, Ph) and 7.77–7.85 (4 H, m, Ph).

The second fraction gave compound **8** (5.17 g, 32%) as a colourless syrup (Found: C, 58.3; H, 6.1. $C_{24}H_{30}O_8S{\cdot}H_2O$ requires C, 58.1; H, 6.5%); $[\alpha]_D^{21}$ −98 (*c* 0.73 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3520 (OH) and 1175 (SO_2); δ_H(270 MHz; $CDCl_3$) 1.16 and 1.25 (each 3 H, 2 s, CMe_2), 2.43 (3 H, s, PhMe), 3.25 (1 H, d, *J* 1.8, OH), 3.42 (3 H, s, OMe), 3.51 (1 H, dd, *J* 5.1, 2.2, 2-H), 3.91 (1 H, dd, *J* 4.8, 2.2, 1-H), 4.06 (1 H, ddd, *J* 5.1, 7.0, 1.8, 3-H), 4.26 (1 H, dd, *J* 8.4, 6.2, 5-H), 4.31 (1 H, dd, *J* 8.4, 7.0, 4-H), 4.35 (1 H, dd, *J* 6.2, 4.8, 6-H), 4.66 and 4.72 (each 1 H, 2 d, *J* 12.1, ArCH_2) and 7.15–7.86 (9 H, m, Ph).

The third fraction gave compound **7** (5.44 g, 34%) as a crystalline residue, m.p. 91–93 °C (from ethanol) (Found: C, 60.0; H, 6.25. $C_{24}H_{30}O_8S$ requires C, 60.2; H, 6.3%); $[\alpha]_D^{21}$ −24 (*c* 1.12 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3494 (OH) and 1169 (SO_2); δ_H(270 MHz; $CDCl_3$) 1.32 and 1.46 (each 3 H, 2 s, CMe_2), 2.45 (3 H, s, PhMe), 2.87 (1 H, d, *J* 5.1, OH), 3.25 (3 H, s, OMe), 3.59 (1 H, dd, *J* 5.1, 2.2, 2-H), 3.78 (1 H, ddd, *J* 7.0, 6.2, 5.1, 4-H), 3.86 (1 H, dd, *J* 5.0, 2.2, 1-H), 4.20 (1 H, dd, *J* 7.0, 7.0, 5-H), 4.36 (1 H, dd, *J* 7.0, 5.0, 6-H), 4.61 (1 H, dd, *J* 6.2, 5.1, 3-H), 4.66 and 4.72 (each 1 H, 2 d, *J* 12.1, ArCH_2) and 7.15–7.85 (9 H, m, Ph).

1D-1,2-*Anhydro*-4-O-*benzyl*-5,6-O-*isopropylidene*-3-O-*methyl*-allo-*inositol* **10**.—To a stirred solution of the toluene-*p*-sulfonate **7** (10.4 g, 27.7 mmol) in methanol (60 cm^3) was added NaOMe in methanol (1 mol dm^{-3}; 24 cm^3, 24 mmol) at 0 °C, and the mixture was stirred at 0 °C for 15 min then at room temperature for 4 h. The reaction mixture was neutralized by adding acetic acid and diluted with EtOAc (500 cm^3). The organic layer was then washed with saturated aq. sodium hydrogen carbonate and brine, and dried. Evaporation of the solvent left a crystalline residue, which was recrystallized from ethanol to give the title compound **10** (6.44 g, 97%) as needles, m.p. 62–64 °C (from ethanol) (Found: C, 66.6; H, 7.1. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.2%); $[\alpha]_D^{22}$ +32 (*c* 1.2 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.32 and 1.41 (each 3 H, 2 s, CMe_2), 3.23 (1 H, ddd, *J* 3.7, 1.5, 0.7, 4-H), 3.42 (1 H, dddd, *J* 4.2, 3.7, 1.1, 0.7, 3-H), 3.45 (3 H, s, OMe), 3.88 (1 H, dd, *J* 4.2, 2.0, 2-H), 3.92 (1 H, ddd, *J* 4.0, 2.0, 0.7, 1-H), 4.28 (1 H, ddd, *J* 5.5, 4.0, 1.5, 4-H), 4.54 (1 H, ddd, *J* 5.5, 1.1, 0.7, 5-H), 4.65 and 4.80 (each 1 H, 2 d, *J* 12.5, ArCH_2) and 7.25–7.41 (5 H, m, Ph).

1D-(1,2,5/3,4)-2-O-*Benzyl*-3,4-O-*isopropylidene*-1-O-*methylcyclohexanepentol* **11**.—To a stirred suspension of lithium aluminium hydride (3.99 g, 105 mmol) in tetrahydrofuran (THF; 40 cm^3) was added a solution of the epoxide **10** (6.44 g, 21 mmol) in THF (30 cm^3) dropwise at 0 °C. After being stirred at 0 °C for 15 min and then at room temperature for 2 h, water (90 cm^3) was added and the mixture was extracted with EtOAc (300 cm^3). The extract was washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate, and dried. Removal of the solvent left the title compound **11** (5.88 g, 91%) as a colourless syrup. This compound was used in the next step without further purification. A part of this syrup was purified with silica gel chromatography and used as an analytical sample (Found: C, 65.8; H, 7.7. $C_{17}H_{25}O_5$ requires C, 66.2; H, 7.8%); $[\alpha]_D^{22}$ +36 (*c* 0.81 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3470 (OH); δ_H(90 MHz; $CDCl_3$) 1.37 and 1.39 (each 3 H, 2 s, CMe_2), 1.84 (1 H, ddd, *J* 14.3, 4.0, 3.9, 6-H$_{eq}$), 2.06 (1 H, ddd, *J* 14.3, 8.2, 7.7, 6-H$_{ax}$), 3.46 (3 H, s, OMe), 3.54 (1 H, dd, *J* 5.9, 3.2, 2-H), 3.73 (1 H, ddd, *J* 8.2, 3.9, 3.2, 1-H), 4.02 (1 H, ddd, *J* 8.1, 7.7, 4.0, 5-H), 4.33 (1 H, dd, *J* 8.1, 5.8, 4-H), 4.43 (1 H, dd, *J* 5.9, 5.8, 3-H), 4.76 (2 H, s, ArCH_2) and 7.23–7.42 (5 H, m, Ph).

1D-(1,2,5/3,4)-5-O-*Acetyl*-2-O-*benzyl*-3,4-O-*isopropylidene*-1-O-*methylcyclohexanepentol* **12**.—A mixture of compound **11** (4.83 g, 15.7 mmol) in pyridine (12 cm^3) and acetic anhydride (12 cm^3) was stirred at room temperature for 15 h. To this mixture at 0 °C, methanol was added. The resulting mixture was concentrated and azeotroped with toluene to give a residue, which was diluted with EtOAc and then washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, and dried. Evaporation of the solvent left a crystalline residue, which was recrystallised from hot ethanol to give the title compound **12** (4.47 g, 81%) as needles, m.p. 105–106 °C (from ethanol) (Found: C, 65.0; H, 7.3. $C_{19}H_{26}O_6$ requires C, 65.1; H, 7.5%); $[\alpha]_D^{23}$ −71 (*c* 1.1 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1722 (ester); δ_H(270 MHz; $CDCl_3$) 1.34 and 1.48 (each 3 H, 2 s, CMe_2), 1.86 (1 H, ddd, *J* 12.9, 10.7, 8.6, 6-H$_{ax}$), 2.08 (3 H, s, OAc), 2.06–2.13 (1 H, m, 6-H$_{eq}$), 3.36 (3 H, s, OMe), 3.60 (1 H, ddd, *J* 8.6, 3.9, 2.4, 1-H), 3.92 (1 H, dd, *J* 4.4, 2.4, 2-H), 4.22 (1 H, dd, *J* 7.8, 5.9, 4-H), 4.34 (1 H, dd, *J* 5.9, 4.4, 3-H), 4.71 and 4.80 (each 1 H, 2 d, *J* 12.2, ArCH_2), 4.88 (1 H, ddd, *J* 10.7, 7.8, 5.9, 5-H) and 7.26–7.37 (5 H, m, Ph).

1D-(1,2,5/3,4)-5-O-*Acetyl*-3,4-O-*isopropylidene*-1-O-*methylcyclohexanepentol* **13**.—A mixture of the acetate **12** (1.50 g, 4.28 mmol) and 20% $Pd(OH)_2$ on carbon (90 mg) in ethanol–EtOAc (1 : 1; 10 cm^3) was hydrogenolysed under an atmospheric pressure of H_2 at room temperature for 4 h. The catalyst was

removed by filtration, and the filtrate was concentrated to give a residue, which was chromatographed on a silica gel column (20 g), with EtOAc–PhMe (1:3) as eluent, to give compound **13** (1.08 g, 97%) as a crystalline residue, m.p. 71–72 °C (from ethanol) (Found: C, 55.0; H, 7.5. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.7%); $[\alpha]_D^{21}$ −72 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3470 (OH) and 1740 (ester); δ_H(90 MHz; $CDCl_3$) 1.40 and 1.50 (each 3 H, 2 s, CMe_2), 1.60–2.10 (2 H, m, 6-H_{eq} and 6-H_{ax}), 2.78 (1 H, br s, OH), 3.39 (3 H, s, OMe), 3.58 (1 H, ddd, *J* 10.5, 4.3, 3.0, 1-H), 4.10–4.38 (3 H, m, 2-, 3- and 4-H) and 4.87 (1 H, ddd, *J* 11.5, 7.7, 5.0, 5-H).

2L-(2,3/4,6)-4-O-*Acetyl*-2,3,4,6-*tetrahydroxy*-2,3-O-*isopropylidene*-6-O-*methylcyclohexanone* **14**.—To a stirred suspension of pyridinium chlorochromate (PCC; 5.49 g, 25.5 mmol) and molecular sieves 4Å (powder; 6 g) in dichloromethane (30 cm^3) at 0 °C was added a solution of compound **13** (947 mg, 3.64 mmol) in dichloromethane (10 cm^3) dropwise. After being stirred at 0 °C for 10 min, and then at room temperature for 4 h, the reaction mixture was partially concentrated and chromatographed on a silica gel column (50 g), with ether as eluent, to give the ketone **14** (890 mg, 95%) as a colourless syrup (Found: M^+, 258.1104. $C_{12}H_{18}O_6$ requires *M*, 258.1103); $[\alpha]_D^{21}$ −47 (*c* 0.96 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O); δ_H(270 MHz; $CDCl_3$) 1.37 and 1.57 (each 3 H, 2 s, CMe_2), 2.06 (3 H, s, OAc), 2.02–2.14 (1 H, m, 5-H), 2.67 (1 H, ddd, *J* 7.7, 3.7, 2.0, 5-H), 3.43 (3 H, s, OMe), 4.10 (1 H, dd, *J* 3.7, 2.5, 6-H), 4.50–4.56 (2 H, m, 2- and 3-H) and 5.01–5.07 (1 H, m, 4-H). Since this compound was relatively unstable at room temperature, it was used immediately in the next reaction step without further purification.

2E-*and* 2Z-(1R,3S,5R,6S)-5-*Acetoxy*-2-(*ethoxycarbonylmethylene*)-3-*methoxy*-8,8-*dimethyl*-7,9-*dioxabicyclo*[4.3.0]*nonane* **15**.—A mixture of the ketone **13** (890 mg, 3.44 mmol) and (ethoxycarbonylmethylene)triphenylphosphorane (2.53 g, 7.27 mmol) in toluene (10 cm^3) was stirred at room temperature for 16 h. The mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (80 g), with EtOAc–PhMe (1:7) as eluent, to give the alkene **15** (1.04 g, 92%) as a colourless syrup. ^{1}H NMR analysis showed this syrup is a 6.6:1 mixture of *E* and *Z* (or *Z* and *E*) isomers (Found: C, 58.5; H, 7.2. $C_{16}H_{24}O_7$ requires C, 58.5; H, 7.4%); ν_{max}(neat)/cm^{-1} 1745 and 1720 (C=O) and 1665 (C=C); δ_H(for the major isomer; 270 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7.3, OCH_2CH_3), 1.41 (1 H, ddd, *J* 12.5, 11.0, 11.0, 4-H), 1.43 and 1.53 (each 3 H, 2 s, CMe_2), 2.07 (3 H, s, OAc), 2.45 (1 H, ddd, *J* 12.5, 5.5, 5.5, 4-H), 3.45 (3 H, s, OMe), 4.12 (1 H, ddd, *J* 11.0, 4.4, 1.8, 3-H), 4.13 (1 H, dd, *J* 7.0, 5.5, 6-H), 4.21 (2 H, q, *J* 7.3, OCH_2CH_3), 5.03 (1 H, ddd, *J* 11.0, 7.0, 4.4, 5-H), 6.04 (1 H, d, *J* 5.5, 1-H) and 6.31 (1 H, d, *J* 1.8, vinyl).

(1R,2R,3S,5R,6S)-5-*Acetoxy*-2-(*ethoxycarbonylmethyl*)-3-*methoxy*-8,8-*dimethyl*-7,9-*dioxabicyclo*[4.3.0]*nonane* **16**.—A mixture of the alkene **15** (733 mg, 2.23 mmol) and Raney-Ni (T-4; *ca.* 1 cm^3) in ethanol (3 cm^3) was hydrogenolysed under an atmospheric pressure of H_2 at room temperature for 63 h. The catalyst was removed by filtration, and the filtrate was concentrated to give a residue, which was chromatographed on a silica gel column (70 g), with EtOAc–hexane (1:10) as eluent, to give compound **16** (707 mg, 96%) as a colourless syrup. ^{1}H NMR analysis showed this syrup is a 35:1 mixture of compound **16** and its 2-epimer (Found: C, 58.1; H, 7.6. $C_{16}H_{26}O_7$ requires C, 58.2; H, 7.9%); $[\alpha]_D^{22}$ +2 (*c* 1.2 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester); δ_H(270 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.0, OCH_2CH_3), 1.31 and 1.47 (each 3 H, 2 s, CMe_2), 2.08 (3 H, s, OAc), 2.07–2.19 (1 H, m, 4-H), 2.22–2.38 (2 H, m, 2-H and 4-H), 2.52 (1 H, dd, *J* 15.9, 8.8, $CHCO_2Et$), 2.76 (1 H, dd, *J* 15.9, 5.3, $CHCO_2Et$), 3.22–3.32 (1 H, m, 3-H), 3.33 (3 H, s, OMe), 4.02 (1 H, dd, *J* 7.5, 5.1, 6-H), 4.15 (2 H, q, *J* 7.0, OCH_2CH_3), 4.41 (1 H, dd, *J* 5.1, 4.0, 1-H) and 4.89 (1 H, ddd, *J* 11.7, 7.5, 4.0, 5-H).

(1R,2S,4R,5S,6R)-2,4,5-*Trihydroxy*-7-*oxabicyclo*[4.3.0]*nonan*-8-*one* **17**.—To a stirred solution of compound **16** (2.10 g, 6.36 mmol) in dichloromethane (10 cm^3) at 0 °C was added a solution of BBr_3 in dichloromethane (1 mol dm^{-3}; 26 cm^3, 26 mmol). After being stirred at room temperature for 17 h, the mixture was concentrated to give a residue. To this residue at 0 °C, water (10 cm^3) was added and the resulting mixture was again concentrated. The resultant syrup was treated with pyridine (20 cm^3) and acetic anhydride (20 cm^3) at room temperature for 40 h. The reaction mixture was concentrated and azeotroped with toluene to give a residue, which was chromatographed on a silica gel column (100 g), with EtOAc–PhMe (1:3) as eluent, to give (1*R*,2*S*,4*R*,5*S*,6*R*)-2,4,5-triacetoxy-7-oxabicyclo[4.3.0]nonan-8-one **18** (1.53 g, 76%) as a crystalline residue, m.p. 162–164 °C (from propan-2-ol) (Found: C, 53.4; H, 5.6. $C_{14}H_{18}O_8$ requires C, 53.5; H, 5.8%); $[\alpha]_D^{27}$ −101 (*c* 1.1 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1787 (γ-lactone), 1750 and 1732 (ester); δ_H(270 MHz; $CDCl_3$) 1.75 (1 H, m, 3-H_{ax}), 2.05, 2.08 and 2.12 (each 3 H, 3 s, OAc × 3), 2.38 (1 H, ddd, *J* 13.6, 4.3, 4.3, 3-H_{eq}), 2.50 (1 H, dd, *J* 11.9, 6.1, 9-H), 2.69 (1 H, dd, *J* 11.9, 8.2, 9-H), 2.74 (1 H, m, 1-H), 4.85 (1 H, dd, *J* 5.5, 3.3, 6-H), 4.85 (1 H, ddd, *J* 9.4, 9.4, 4.3, 2-H), 5.17 (1 H, ddd, *J* 8.4, 3.3, 1.5, 5-H) and 5.21 (1 H, ddd, *J* 8.4, 8.4, 4.3, 4-H).

A solution of the triacetate **18** (1.53 g, 4.86 mmol) in THF (15 cm^3) and aq. HCl (2 mol dm^{-3}; 15 cm^3) was heated at 60 °C for 3 h. The mixture was concentrated and azeotroped with EtOH to afford a syrup, which was chromatographed on a silica gel column (20 g), with $CHCl_3$–MeOH (10:1) as eluent, to give compound **16** (914 mg, 100%) as plates, m.p. 179–181 °C (from propanol) (Found: C, 51.3; H, 6.1. $C_8H_{12}O_5$ requires C, 51.1; H, 6.4%); $[\alpha]_D^{25}$ −64 (*c* 0.24 in MeOH); ν_{max}(neat)/cm^{-1} 3350 (OH) and 1760 (γ-lactone); δ_H(270 MHz; [$^2H_4$]MeOH) 1.46 (1 H, ddd, *J* 11.6, 11.6, 11.6, 3-H), 2.13 (1 H, ddd, *J* 11.6, 4.0, 4.0, 3-H), 2.33 (1 H, dddd, *J* 9.2, 6.6, 4.0, 1.3, 1-H), 2.57 (1 H, dd, *J* 17.2, 1.3, 9-H), 2.78 (1 H, dd, *J* 17.2, 6.6, 9-H), 3.43 (1 H, ddd, *J* 11.6, 9.2, 4.0, 2-H), 3.57 (1 H, dd, *J* 9.2, 4.0, 5-H), 3.68 (1 H, ddd, *J* 11.6, 9.2, 4.0, 4-H) and 4.70 (1 H, dd, *J* 4.0, 4.0, 6-H).

(1R,2S,4R,5R)-4-*Hydroxy*-2-[(2E)-4-*oxooct*-2-*enyl*]-3,6-*dioxabicyclo*[3.3.0]*octan*-7-*one* **20E** *and its Z-isomer* **20Z**.—To a stirred solution of the triol **17** (120 mg, 0.64 mmol) in acetone–water (5:1; 6 cm^3) at 0 °C was added an aqueous solution (14 cm^3) of sodium periodate (1.37 g, 6.40 mmol) dropwise. The pH of the reaction mixture was maintained at 6–7 by adding solid sodium hydrogen carbonate. After being stirred at 0 °C for 2 h, the mixture was concentrated to give a residue. This residue was suspended in EtOAc–Me_2CO (10:1; v/v) and the insoluble materials were removed by filtration through a pad of Celite. The filtrate was concentrated to afford a crude mixture of compounds **19a** and **19b** as a syrup. This crude syrup was dissolved in acetonitrile (8 cm^3). To this solution was added valerylmethylenetriphenylphosphorane (462 mg, 1.28 mmol) and the mixture was stirred at room temperature for 10 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (40 g), with EtOAc–PhMe (1:2) as eluent, to afford, first, compound **20Z** (20 mg, 11%) as a crystalline residue, m.p. 54–57 °C (from ether–hexane) (Found: C, 62.7; H, 7.55. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%); $[\alpha]_D^{26}$ −70 (*c* 0.24 in $CHCl_3$, 5 min) and −67 (12 h); ν_{max}(neat)/cm^{-1} 3430 (OH), 1780 (γ-lactone), 1690 (C=O) and 1620 (C=C); δ_H(270 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.3, 8′-H_3), 1.33 (2 H, sext, *J* 7.3, 7′-H_2), 1.58 (2 H, quint, *J* 7.3, 6′-H_2), 2.48 (2 H, t, *J* 7.3, 5′-H_2), 2.54 (1 H, dd, *J* 18.6, 8.8, 8-H_a), 2.65 (1 H, dd, *J* 18.6, 5.4, 8-H_b), 2.78 (1 H, m, 1′-H_a), 3.09 (1 H, m, 1′-H_b), 3.21 (1 H, m, 1-H), 4.47 (1 H, ddd, 9.0, 5.6, 4.9, 2-H), 4.92 (1 H, dd, *J* 6.8,

1.0, 5-H), 5.54 (1 H, d, *J* 1.0, 4-H), 6.13 (1 H, ddd, J 11.2, 7.3, 6.4, 2′-H) and 6.28 (1 H, dt, *J* 11.2, 1.5, 3′-H); δ_C(67 MHz; $CDCl_3$) 13.9, 22.3, 25.9, 27.8, 30.6, 40.0, 44.1, 78.4, 87.6, 100.1, 128.3, 142.1, 176.1 and 201.9.

The second fraction gave compound **20*E*** (103 mg, 60%) as a colourless syrup (Found: C, 62.4; H, 7.3. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%); $[\alpha]_D^{27}$ −53 (*c* 1.05 in $CHCl_3$, 5 min); ν_{max}(neat)/cm^{-1} 3400 (OH), 1785 (γ-lactone), 1670 (C=O) and 1630 (C=C); δ_H(270 MHz; $CDCl_3$) 0.84 (3 H, t, *J* 7.3, 8′-H_3), 1.33 (2 H, sext, *J* 7.3, 7′-H_2), 1.59 (2 H, quint, *J* 7.3, 6′-H_2), 2.35–2.65 (6 H, m, 1′-, 5′-H_2, 8-H), 3.22 (1 H, m, 1-H), 4.51 (1 H, ddd, *J* 8.6, 5.9, 5.4, 2-H), 4.94 (1 H, dd, *J* 7.3, 1.5, 5-H), 5.47 (1 H, d, *J* 1.5, 4-H), 6.23 (1 H, dt, *J* 16.1, 1.5, 3′-H) and 6.79 (1 H, ddd, *J* 16.1, 6.8, 6.8, 2′-H); δ_C(67 MHz; $CDCl_3$) 14.1, 22.5, 26.3, 28.1, 33.8, 39.8, 40.6, 77.7, 87.9, 100.0, 132.4, 141.3, 176.2 and 200.9.

(1R,2S,4R,5R)-4-*Hydroxy*-2-(4-*oxooctyl*)-3,6-*dioxabicyclo*[3.3.0]*octan*-7-*one* **21**.—A mixture of the alkene **20** (20.0 mg, 0.075 mmol) and 20% $Pd(OH)_2$ on carbon (8 mg) in ethanol (1 cm^3) was hydrogenolysed under an atmospheric pressure of H_2 at room temperature for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated to give a residue, which was chromatographed on a silica gel column (1 g), with EtOAc–PhMe (1:3) as eluent, to give compound **13** (20 mg, 100%) as a colourless syrup (Found: C, 62.0; H, 8.1. $C_{14}H_{22}O_5$ requires C, 62.2; H, 8.2%); $[\alpha]_D^{19}$ −34 (*c* 1.1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 (OH), 1780 (γ-lactone) and 1705 (ketone); δ_H(270 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.3, 8′-H_3), 1.31 (2 H, sext, *J* 7.3, 7′-H_2), 1.45–1.80 (6 H, m, 1′-, 2′-, 6′-H_2), 2.41 (2 H, t, *J* 7.3, 5′-H_2), 2.46–2.65 (4 H, m, 3′-, 8-H_2), 3.16 (1 H, dddd, *J* 8.8, 6.8, 6.2, 5.9, 1-H), 4.35 (1 H, ddd, *J* 6.2, 6.2, 6.2, 2-H), 4.93 (1 H, dd, *J* 6.8, 2.0, 5-H) and 5.44 (1 H, d, *J* 2.0, 4-H); δ_C(67 MHz; $CDCl_3$) 13.8, 20.3, 22.3, 25.9, 27.6, 30.0, 39.6, 42.0, 42.6, 78.4, 87.8, 99.8, 176.4 and 211.1.

(1R,2S,5R)-2-(4-*Oxooctyl*)-3,6-*dioxabicyclo*[3.3.0]*octane*-4,7-*dione* **22**.—To a stirred suspension of pyridinium chlorochromate (113 mg, 0.52 mmol) and molecular sieves 4Å (powder; 110 mg) in dichloromethane (1 cm^3) at 0 °C was added a solution of the lactol **21** (20 mg, 0.075 mmol) in dichloromethane (1 cm^3) dropwise. After being stirred at 0 °C for 15 min, and then at room temperature for 2 h, the reaction mixture was partially concentrated and chromatographed on a silica gel column (600 mg), with ether as eluent, to give the crude ketone. This was recrystallised from EtOAc–hexane (1:1, v/v) to give compound **22** (13.5 mg, 68%) as plates, m.p. 54–55 °C (Found: C, 62.6; H, 7.4. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%); $[\alpha]_D^{18}$ −12 (*c* 0.6 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1774 (γ-lactone) and 1710 (ketone); δ_H(270 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.3, 8′-H_3), 1.31 (2 H, sext, *J* 7.3, 7′-H_2), 1.56 (2 H, quint, *J* 7.3, 6′-H_2), 1.62–1.79 (4 H, m, 1′-, 2′-H_2), 2.41 (2 H, t, *J* 7.3, 5′-H_2), 2.49–2.55 (2 H, m, 3′-H_2), 2.61 (1 H, dd *J* 18.2, 9.5, 8-H_a), 2.69 (1 H, dd, *J* 18.2, 9.5, 8-H_b), 3.51 (1 H, dddd, *J* 9.5, 9.5, 8.4, 5.5, 1-H), 4.58–4.65 (1 H, m, 2-H) and 5.16 (1 H, d, *J* 8.4, 5-H); δ_C(67 MHz; $CDCl_3$) 13.8, 19.5, 22.3, 25.9, 26.9, 30.8, 39.3, 41.4, 42.7, 76.8, 78.6, 170.4, 173.6 and 210.2.

(1R,2S,5R)-2-*Octyl*-3,6-*dioxabicyclo*[3.3.0]*octane*-4,7-*dione* **3**.—The ketone **22** (12 mg, 0.043 mmol) was dissolved in dry ether (4 cm^3) saturated with hydrogen chloride at 0 °C and stirred at 0 °C for 15 min. Active zinc powder (170 mg, 2.60 mmol) was added to the resulting solution. After being stirred at 0 °C for 3 h, the reaction mixture was poured into iced water and then extracted three times with EtOAc. The organic layer was washed with brine and dried. Removal of the solvent afforded the residue, which was chromatographed on a silica gel column (200 mg), with EtOAc–PhMe (1:5) as eluent, to give the known synthetic intermediate for (−)-isoavenaciolide **3** (9 mg, 81%) as needles, m.p. 109–111 °C [from ether–hexane (1:10, v/v)] (lit.,[12] 109–111 °C) (Found: C, 66.1; H, 8.85. Calc. for $C_{14}H_{22}O_4$: C, 66.1; H, 8.7%); $[\alpha]_D^{20}$ −17 (*c* 1.0 in $CHCl_3$) [lit.,[12] −21 (*c* 1.0 in $CHCl_3$)]; ν_{max}(KBr)/cm^{-1} 1774 (γ-lactone); δ_H(270 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.8, 8′-H_3), 1.28–1.89 (14 H, m, 1′, 2′, 3′, 4′, 5′, 6′-, 7′-H_2), 2.64 (2 H, d, *J* 9.5, 8-H_2), 3.47 (1 H, dddd, *J* 9.5, 9.5, 8.4, 5.5, 1-H), 4.62 (1 H, ddd, *J* 8.4, 5.5, 5.5, 2-H) and 5.16 (1 H, d, *J* 8.4, 5-H); δ_C(67 MHz; $CDCl_3$) 14.1, 22.6, 25.5, 26.8, 29.1, 29.2, 29.3, 31.4, 31.8, 39.4, 77.0, 78.7, 170.6 and 173.7. The ^{1}H and ^{13}C NMR data were fully identical with those of the authentic compound.[12]

(1R,2S,4S,5R)-4-(1-*Ethoxyethoxy*)-2-*formylmethyl*-3,6-*dioxabicyclo*[3.3.0]*octan*-7-*one* **23**.—The triol **17** (20 mg, 0.11 mmol) was treated with sodium periodate (97 mg, 0.45 mmol) similarly as described for the preparation of compound **20*E*** and **20*Z*** to afford a crude mixture of **19a** and **19b** as a syrup. This syrup was treated with ethyl vinyl ether (0.031 cm^3, 0.32 mmol) and pyridinium toluene-*p*-sulfonate (6.5 mg, 0.026 mmol) in acetonitrile (1.5 cm^3) at room temperature for 60 h. During the course of the reaction, additional ethyl vinyl ether (0.062 cm^3 at 18 h and 0.031 cm^3 at 25 h) and pyridinium toluene-*p*-sulfonate (13.0 mg at 18 h and 6.5 mg at 25 h) were added to the reaction mixture. To the resulting mixture was added saturated aq. sodium hydrogen carbonate (0.3 cm^3) at 0 °C, and the mixture was concentrated to give a residue, which was dissolved in EtOAc and washed with brine, then dried. Removal of the solvent left a residue, which was roughly purified on a silica gel column (2 g), with acetone–hexane (1:4) as eluent, to give the aldehyde **23** (8.5 mg, 51%) as a colourless syrup. ^{1}H NMR spectrum revealed that compound **23** is a *ca.* 1.4:1 mixture of the diastereoisomers arising from the presence of the ethoxyethyl ether. This compound was found to be somewhat unstable, and so used in the next step without further purification; ν_{max}(neat)/cm^{-1} 1790 (γ-lactone) and 1720 (aldehyde); δ_H(270 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.3, OCH_2CH_3), 1.34 (3 H × 7/12, d, *J* 5.4, $OCHCH_3$), 1.36 (3 H × 5/12, d, *J* 5.4, $OCHCH_3$), 2.35–2.44 (1 H, m, 8-H_a), 2.54–2.70 (2 H, m, 8-H_b, 1′-H_a), 2.89–2.97 (1 H, m, 1′-H_b), 3.00–3.37 (1 H, m, 1-H), 3.40–3.78 (2 H, m, OCH_2CH_3), 4.66 (1 H × 7/12, ddd, *J* 6.4, 6.4, 7.3, 2-H), 4.75 (1 H × 5/12, ddd, *J* 6.4, 6.4, 7.3, 2-H), 4.84 (1 H × 5/12, q, *J* 5.4, $OCHCH_3$), 4.88 (1 H × 7/12, q, *J* 5.4, $OCHCH_3$), 4.95 (1 H × 5/12, d, *J* 7.3, 5-H), 4.98 (1 H × 7/12, d, *J* 7.3, 5-H), 5.30 (1 H × 5/12, s, 4-H), 5.36 (1 H × 7/12, s, 4-H) and 9.81 (1 H, s, *CHO*).

(1R,2S,4S,5R)-4-(1-*Ethoxyethoxy*)-2-(2-*hydroxyethyl*)-3,6-*dioxabicyclo*[3.3.0]*octan*-7-*one* **24**.—To a stirred solution of the aldehyde **23** (14.2 mg, 0.055 mmol) in methanol and THF (1:1; v/v, 2 cm^3) at 0 °C was added sodium borohydride (2.1 mg, 0.055 mmol). After stirring at 0 °C for 10 min, additional sodium borohydride (2.1 mg) was added and the resulting mixture was stirred at 0 °C for 10 min. The reaction mixture was neutralized with acetic acid and then concentrated to give a residue, which was diluted with EtOAc and washed with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (1 g), with acetone–hexane (2:7) as eluent, to give the alcohol **24** (7.3 mg, 26% overall yield from compound **17**), which was a 1.4:1 mixture of two diastereomers arising from the presence of the ethoxyethyl ether, as a colourless syrup (Found: C, 55.1; H, 7.5. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.7%); ν_{max}(neat)/cm^{-1} 3500 (OH) and 1780 (γ-lactone); δ_H(270 MHz; $CDCl_3$) 1.22 (3 H × 5/12, t, *J* 7.1, OCH_2CH_3), 1.23 (3 H × 7/12, t, *J* 7.1, OCH_2CH_3), 1.36 (3 H × 7/12, d, *J* 5.4, $OCHCH_3$), 1.37 (3 H × 5/12, d, *J* 5.4, $OCHCH_3$), 1.52–1.94 (3 H, m, 1′-H_2 and OH), 2.49–2.67 (2 H, m, 8-H_2), 3.12–3.23 (1 H, m, 1-H), 3.43–3.86 (4 H, m, 2′-H_2 and OCH_2CH_3), 4.38 (1

H × 7/12, ddd, *J* 4.6, 5.9, 9.0, 2-H), 4.46 (1 H × 5/12, ddd, *J* 4.6, 5.9, 9.0, 2-H), 4.85 (1 H × 5/12, q, *J* 5.4, OC*H*CH_3), 4.88 (1 H × 7/12, q, *J* 5.4, OC*H*CH_3), 4.93 (1 H × 5/12, d, *J* 7.3, 5-H), 4.97 (1 H × 7/12, d, *J* 7.3, 5-H), 5.30 (1 H × 5/12, s, 4-H) and 5.36 (1 H × 7/12, s, 4-H).

(1R,2S,4S,5R)-4-(1-*Ethoxyethoxy*)-2-(2-*iodoethyl*)-3,6-*dioxabicyclo*[3.3.0]*octan*-7-*one* **25**.—To a stirred solution of the alcohol **24** (7.3 mg, 0.028 mmol) and triphenylphosphine (51.5 mg, 0.196 mmol) in THF (1 cm^3) at 0 °C under Ar was added diethyl azodicarboxylate (0.031 cm^3, 0.196 mmol). After being stirred at 0 °C for 5 min, methyl iodide (0.012 cm^3, 0.196 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and washed successively with saturated aq. sodium thiosulfate, saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (2 g), with acetone–hexane (1:9) as eluent, to give the iodide **25** (7.0 mg, 67%), which was a 1.4:1 mixture of two diastereoisomers arising from the presence of the ethoxyethyl ether, as a colourless syrup (Found: M^+, 370.0250. $C_{12}H_{19}IO_5$ requires *M*, 370.0277); ν_{max}(neat)/cm^{-1} 1790 (γ-lactone); δ_H(270 MHz; $CDCl_3$) 1.22 (3 H × 7/12, t, *J* 7.1, OCH_2CH_3), 1.23 (3 H × 5/12, t, *J* 7.1, OCH_2CH_3), 1.37 (3 H × 7/12, d, *J* 5.4, OCHCH_3), 1.38 (3 H × 5/12, d, *J* 5.4, OCHCH_3), 1.89–2.22 (2 H, m, 1′-H_2), 2.46–2.66 (2 H, m, 8-H_2), 3.13–3.39 (3 H, m, 1-H and 2′-H_2), 3.45–3.86 (2 H, m, OCH_2CH_3), 4.34 (1 H × 7/12, ddd, *J* 3.4, 6.1, 9.3, 2-H), 4.46 (1 H × 5/12, ddd, *J* 3.4, 6.1, 9.3, 2-H), 4.86 (1 H × 5/12, q, *J* 5.4, OC*H*CH_3), 4.91 (1 H × 7/12, q, *J* 5.4, OC*H*CH_3), 4.94 (1 H × 5/12, d, *J* 7.3, 5-H), 4.97 (1 H × 7/12, d, *J* 7.3, 5-H), 5.28 (1 H × 5/12, s, 4-H) and 5.35 (1 H × 7/12, s, 4-H).

(1R,2S,4S,5R)-4-(1-*Ethoxyethoxy*)-2-*ethyl*-3,6-*dioxabicyclo*-[3.3.0]*octan*-7-*one* **26**.—A mixture of the iodide **25** (7.0 mg, 0.019 mmol) and Raney-Ni (T-4; *ca.* 0.5 cm^3) in EtOAc (1 cm^3) was hydrogenolysed under an atmospheric pressure of H_2 at room temperature for 0.5 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue. This residue was diluted with EtOAc and washed with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (0.7 g), with acetone–hexane (1:9) as eluent, to give the title compound **26** (4.6 mg, 97%), which was a 1.4:1 mixture of two diastereoisomers arising from the presence of the ethoxyethyl ether, as a colourless syrup (Found: C, 58.7; H, 8.1. $C_{12}H_{20}O_5$ requires C, 59.0; H, 8.25%); ν_{max}(neat)/cm^{-1} 1790 (γ-lactone); δ_H(270 MHz; $CDCl_3$) 0.99 (3 H × 7/12, t, *J* 7.3, CH_2CH_3), 1.00 (3 H × 5/12, t, *J* 7.3, CH_2CH_3), 1.22 (3 H × 5/12, t, *J* 7.1, OCH_2CH_3), 1.23 (3 H × 7/12, t, *J* 7.1, OCH_2CH_3), 1.34 (3 H × 7/12, d, *J* 5.4, OCHCH_3), 1.37 (3 H × 5/12, d, *J* 5.4, OCHCH_3), 1.61–1.80 (2 H, m, 1′-H_2), 2.45–2.64 (2 H, m, 8-H_2), 3.06–3.18 (1 H, m, 1-H), 3.43–3.79 (2 H, m, OCH_2CH_3), 4.10 (1 H × 7/12, ddd, *J* 6.1, 6.1, 7.8, 2-H), 4.19 (1 H × 5/12, ddd, *J* 6.1, 6.1, 7.8, 2-H), 4.83 (1 H × 5/12, q, *J* 5.4, OC*H*CH_3), 4.88 (1 H × 7/12, q, *J* 5.4, OC*H*CH_3), 4.93 (1 H × 5/12, d, *J* 7.3, 5-H), 4.96 (1 H × 7/12, d, *J* 7.3, 5-H), 5.24 (1 H × 5/12, s, 4-H) and 5.32 (1 H × 7/12, s, 4-H).

(1R,2S,5R)-2-*Ethyl*-3,6-*dioxabicyclo*[3.3.0]*octane*-4,7-*dione* **4**.—To a stirred solution of compound **26** (4.6 mg, 0.019 mmol) in acetone (1 cm^3) at 0 °C was added Jones reagent (2.67 mol dm^{-3} solution; 0.071 cm^3, 0.19 mmol), and the resulting mixture was stirred at 0 °C for 2 h. The excess of reagent was destroyed by adding propan-2-ol and the insoluble materials were removed by filtration through a pad of Celite. The filtrate was concentrated to give a residue, which was diluted with EtOAc and then washed with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a crystalline residue, which was chromatographed on a silica gel column (0.5 g), with acetone–hexane (1:4) as eluent, to give the known synthetic intermediate for (−)-ethisolide **4** (1.8 mg, 56%) as needles, m.p. 106–107 °C (from EtOAc) (lit.,[11] 97–100 °C) (Found: C, 56.5; H, 6.15. Calc. for $C_8H_{10}O_4$: C, 56.5; H, 5.9%); $[\alpha]_D^{20}$ −27 (*c* 1.1 in $CHCl_3$) [lit.,[11] −27.2 (*c* 1.39 in $CHCl_3$)]; ν_{max}(KBr)/cm^{-1} 1787 (γ-lactone); δ_H(270 MHz; $CDCl_3$) 1.08 (3 H, t, *J* 7.6, 2′-H_3), 1.63 (1 H, dq, *J* 5.9, 7.6, 1′-H_a), 1.90 (1 H, dq, *J* 8.3, 7.6, 1′-H_b), 2.60 (1 H, dd, *J* 9.3, 18.1, 8-H_a), 2.67 (1 H, dd, *J* 9.3, 18.1, 8-H_b), 3.48 (1 H, dddd, *J* 5.9, 8.3, 9.3, 9.3, 1-H), 4.54 (1 H, ddd, *J* 5.9, 5.9, 8.3, 2-H) and 5.16 (1 H, d, *J* 8.3, 5-H); δ_C(67 MHz; $CDCl_3$) 9.8, 24.6, 26.8, 39.1, 77.0, 80.1, 170.6 and 173.8. The ^1H and ^{13}C NMR spectroscopic data were fully identical with those of the authentic compound.[11]

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