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A chemoenzymatic synthesis of the linear triquinane (−)-hirsutene and identification of possible precursors to the naturally occurring (+)-enantiomer

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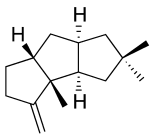
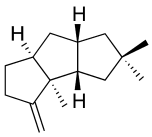
Abstract—An enantiomerically pure *cis*-1,2-dihydrocatechol, which is readily obtained via a toluene dioxygenase-mediated dihydroxylation of toluene in a whole-cell biotransformation process, has been converted over 17 steps into the linear triquinane (−)-hirsutene. Since the enantiomer of the starting material is also available this work constitutes a formal total synthesis of the naturally occurring (+)-form of hirsutene. Furthermore, minor modifications of the route used here offer the possibility of accessing (+)-hirsutene from the original starting material.

1. Introduction

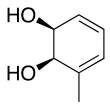
The linear triquinane-type[1] sesquiterpene (+)-hirsutene [(+)-**1**)][2] is the biogenetic precursor to a range of oxygenated derivatives, including hirsutic acid C,[3] complicatic acid,[3] coriolin[4] and hypnophilin,[5] many of which display significant biological properties. As such, this hydrocarbon has been a popular synthetic target and many ingenious approaches to it have been devised.[1,6] Remarkably, only one enantioselective total synthesis of (+)-hirsutene has been achieved,[6a] although others have claimed formal preparations[6b,c,e] of the same target. Weinges et al. have reported[7] the synthesis of the non-natural (−)-enantiomer **1** from (−)-carvone using Curran's tandem radical cyclization strategy[8] as a key element. Herein we report full details of our recently communicated[9] synthesis of (−)-hirsutene (**1**) from the *cis*-1,2-dihydrocatechol **2**, a compound available in enantiomerically pure form via the toluene dioxygenase (TDO)-mediated whole-cell biotransformation of toluene.[10] Since the enantiomeric form of this starting material, viz. *ent*-**2**, is also available[11] the present work constitutes a formal total synthesis of (+)-hirsutene, viz. (+)-**1**. Moreover, minor modifications to the route used here (and discussed below) would appear to offer the possibility that compound **2** could also serve as a precursor to (+)-hirsutene, thus highlighting the potential for the enantiodivergent synthesis of various terpenoids from this readily available chiron.[12]



(+)-**1**



(−)-**1**



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2. Results and discussion

The retrosynthetic analysis of (−)-hirsutene [(−)-**1**)] employed in the present work is shown in Figure 1. Thus, the closing stages of the synthesis would involve reductive cleavage of the three-membered ring associated with the cyclopropa-fused triquinane **3**, followed by deletion of the carbonyl group and, finally, manipulation of the protected hydroxyl group so as to install the exocyclic methylene unit associated with target **1**. Formation of compound **3** was to involve a photochemically-induced oxa-di-π-methane rearrangement of the cyclopentannulated bicyclo[2.2.2]-oct-5-en-2-one **4**, a protocol for triquinane synthesis originally enunciated by Demuth[1c] and recently exploited by Singh et al.[6e] in their preparation of (±)-hirsutene. Compound **4** was, in turn, to be generated via a Diels–Alder cycloaddition reaction between *cis*-1,2-dihydrocatechol **2** and the *gem*-dimethylated cyclopentenone **5**, the last compound being available by established routes[13] from the dimethylketene dimer **6**.

On the basis of recent studies carried out in our laboratories (and to be reported shortly), we anticipated that a high pressure promoted Diels–Alder reaction between diene **2**

Keywords: Chemoenzymatic; Hirsutene; Sesquiterpene; Triquinane; Oxa-di-π-methane; Enantiodivergence; Cycloaddition; *cis*-1,2-Dihydrocatechol.
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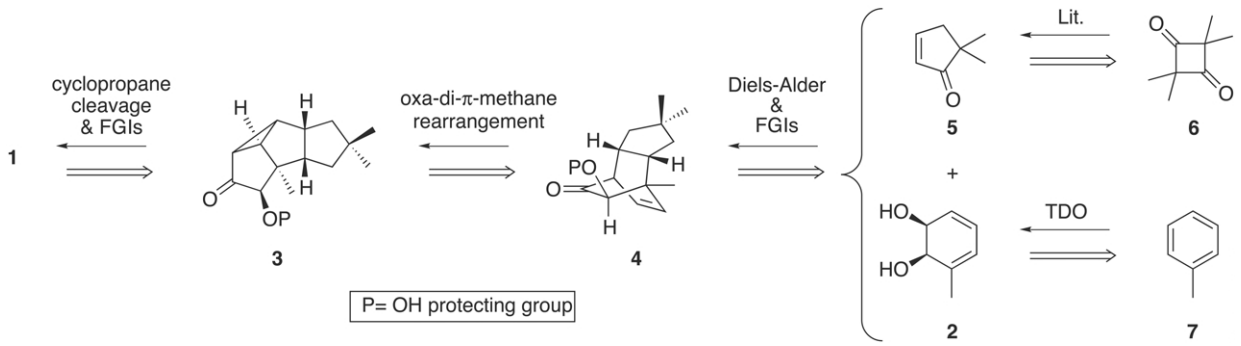
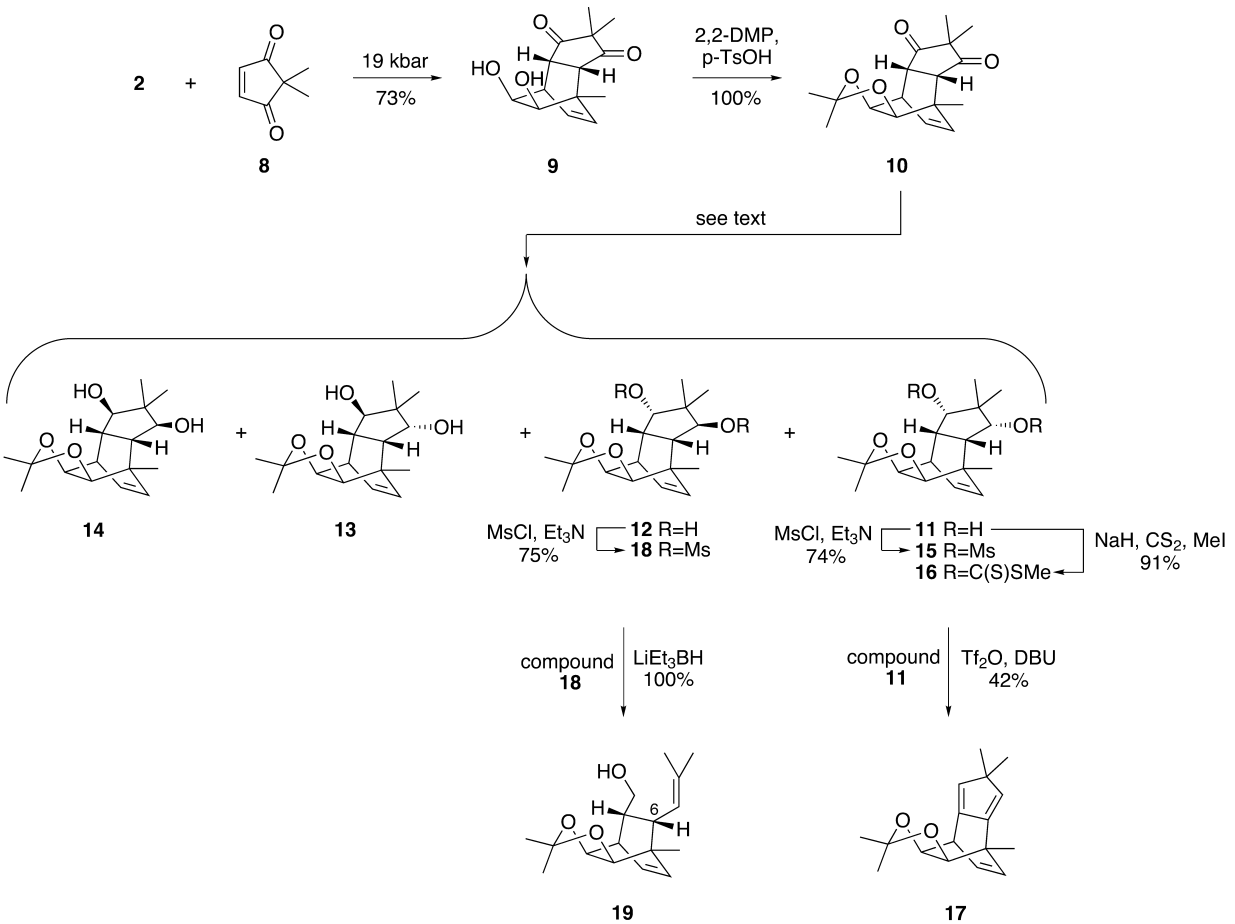


Figure 1.

and dienophile **5** should proceed efficiently and in a *syn*-selective fashion.[14,15] However, all efforts to implement such a reaction failed to produce preparatively useful quantities of the desired cycloaddition product or any other adduct. On the basis that the steric inhibition to this process caused by the *gem*-dimethyl unit of the dienophile could be offset by further carbonyl activation, the reaction of the readily available cyclopentenedione **8** with diene **2** at 19 kbar was examined (Scheme 1). Gratifyingly, the anticipated adduct **9** was obtained and its structure established by X-ray crystallographic studies, details of which will be reported elsewhere. The readily derived acetonide **10** (100%) was prepared in anticipation of examining protocols for the reductive removal, via the corresponding alcohols, of the two now redundant ketone carbonyl units associated with the Diels–Alder adduct. Exposure of compound **10** to various reducing agents led to varying combinations (Table 1) of some or all of the four possible diols **11**–**14**, the first three of which could be purified and then subjected to comprehensive characterization.

Compound **11** was obtained as a crystalline solid such that an X-ray crystallographic analysis could be undertaken, the results of which are presented in Figure 2 and the Experimental section. Unfortunately, all efforts to exploit this diol in the required deoxygenation process have failed. Thus, the derived *bis*-mesylate **15** only produced complex mixtures of products on exposure to hydride donors such as lithium aluminium hydride while the derived *bis*-xanthate



Scheme 1.

Table 1. Product distributions from reduction of dione **10** under various conditions

Entry	Reductant/conditions	% Diol **11**	% Diol **12**	% Diol **13**	% Diol **14**
1	$LiAlH_4$, THF, Δ	10	75	5	9
2	$LiAlH_4$, Et_2O, Δ	28	31	26	10
3	DIBALH, THF, −78 °C	99	0	0	0

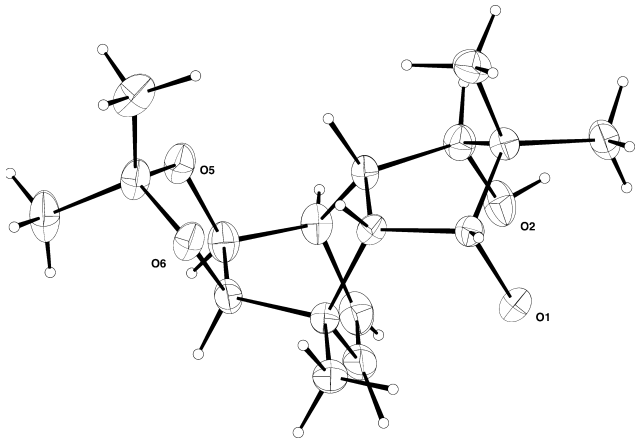
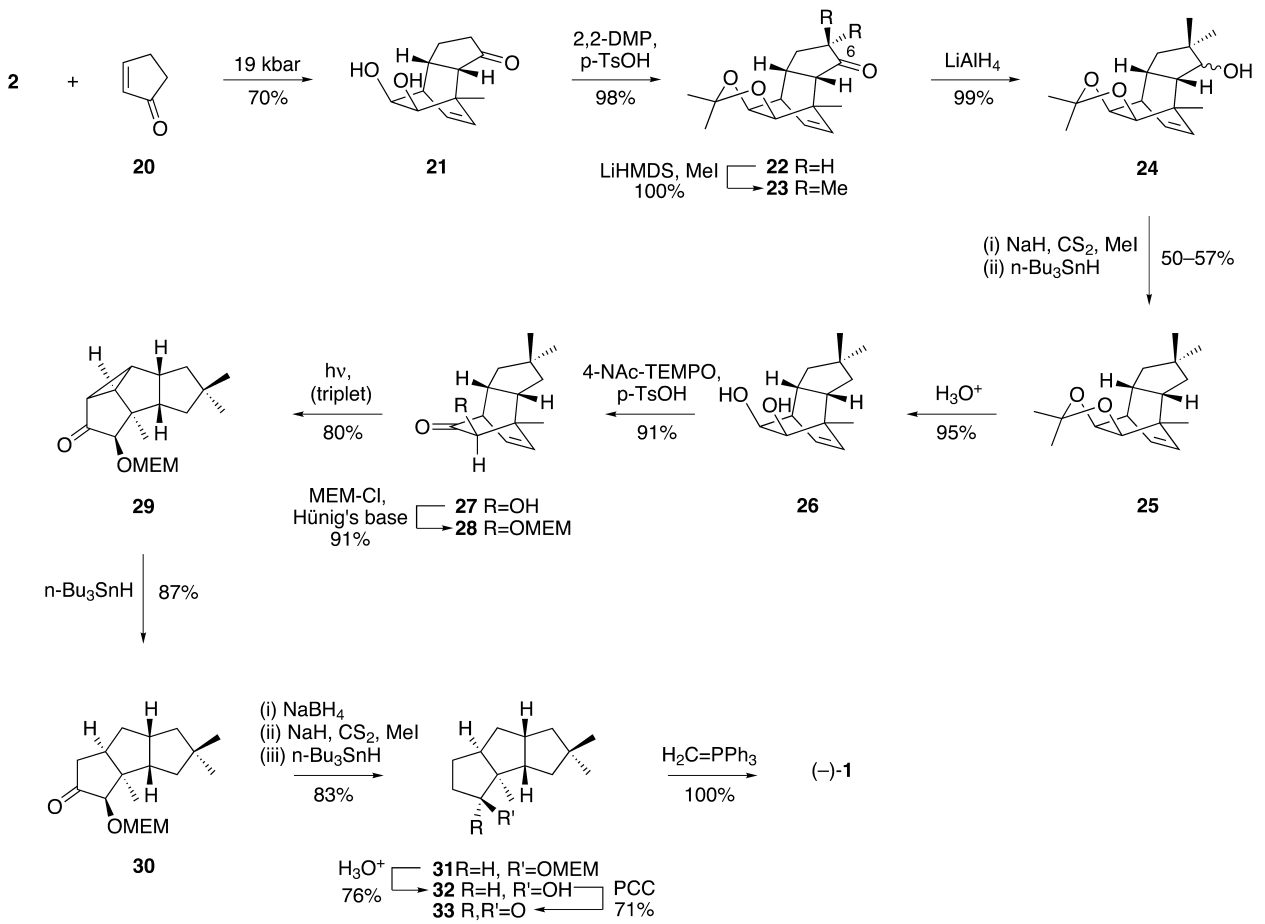


Figure 2. ADEP derived from single-crystal X-ray analysis of diol **11**.

suffered a similar fate during attempts to engage it in Barton–McCombie-type deoxygenation[16] processes. The related *bis*-triflate could not be isolated but underwent two-fold elimination under the conditions of its formation and thus providing the cyclopentadiene **17** (42%) as the only isolable reaction product. In principle, this triene could be subjected to a selective dihydrogenation reaction so as to provide a product capable of being carried forward to (−)-**1**, but the issues of regio- and stereo-selectivity that would need to be addressed in achieving such ends looked too formidable to warrant serious consideration. In a final attempt to effect deoxygenation, the *bis*-mesylate, **18**, derived from diol **12** was subject to reaction with lithium triethylborohydride (Super-Hydride®) but the only product of reaction was the fragmentation product **19** (100%) the structure of which follows from detailed NMR spectroscopic analysis, including the use of NOESY techniques, which revealed an interaction between H6 and the bridgehead methyl protons. The formation of compound **19** from precursor **18** highlights the potential for fragmentation during attempts to reductively deoxygenate 1,3-dioxygenated systems[17] and led us to abandon this approach to substrates (viz. **4**, Fig. 1) suitable for studying the foreshadowed oxa-di-π-methane rearrangement.

The ultimately successful route to (−)-hirsutene [(−)-**1**] is shown in Scheme 2 and the abovementioned problems were addressed by reverting to a protocol that avoids the need for using a 1,3-deoxygenation regime but now requiring a *gem*-dimethylation step after the Diels–Alder cycloaddition reaction. Thus, *cis*-1,2-dihydrocatechol **2** was reacted with cyclopentenone **20** at 19 kbar and the *syn*-addition product **21** (70%) was obtained, together with small quantities (ca. 9%) of the corresponding *anti*-isomer. These adducts were readily separated by flash chromatography and the structure of the former established by single-crystal X-ray analysis, details of which will be published elsewhere. The *cis*-1,2-diol moiety associated with compound **21** was protected, using standard methods, as the corresponding acetonide **22** (98%) which could then be subjected to *gem*-dimethylation at C6 using LiHMDS as base and methyl iodide as the alkylating agent. The resulting ketone **23** (100%) was reduced with lithium aluminium hydride to give a chromatographically separable and 9:1 mixture of the two epimeric forms of alcohol **24** (99% combined yield) which were each converted into their respective xanthates by standard methods and in essentially quantitative yield. In contrast to the difficulties detailed earlier, these esters each underwent a smooth Barton–McCombie deoxygenation reaction to give the, by now, long sought after compound **25** (57%). As observed in related systems,[18] acid-catalysed removal of the acetonide group within this latter compound proved a sluggish process and even when forcing conditions and extended reaction times were used, complete conversion of substrate **25** into diol **26** (95% at 44% conversion) could not be achieved. Nevertheless, preparatively useful quantities of compound **26** were available by such means and the less hindered hydroxy group associated with this compound could be selectively oxidized to the corresponding ketone using the sterically demanding oxoammonium ion derived from 4-acetamido-TEMPO.[19] The acyloin **27** (91% at 96% conversion) thus obtained proved rather unstable and the product resulting from its oxa-di-π-methane rearrangement was even more so. Consequently, compound **27** was protected as the corresponding and now completely stable MEM-ether[20] **28** (91%).

Subjection of compound **28** to triplet sensitized photolysis resulted in the anticipated oxa-di-π-methane rearrangement process and thus provided the tetracyclic product **29** (80% at 71% conversion) as a crystalline solid suitable for single crystal X-ray analysis, results of which have been reported previously.[9] Whilst a number of methods are available for the reductive cleavage of carbonyl-conjugated cyclopropyl groups[21] we favored one using tri-*n*-butyltin hydride[22] as successfully employed by Singh et al. in their recently reported[6e] synthesis of (±)-hirsutene. Thus, treatment of compound **29** with this hydride in the presence of AIBN resulted in smooth reduction to the triquinane **30** (87% at 81% conversion) the carbonyl group of which was reduced, with sodium borohydride, to the corresponding alcohol (98%) which was obtained as a single diastereoisomer and presumably that possessing a β-hydroxy group as a result of hydride delivery to the *exo*-face of the precursor ketone. The readily derived xanthate ester (92%) was then deoxygenated under Barton–McCombie conditions to give the MEM-ether **31** (92% from **30**). Cleavage of the MEM-group within the latter compound could be achieved under the conditions described by Monti et al.[23] and so affording the extremely volatile and, therefore, refractory alcohol **32** (76%), the racemic form of which has been employed in previous syntheses of (±)-hirsutene. PCC-promoted oxidation of



Scheme 2.

compound **32** afforded the corresponding ketone **33** (71%), which also proved a difficult compound to handle because of its high vapor pressure. In the final step of the synthesis compound **33** was methylenated using methylene triphenylphosphorane under standard conditions. The sterically hindered nature of ketone **33** led to difficulties in driving this reaction to completion with the result that whilst near quantitative yields of target **1** were obtained this could only be accomplished at modest (32%) conversions. Nevertheless, by such means, very clean samples of (−)-hirsutene could be obtained and the derived spectral data were in complete accord with the assigned structure and a good match for the excellent data presented by Weinges et al.[7] In particular, there was excellent agreement between the specific rotations, viz. $[\alpha]_D=-26$ (*c* 0.2, $CDCl_3$) vs $[\alpha]_D=-29.4$ (*c* 1.0, pentane).[7]

As noted earlier, since the enantiomer of *cis*-1,2-dihydrocatechol **2** is known,[11] the present work also represents a formal total synthesis of the naturally occurring or (+)-form of hirsutene. However, there are also interesting possibilities for accessing (+)-hirsutene from compound **2** itself. In particular, we have observed (Fig. 3) that the known[24] acetonide derivative, **34**, of diol **2** engages in an efficient high pressure-promoted Diels–Alder cycloaddition reaction with cyclopentenone **20** to give the adduct **35** in 56% yield and incorporating a bicyclo[2.2.2]oct-5-en-2-one residue that is enantiomerically related to the one associated with isomer **22**. In other words, compounds **20** and **35** can be regarded as pseudo-enantiomers, each of which is accessible from the common precursor **2** by controlling the facial selectivity of its reaction with the dienophile **20**. Such control is achieved by simply employing either the

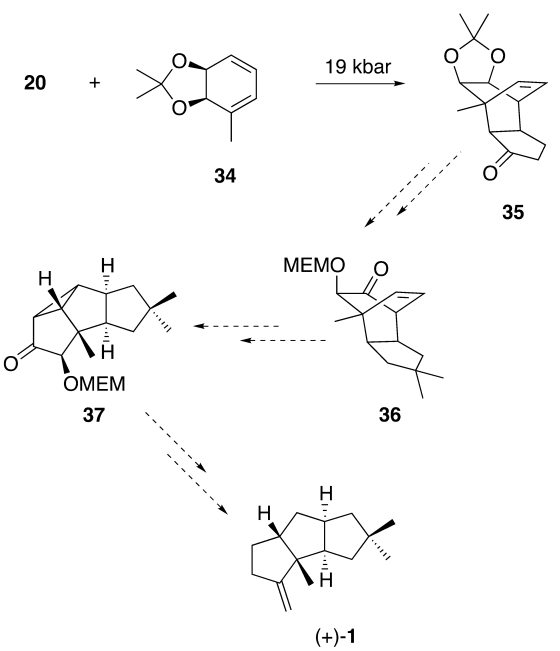


Figure 3.

unprotected or protected forms of **2** in the Diels–Alder reaction. Given the foregoing and considering the application of the chemistry defined in Scheme 2 to adduct **35**, it might reasonably be anticipated that the acyloin **36** (Fig. 3) could be obtained and that this would engage in an oxa-di-π-methane rearrangement, thus, delivering the cyclopropa-fused triquinane **37**, a pseudo-enantiomer of compound **29** and a seemingly realistic precursor to (+)-**1**. The pursuit of such possibilities will be the subject of further reports from these laboratories although it is already clear from earlier work, described by us,[12b,c,18,25] that the *cis*-1,2-dihydrocatechol **2** offers significant opportunities for the enantiodivergent synthesis of a range of biologically relevant carbocyclic frameworks. A further noteworthy aspect of the work described in Schemes 1 and 2 is that the strategies and chemistries defined therein should lend themselves to the synthesis of various oxygenated and, therefore, biologically interesting linear triquinane-type natural products such as those mentioned in the introduction.

3. Experimental

3.1. General

Melting points were measured on a Reichert hot-stage microscope apparatus and are uncorrected. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on either a Varian Inova 600 spectrometer operating at 600 MHz for proton or a Gemini 300 NMR spectrometer, operating at 300 MHz (for proton) and 75 MHz (for carbon). Unless otherwise specified spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) which had been filtered through basic alumina prior to use. Chemical shifts were recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on NaCl plates. Low resolution mass spectra were recorded on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-MS or VG Quattro II triple quadrupole MS instrument using electron impact techniques. High resolution mass spectra were acquired by liquid secondary ion MS methods on a Kratos Analytical Concept ISQ instrument located at the University of Tasmania. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g 100 mL^{-1}) indicated using spectroscopic grade $CHCl_3$ unless otherwise specified. The measurements were carried out between 17 and 28 °C in a cell with a path length (*l*) of 1 dm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D=100\ \alpha/(c\ l)$ and are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia. All reactions were performed under a nitrogen atmosphere. Anhydrous solvents were obtained by distillation from appropriate drying agents under a nitrogen atmosphere.

3.2. Synthetic studies

3.2.1. (3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-dione (10). A magnetically stirred solution of diol **9** (1.07 g, 4.27 mmol) in 2,2-dimethoxypropane (7.5 mL, 61 mmol, 14 mole equiv.) and dichloromethane (7.5 mL) was treated with *p*-TsOH·H_2O (12.2 mg, 1.5 mole%) and the resulting mixture stirred at 18 °C for 24 h then concentrated under reduced pressure. Subjection of the ensuing deep-red oil to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.9 in 1:1 v/v ethyl acetate–hexane), the title compound *acetonide* **10** (1.24 g, 100%) as a clear, colourless oil, $[\alpha]_D=+29$ (*c* 0.2, $CHCl_3$) (Found: M$^{+\cdot}$, 290.1524. $C_{17}H_{22}O_4$ requires M$^{+\cdot}$, 290.1518). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02 (dd, *J*=8.4, 6.6 Hz, 1H), 5.82 (d, *J*=8.4 Hz, 1H), 4.11 (dd, *J*=8.1, 3.9 Hz, 1H), 3.68 (d, *J*=8.4 Hz, 1H), 3.52 (dd, *J*=10.2, 3.0 Hz, 1H), 3.42–3.40 (m, 1H), 3.22 (d, *J*=10.2 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.4, 219.7, 138.7, 132.1, 112.5, 80.8, 75.1, 54.6, 48.0, 45.4, 42.1, 37.4, 26.9, 24.7, 23.6, 20.5, 16.8; IR, ν_{max} 2976, 2930, 1759, 1720, 1460, 1375, 1265, 1206, 1163, 1109, 1065, 1049, 880, 710 cm^{-1}; MS, *m*/*z* (EI, 70 eV) 290 (M$^{+\cdot}$, 11%), 275 (16), 232 (28), 189 (28), 161 (87), 134 (100), 105 (88), 100 (75), 70 (98).

3.2.2. (3a*R*,4*S*,4a*S*,5*R*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol (11), (3a*R*,4*S*,4a*S*,5*S*,7-*R*,4*S*,4a*S*,5*S*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol (12), (3a*R*,4*S*,4a*S*,5*R*,7*R*,7a*S*,8-*R*,4*S*,4a*S*,5*R*,7*R*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol (13) and (3a*R*,4*S*,4a*S*,5*S*,7*R*,7a*S*,8-*R*,4*S*,4a*S*,5*S*,7*R*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol (14).

3.2.2.1. Method A. A magnetically stirred solution of the dione **10** (102.6 mg, 0.35 mmol) in THF (1.7 mL) maintained at −78 °C (acetone-dry ice bath) was treated, dropwise, with DIBAL-H (1.55 mL of a 1 M solution in hexane, 0.155 mmol). After 3 h the reaction mixture was warmed to 18 °C, stirring continued for a further 3 h, then water (10 mL), NH_4Cl (10 mL of a saturated aq. solution) and diethyl ether (10 mL) were added (CAUTION!). The separated aqueous phase was extracted with diethyl ether (4×10 mL) and the combined organic phases washed with brine (1×10 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oily solid. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.4), the title compound *diol* **11** (103 mg, 99%) as a white crystalline solid, mp 106–107 °C (with sublimation), $[\alpha]_D=+45$ (*c* 0.8, $CHCl_3$) (Found: M$^{+\cdot}$, 294.1826. C, 69.1; H, 8.6. $C_{17}H_{26}O_4$ requires M$^{+\cdot}$, 294.1831. C, 69.4; H, 8.9%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.08 (dd, *J*=8.1, 6.9 Hz, 1H), 5.88 (d, *J*=8.1 Hz, 1H), 4.11 (dd, *J*=8.1, 3.9 Hz, 1H), 3.75 (d, *J*=8.1 Hz, 1H), 3.71–3.68 (m, 2H), 3.10 (ddd, *J*=11.4, 6.0, 2.4 Hz, 1H), 2.95–2.92 (m, 1H), 2.81 (dd, *J*=11.4, 5.7 Hz, 1H), 1.91 (broad s, 1H), 1.62 (broad s, 1H), 1.47 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.12 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 131.6, 112.1, 84.1, 83.2,

81.8, 76.8, 49.7, 47.5, 43.2, 40.8, 36.6, 26.8, 24.7, 24.6, 20.4, 17.8; IR, ν_{max} 3288, 2946, 2890, 1455, 1378, 1257, 1208, 1160, 1061, 1030, 979, 876 cm^{-1}; MS, *m/z* (EI, 70 eV) 294 ($M^{+\cdot}$, 2%), 279 (12), 265 (64), 194 (89), 135 (93), 134 (92), 84 (100).

3.2.2.2. Method B. A magnetically stirred solution of dione **10** (103 mg, 0.35 mmol) in THF (20 mL) was treated with $LiAlH_4$ (ca 1.00 g, 26.7 mmol). The resulting mixture was heated at reflux for 48 h then cooled and treated with NH_4Cl (10 mL of a saturated aq. solution—CAUTION!) and the separated aqueous phase extracted with diethyl ether (4×10 mL). The combined organic phases were washed with brine (1×10 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:4→3:7 v/v ethyl acetate–hexane gradient elution) afforded three fractions, A–C.

Concentration of fraction A (R_f 0.4 in 1:1 v/v ethyl acetate–hexane) afforded diol **11** (10 mg, 10%) identical, in all respects, with the material obtained via Method A.

Concentration of fraction B [R_f 0.2(3) in 1:1 v/v ethyl acetate–hexane] afforded a clear, colourless glass (40 mg) tentatively identified as diol **12** (75 mg, 75%), $[\alpha]_D=-9$ (*c* 0.2, $CHCl_3$) (Found: $M^{+\cdot}$, 294.1826. C, 69.3; H, 9.2. $C_{17}H_{26}O_4$ requires $M^{+\cdot}$, 294.1831. C, 69.4; H, 8.9%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.30 (dd, *J*=8.1, 6.6 Hz, 1H), 5.82 (dm, *J*=8.1 Hz, 1H), 4.09 (dd, *J*=8.1, 3.9 Hz, 1H), 3.77 (d, *J*=8.4 Hz, 1H), 3.66 (d, *J*=6.6 Hz, 1H), 3.43 (d, *J*=9 Hz, 1H), 3.07 (ddd, *J*=11.1, 6.6, 2.4 Hz, 1H), 2.87–2.82 (m, 1H), 2.36–2.29 (m, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 135.2, 112.3, 81.7, 81.2, 80.8, 76.5, 48.7, 46.0, 41.3, 40.4, 37.2, 26.7, 24.7, 20.7, 20.4, 20.1; IR, ν_{max} 3467, 2958, 2930, 2873, 1457, 1381, 1371, 1262, 1207, 1160, 1061, 1032, 876, 710 cm^{-1}; MS, *m/z* (EI, 70 eV) 294 ($M^{+\cdot}$, <1%), 297 (7), 265 (16), 236 (29), 194 (100), 134 (73), 84 (94).

Concentration of fraction C [R_f 0.1(7) in 1:1 v/v ethyl acetate–hexane] afforded an oily solid (15 mg) tentatively identified as a ca. 4:1 mixture of diols **13** and **14** (14%). IR, ν_{max} 3434, 2959, 2930, 2873, 1464, 1381, 1372, 1263, 1207, 1164, 1155, 1082, 1045, 882, 731 cm^{-1}.

The semi-solid obtained on concentration of fraction C was triturated (ethyl acetate) to afford *diol* **13** (11.6 mg. 11%) as white crystalline masses, mp 107–108 °C (with sublimation), $[\alpha]_D=+27$ (*c* 0.1 in $CHCl_3$) (Found: $M^{+\cdot}$, 294.1829. C, 69.1; H, 9.0. $C_{17}H_{26}O_4$ requires 294.1831. C, 69.4; H, 8.9%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.16 (t, *J*=7.8 Hz, 1H), 5.90 (dm, *J*=7.8 Hz, 1H), 4.15 (dd, *J*=8.1, 4.2 Hz, 1H), 3.76 (d, *J*=8.1 Hz, 1H), 3.22–3.13 (complex m, 2H), 2.98–2.93 (m, 1H), 2.55–2.47 (m, 1H), 2.24 (dd, *J*=11.4, 8.7 Hz, 1H), 1.47 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.27 (dd, *J*=7.8, 4.5 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.7, 133.6, 112.1, 81.1, 80.9, 80.7, 76.2, 46.5, 44.0, 43.9, 41.7, 37.4, 26.7, 24.7, 24.3, 20.4, 14.8; IR, ν_{max} 3335, 2974, 2936, 2873, 1381, 1369, 1262, 1205, 1059, 1040, 880, 748 cm^{-1}.

3.2.3. (3a*R*,4*S*,4a*S*,5*R*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol *bis*-methanesulfonate (15). A magnetically stirred solution of diol **11** (40 mg, 0.14 mmol) and pyridine (1 mL) in dichloromethane (1.4 mL) was cooled to 0 °C (ice-water bath) then treated with methanesulfonyl chloride (23 μL, 0.30 mmol) and triethylamine (42 μL, 0.30 mL). The resulting mixture was warmed to 18 °C and stirred at this temperature for 72 h, then concentrated under reduced pressure. The residue thus obtained was partitioned between ethyl acetate (5 mL) and water (5 mL) and the separated aqueous phase extracted with ethyl acetate (5×5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the ensuing light-brown oil subjected to flash chromatography (silica, 1:1 v/v ethyl acetate–hexane elution). Concentration of the appropriate fractions (R_f 0.5) gave the *bis-mesylate* **15** (45 mg, 74%) as a clear, light-yellow oil, $[\alpha]_D=+47$ (*c* 0.7, $CHCl_3$) (Found: $M^{+\cdot}$, 450.1381. $C_{19}H_{30}O_8S_2$ requires $M^{+\cdot}$, 450.1382). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.05 (dd, *J*=8.1, 6.3 Hz, 1H), 5.86 (d, *J*=8.1 Hz, 1H), 4.94 (d, *J*=6.0 Hz, 1H), 4.76 (dd, *J*=6.6, 0.9 Hz, 1H), 4.09 (dd, *J*=8.1, 3.9 Hz, 1H), 3.76 (d, *J*=8.1 Hz, 1H), 3.30 (ddd, *J*=11.1, 6.6, 2.1 Hz, 1H), 3.05 (s, 3H), 3.05–2.97 (m, partially obscured, 2H), 2.99 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 130.6, 112.4, 91.9, 91.4, 81.4, 76.1, 50.0, 47.7, 41.9, 40.4, 39.9, 38.8, 36.7, 27.0, 25.4, 24.7, 20.4, 19.9; IR, ν_{max} 2980, 2936, 1373, 1334, 1207, 1170, 1063, 932, 894, 730 cm^{-1}; MS, *m/z* (EI, 70 eV) 450 ($M^{+\cdot}$, 1%), 435 (6), 421 (26), 392 (14), 350 (22), 296 (15), 200 (100), 171 (47), 100 (45).

3.2.4. (3a*R*,4*S*,4a*S*,5*R*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol *bis*-*S*-methyl xanthate (16). A magnetically stirred mixture of diol **11** (14.4 mg, 0.05 mmol), NaH (5.8 mg of a 60% dispersion in mineral oil, 0.15 mmol) and imidazole (two crystals) in THF (1 mL) maintained at 18 °C was treated, after 1 h, with CS_2 (18 μL, 0.30 mmol). Stirring was continued for a further 1 h then methyl iodide (11 μL, 0.18 mmol) was added and the resulting mixture stirred overnight at 18 °C. The reaction mixture was quenched with acetic acid (glacial, 20 μL) then partitioned between ethyl acetate (10 mL) and water (10 mL) and the separated aqueous phase extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with $NaHCO_3$ (1×5 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate–hexane elution) and concentration of the appropriate fractions (R_f 0.9 in 1:4 v/v ethyl acetate–hexane) gave the title compound **16** (21.1 mg, 91%) as colourless crystals, mp 124–126 °C, $[\alpha]_D=+49$ (*c* 0.1, $CHCl_3$) (Found: $M^{+\cdot}$, 474.1024. $C_{21}H_{30}O_4S_4$ requires $M^{+\cdot}$, 474.1027). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.19 (d, *J*=6.3 Hz, 1H), 6.04–5.97 (complex m, 2H), 5.85 (d, *J*=8.1 Hz, 1H), 4.06 (dd, *J*=8.4, 4.2 Hz, 1H), 3.73 (d, *J*=8.4 Hz, 1H), 3.39 (ddd, *J*=11.1, 6.0, 2.1 Hz, 1H), 3.10 (dd, *J*=11.1, 6.0 Hz, 1H), 2.99–2.95 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H), 1.17 (s, 6H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.4, 215.4, 137.6, 130.3, 112.3, 93.2, 91.9, 81.3, 76.3, 51.0, 46.7, 42.6, 40.5, 36.2, 26.9, 25.2, 24.7, 20.4, 19.4, 19.2, 18.1; IR, ν_{max} 2966,

2931, 1369, 1220, 1205, 1184, 1058, 1034 cm^{-1}; MS, *m/z* (EI, 70 eV) 474 ($M^{+\cdot}$, 4%), 427 (10), 383 (16), 309 (10), 201 (43), 159 (64), 91 (100).

3.2.5. (3a*R*,4*S*,8*R*,8a*S*)-3a,6,8,8a-Tetrahydro-2,2,4,6,6-pentamethyl-4,8-etheno-6*H*-indeno[5,6-*d*]-1,3-dioxole (17). A chilled (ice-water bath) magnetically stirred solution of diol **11** (50.4 mg, 0.17 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (169 mg, 0.82 mmol) in dichloromethane (3 mL) was treated with triflic anhydride (64 μL, 0.38 mmol). The reaction mixture was then allowed to warm to 18 °C and after 48 h treated with triethylamine (1 mL) then water (10 mL) and dichloromethane (10 mL). The separated aqueous phase was extracted with dichloromethane (4×10 mL) and the combined organic phases washed with brine (1×5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-brown residue thus obtained was subject to flash chromatography (silica, 0:1→1:19 v/v ethyl acetate–hexane gradient elution) and concentration of the appropriate fractions (R_f 0.9 in 1:1 v/v ethyl acetate–hexane elution) afforded the title *triene* **17** (18.6 mg, 42%) as a clear, colourless oil (Found: $M^{+\cdot}$, 258.1620. $C_{17}H_{22}O_2$ requires $M^{+\cdot}$, 258.1620). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.25 (dd, *J*=8.0, 6.3 Hz, 1H), 5.96 (dd, *J*=8.0, 1.0 Hz, 1H), 5.77 (broadened s, 1H), 5.68 (broadened s, 1H), 4.34 (dd, *J*=7.7, 4.0 Hz, 1H), 4.03 (d, *J*=7.7 Hz, 1H), 3.62–3.58 (m, 1H), 1.43 (s, 3H), 1.29 (4) (s, 3H), 1.28 (5) (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.7, 141.0, 139.3, 135.0, 133.7, 132.7, 112.3, 82.0, 77.6, 55.5, 43.5, 40.1, 26.5, 24.8, 23.3, 23.2, 17.3; IR, ν_{max} 2978, 2931, 1740, 1701, 1461, 1381, 1266, 1207, 1064, 706 cm^{-1}; MS, *m/z* (EI, 70 eV) 258 ($M^{+\cdot}$, 6%), 243 (8), 200 (8), 171 (90), 158 (100), 156 (46), 143 (34), 141 (25).

3.2.6. (3a*R*,4*S*,4a*S*,5*R*,7*R*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol *bis*-methanesulfonate (18). Reaction of diol **12** (26 mg, 0.09 mmol) with methanesulfonyl chloride (15 μL, 22 mg, 0.19 mmol, 2.2 mole equiv.) under the same conditions as employed during the conversion **11→15** (see above) afforded a light-brown oil on work-up. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.6), the title *bis-mesylate* **18** (29 mg, 75%) as a clear, colourless oil, $[\alpha]_D$=+36 (*c* 0.3, $CHCl_3$) (Found: $M^{+\cdot}$, 450.1380. $C_{19}H_{30}O_8S_2$ requires $M^{+\cdot}$, 450.1382). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.27 (dd, *J*=8.4, 6.6 Hz, 1H), 5.78 (d, *J*=8.1 Hz, 1H), 4.73 (d, *J*=6.6 Hz, 1H), 4.65 (d, *J*=9.3 Hz, 1H), 4.08 (dd, *J*=8.1, 3.9 Hz, 1H), 3.79 (d, *J*=8.1 Hz, 1H), 3.27 (ddd, *J*=11.4, 6.9, 2.4 Hz, 1H), 3.06 (s, 3H), 3.00–2.95 (m, 1H), 2.99 (s, 3H), 2.71–2.64 (m, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7, 134.7, 112.4, 89.3, 88.3, 81.5, 76.0, 46.1, 45.8, 40.5, 39.8, 39.0, 38.9, 37.2, 26.8, 24.6, 21.1, 21.0, 20.6; IR, ν_{max} 2981, 2937, 1336, 1173, 1059, 933, 881, 860, 527 cm^{-1}; MS, *m/z* (EI, 70 eV) 450 ($M^{+\cdot}$, 2%), 435 (6), 421 (7), 392 (10), 200 (100), 185 (34), 171 (52), 158 (44), 100 (54).

3.2.7. (3a*R*,4*S*,7*R*,7a*S*,8*R*,9*S*)-3a,4,7,7a-Tetrahydro-8-(hydroxymethyl)-2,2,4-trimethyl-6-(2-methyl-1-propenyl)-4,7-ethano-1,3-benzodioxole (19). A magnetically stirred mixture of the *bis*-mesylate **18** (20 mg, 0.05 mmol) in THF (3 mL) maintained at 18 °C was treated with $LiEt_3BH$ (178 μL of a 1 M solution in THF, 0.18 mmol). The resulting mixture was heated at reflux for 4 h then cooled and quenched with NH_4Cl (5 mL of a saturated aqueous solution). The resulting mixture was extracted with ethyl acetate (4×10 mL) and the combined organic phases washed with brine (1×2 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the ensuing light-brown oil to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.7 in 2:3 v/v ethyl acetate–hexane), the title *dienol* **19** (12.4 mg, 100%) as a clear, colourless oil, $[\alpha]_D$=+24 (*c* 0.4, $CHCl_3$) [Found: $(M-CH_3\cdot)^+$, 263.1640. $C_{17}H_{26}O_3$ requires $(M-CH_3\cdot)^+$, 263.1647]. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.14 (t, *J*=7.7 Hz, 1H), 5.86 (d, *J*=8.1 Hz, 1H), 4.92 (dt, *J*=11.5, 1.2 Hz, 1H), 4.08 (dd, *J*=8.1, 3.6 Hz, 1H), 3.78 (d, *J*=8.1 Hz, 1H), 3.43 (d, *J*=11.1, 8.5 Hz, 1H), 3.24 (dd, *J*=11.1, 6.8 Hz, 1H), 3.10 (t, *J*=11.1 Hz, 1H), 2.76–2.60 (complex m, 2H), 1.71 (d, *J*=1.1 Hz, 3H), 1.71–1.63 (m, partially obscured, 1H), 1.67 (d, *J*=1.2 Hz, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 135.2, 132.1, 124.5, 112.0, 80.7, 76.2, 64.7, 42.6, 39.0, 38.5, 37.8, 26.6, 26.2, 24.8, 20.5, 18.5; IR, ν_{max} 3436, 2963, 2927, 1452, 1373, 1262, 1207, 1061, 1045, 875, 711 cm^{-1}; MS, *m/z* (EI, 70 eV) 278 ($M^{+\cdot}$, 1%), 263 (11), 220 (30), 147 (32), 112 (100), 94 (92), 79 (46), 69 (38), 56 (60).

3.2.8. (3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4-trimethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one (22). A magnetically stirred solution of diol **21** (2.38 g, 11.5 mmol) and *p*-$TsOH\cdot H_2O$ (24.6 mg, 0.13 mmol) in dichloromethane (20 mL) maintained at 0 °C was treated with 2,2-dimethoxypropane (10 mL, 81.3 mmol). The resulting mixture was stirred at 0 °C for 3 h then warmed to 18 °C and maintained at this temperature for 72 h. The reaction mixture was then concentrated under reduced pressure and the ensuing deep-red residue subjected to flash chromatography (silica, 1:4→3:7 v/v ethyl acetate–hexane gradient elution). Concentration of the appropriate fractions (R_f 0.7 in 1:1 v/v ethyl acetate–hexane) afforded the title *acetonide* **22** (2.80 g, 98%) as a clear, colourless oil, $[\alpha]_D$=−122 (*c* 0.6, $CHCl_3$) (Found: $M^{+\cdot}$, 248.1412. C, 72.6; H, 8.1. $C_{15}H_{20}O_3$ requires $M^{+\cdot}$, 248.1412. C, 72.6; H, 8.1%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.17 (dd, *J*=8.1, 6.6 Hz, 1H), 5.84 (dd, *J*=8.1, 0.9 Hz, 1H), 4.07 (dd, *J*=9.0, 3.9 Hz, 1H), 3.70 (d, *J*=8.1 Hz, 1H), 3.13–3.05 (m, 1H), 2.89–2.85 (m, 1H), 2.55 (d, *J*=9.0 Hz, 1H), 2.15–1.95 (complex m, 3H), 1.58–1.48 (complex m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 222.5, 138.5, 132.1, 112.2, 80.9, 76.2, 49.9, 42.3, 41.4, 39.7, 32.8, 26.7, 25.1, 24.8, 19.9; IR, ν_{max} 2987, 2962, 2933, 2904, 2880, 1731, 1458, 1381, 1372, 1261, 1207, 1165, 1067, 1050, 1034, 879, 715 cm^{-1}; MS, *m/z* (EI, 70 eV) 248 ($M^{+\cdot}$, 6%), 233 (20), 190 (47), 161 (58), 134 (68), 119 (56), 105 (100), 100 (95), 91 (76), 75 (75).

3.2.9. (3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one (23). A magnetically stirred solution of

the ketone **22** (2.77 g, 11.2 mmol) in THF (20 mL) maintained at 0 °C was treated, dropwise over 5 min., with LiHMDS (11.7 mL of a 1 M solution in THF, 11.7 mmol). The resulting mixture was stirred at 0 °C for 0.75 h then warmed to 18 °C over 1.25 h. The reaction mixture was re-cooled to 0 °C then treated, dropwise, with MeI (0.73 mL, 11.73 mmol), allowed to stir for 0.75 h, then warmed to 18 °C over a period of 1.25 h. The reaction mixture was then re-cooled to 0 °C and treated with a further aliquot of LiHMDS (11.7 mL of a 1 M solution in THF, 11.7 mmol) then MeI (0.73 mL, 11.73 mmol) using the warming and cooling cycle mentioned above. This process was repeated twice more then the reaction mixture treated, at 18 °C, with NH_4Cl (20 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (4×30 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a dark-yellow oil containing small amounts of lithium iodide. This material was subjected to flash chromatography (silica, 1:4→2:3 v/v ethyl acetate–hexane gradient elution) and concentration of the appropriate fractions (R_f 0.8 in 1:1 v/v ethyl acetate–hexane) afforded the title *ketone* **23** (3.08 g, 100%) as a white crystalline solid, mp 70–72 °C, $[\alpha]_D=-47$ (*c* 0.6, $CHCl_3$) (Found: $M^{+\cdot}$, 276.1724. C, 73.5. H, 8.5. $C_{17}H_{24}O_3$ requires $M^{+\cdot}$, 276.1725. C, 73.5. H, 8.5%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.00 (broad t, *J*=7.4 Hz, 1H), 5.88 (dd, *J*=8.1, 0.6 Hz, 1H), 4.13 (dd, *J*=8.1, 3.9 Hz, 1H), 3.68 (d, *J*=8.4 Hz, 1H), 3.08 (ddd, *J*=19.8, 9.3, 2.1 Hz, 1H), 2.88–2.78 (complex m, 2H), 1.85 (dd, *J*=12.9, 9.0 Hz, 1H), 1.55 (s, 3H), 1.50 (s, 3H), 1.34 (s, 3H), 1.25 (dd, *J*=12.9, 9.3 Hz, 1H), 1.01 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 223.9, 138.9, 132.0, 112.0, 81.8, 76.0, 47.1, 46.1, 41.6, 40.4, 40.2, 29.6, 26.8, 24.8, 22.5, 19.9 (one signal obscured or overlapping); IR, ν_{max} 2961, 2933, 2899, 1736, 1381, 1373, 1263, 1207, 1063, 1052, 881, 711 cm^{-1}; MS, *m/z* (EI, 70 eV) 276 ($M^{+\cdot}$, 4%), 261 (10), 218 (27), 176 (55), 134 (67), 105 (100), 91 (37), 75 (57).

3.2.10. (3a*R*,4*S*,4a*S*,5*S*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-ol (24a) and (3a*R*,4*S*,4a*S*,5-*R*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-ol (24b).

A magnetically stirred solution of lithium aluminium hydride (852 mg, 22.4 mmol) in THF (80 mL) maintained at 0 °C (ice bath) was treated, dropwise over 4 h, with a solution of ketone **23** (6.07 g, 22.0 mmol) in THF (60 mL). After a further 2 h at 0 °C the reaction mixture was heated at 50 °C for 18 h then cooled to 0 °C and treated with Na_2SO_4 (3 mL of a saturated aqueous solution, CAUTION!). The resulting grey-white precipitate was removed by filtration and washed with ethyl acetate (multiple small washings to a total volume of 250 mL). The combined filtrate was concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.5 in 3:7 v/v ethyl acetate–hexane), afforded the β-epimeric form of the title *alcohol* **24a** (502 mg, 8%) as a white crystalline solid, mp 61–62 °C, $[\alpha]_D=+75$ (*c* 0.2, $CHCl_3$) [Found: $(M-CH_3\cdot)^+$, 263.1648.C, 73.0; H, 9.2. $C_{17}H_{26}O_3$ requires $(M-CH_3\cdot)^+$, 263.1647. C, 73.4; H, 9.4%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.14–6.03 (complex m, 2H), 4.09 (dd, *J*=8.1, 3.9 Hz, 1H), 3.73 (d, *J*=8.1 Hz, 1H), 3.56 (dd, *J*=10.5, 6.0 Hz, 1H), 2.93–2.82 (m, 1H), 2.78–2.70 (m, partially obscured, 1H), 2.72 (dd, *J*=10.8, 6.0 Hz, 1H), 1.48 (s, 3H), 1.44–1.35 (m, partially obscured, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.12 (d, *J*=10.8 Hz, 1H), 1.08 (t, *J*=11.7 Hz, 1H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4, 131.6, 112.1, 83.0, 81.3, 47.1, 43.9, 41.6, 41.0, 39.0, 37.2, 26.8, 26.2, 24.9, 23.0, 20.6 (one signal overlapping or obscured); IR, ν_{max} 3500, 2935, 1464, 1380, 1371, 1261, 1207, 1081, 1056, 1028, 880 cm^{-1}; MS, *m/z* (EI, 70 eV) 279 [$(M+H)^+$, 2%], 263 (5), 249 (15), 220 (23), 178 (42), 106 (48), 105 (37), 93 (39), 75 (100).

Concentration of fraction B (R_f 0.4 in 3:7 v/v ethyl acetate–hexane), afforded the α-epimeric form of the title *alcohol* **24b** (5.54 g, 91%) as a white crystalline solid, mp 88–89 °C, $[\alpha]_D=+18$ (*c* 0.4, $CHCl_3$) [Found: $(M-CH_3\cdot)^+$, 263.1648. C, 73.4; H, 9.3. $C_{17}H_{26}O_3$ requires $(M-CH_3\cdot)^+$, 263.1647. C, 73.4; H, 9.3%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.10 (broad t, *J*=7.2 Hz, 1H), 5.87 (dm, *J*=8.1 Hz, 1H), 4.11 (dd, *J*=8.1, 3.9 Hz, 1H), 3.77 (d, *J*=8.1 Hz, 1H), 3.25 (t, *J*=7.2 Hz, 1H), 2.83–2.72 (m, 1H), 2.67–2.62 (m, 1H), 2.17 (dd, *J*=10.5, 9.0 Hz, 1H), 1.51–1.44 (m, partially obscured, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.24 (d, *J*=7.2 Hz, 1H), 0.95 (m, partially obscured, 1H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 133.5, 111.9, 83.5, 81.2, 76.7, 47.9, 41.9, 41.6, 40.6, 39.7, 33.9, 26.7, 26.6, 24.8, 21.5, 20.6; IR, ν_{max} 3494, 2948, 2930, 1457, 1380, 1371, 1263, 1205, 1064, 1053, 1038, 877, 729, 711 cm^{-1}; MS, *m/z* (EI, 70 eV) 279 [$(M+H)^+$, 1%], 278 ($M^{+\cdot}$, <1), 263 (1), 220 (23), 187 (26), 178 (100), 106 (61), 105 (43), 91 (35).

3.2.11. (3a*R*,4*S*,4a*S*,7a*R*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole (25).

3.2.11.1. Step (i). THF (10 mL) was cooled to 0 °C and treated with alcohol **24a** (407 mg, 1.46 mmol) and sodium hydride (298 mg of a 60% dispersion in mineral oil, 7.44 mmol). The resulting mixture was heated at reflux for 6 h then cooled to 18 °C and treated rapidly with carbon disulfide (880 μL, 14.6 mmol). After 11 h the reaction mixture was heated at reflux for 2 h then cooled to 18 °C again and treated with methyl iodide (1.00 mL, 16.08 mmol). After 2 h the reaction mixture was heated at reflux for 6 h then cooled to 18 °C. The reaction mixture was then quenched with acetic acid (0.5 mL). The resulting mixture was filtered through a short pad of Celite® and the solids thus retained washed with ethyl acetate (4×10 mL). The combined filtrates were washed with $NaHCO_3$ (2×10 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 0:4→1:4 v/v ethyl acetate–hexane gradient elution) and concentration of the appropriate fractions (R_f 0.4 in 1:9 v/v ethyl acetate–hexane) afforded *(3a*R*,4*S*,4a*S*,5*S*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-ol* S-*methyl xanthate* (538 mg, 87%) as a clear, colourless

oil, $[\alpha]_D$=+19 (*c* 0.3, $CHCl_3$) (Found: $M^{+\cdot}$, 368.1487. C, 61.7; H, 7.9; S, 17.5. $C_{19}H_{28}O_3S_2$ requires $M^{+\cdot}$, 368.1480. C, 61.9; H, 7.7; S, 17.4%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.00–5.92 (complex m, 3H), 4.14 (dd, *J*=8.1, 3.9 Hz, 1H), 3.72 (d, *J*=8.1 Hz, 1H), 2.95–2.82 (complex m, 2H), 2.81–2.76 (m, 1H), 2.57 (s, 3H), 1.47 (s, 3H), 1.44–1.34 (complex m, 2H), 1.33 (s, 3H), 1.12 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.3, 140.6, 128.6, 112.0, 92.9, 81.4, 76.6, 45.9, 45.0, 42.4, 40.9, 38.4, 36.6, 26.8, 25.8, 24.7, 22.8, 20.5, 19.3; IR, ν_{max} 2962, 2932, 1456, 1380, 1369, 1261, 1233, 1224, 1185, 1050, 1029, 879, 713 cm^{-1}; MS, *m/z* (EI, 70 eV) 368 ($M^{+\cdot}$, 18%), 353 (12), 261 (54), 203 (95), 185 (50), 160 (42), 95 (100).

Reaction of alcohol **24b** under the same conditions as described above for congener **24a** afforded a yellow oil on work-up. Subjection of this material to flash chromatography (silica, 0:4→1:4 v/v ethyl acetate–hexane gradient elution) and concentration of the appropriate fractions (R_f 0.4 in 1:9 v/v ethyl acetate–hexane) afforded *(3a*R*,4*S*,4a*S*,5*R*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno-[5,6-*d*]-1,3-dioxol-5-ol* S-*methyl xanthate* (100%) as a clear, colourless oil, $[\alpha]_D$=+77 (*c* 0.2, $CHCl_3$) (Found: $M^{+\cdot}$, 368.1484. C, 61.3; H, 7.9; S, 17.3. $C_{19}H_{28}O_3S_2$ requires $M^{+\cdot}$, 368.1480. C, 61.9; H, 7.7; S, 17.4%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.17 (broad t, *J*=7.5 Hz, 1H), 5.94 (d, *J*=7.5 Hz, 1H), 5.66 (d, *J*=8.7 Hz, 1H), 4.11 (dd, *J*=8.1, 3.9 Hz, 1H), 3.78 (d, *J*=8.4 Hz, 1H), 2.97–2.86 (m, 1H), 2.71–2.64 (m, 2H), 2.56 (s, 3H), 1.58–1.52 (m, partially obscured, 1H), 1.52 (s, 3H), 1.33 (s, 3H), 1.17 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.1, 139.1, 133.5, 112.0, 91.9, 81.2, 76.4, 45.2, 42.6, 42.1, 41.2, 39.7, 33.7, 27.0, 26.8, 24.7, 23.0, 20.3, 19.2; IR, ν_{max} 2957, 2932, 1460, 1380, 1370, 1258, 1224, 1206, 1054, 1027, 878, 714 cm^{-1}; MS, *m/z* (EI, 70 eV) 368 ($M^{+\cdot}$, <1%), 353 (11), 260 (71), 231 (35), 203 (72), 202 (62), 187 (65), 160 (71), 95 (100).

3.2.11.2. Step (ii). A magnetically stirred solution of the relevant xanthate (538 mg, 1.46 mmol), formed as described above, and AIBN (3.4 mg, 0.02 mmol) in toluene (20 mL) was treated with tri-*n*-butyltin hydride (1.20 mL, 4.46 mmol) and the resulting mixture heated at 100 °C for 17 h. The cooled reaction mixture was treated with additional tri-*n*-butyltin hydride (0.80 mL, 2.97 mmol) and AIBN (5.0 mg) and the resulting mixture heated at reflux for 1 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 0:100→5:95 v/v ethyl acetate–hexane gradient elution). Concentration of the relevant fractions (R_f 0.7 in 3:7 v/v ethyl acetate–hexane) afforded a solid. Recrystallization (ethyl acetate) of this material afforded the title *acetonide* **25** (218 mg, 57%) as a white, crystalline solid, mp 65–66 °C, $[\alpha]_D$=+39 (*c* 0.4, $CHCl_3$) [Found: $(M-CH_3\cdot)^+$, 247.1697. C, 77.5; H, 10.0. $C_{17}H_{26}O_2$ requires $(M-CH_3\cdot)^+$, 247.1698. C, 77.8; H, 10.0%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.07 (broad t, *J*=7.2 Hz, 1H), 5.79 (dt, *J*=8.4, 0.9 Hz, 1H), 4.13 (dd, *J*=8.4, 3.9 Hz, 1H), 3.79 (d, *J*=8.4 Hz, 1H), 2.85–2.66 (complex m, 2H), 2.57–2.48 (m, 1H), 1.50 (s, 3H), 1.44–1.32 (complex m, partially obscured, 2H), 1.34 (s, 3H), 1.15 (s, 3H), 1.01–0.93 (m, partially obscured, 2H), 0.96 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.0, 132.9, 111.8, 81.0, 76.9, 45.3, 44.1, 42.1, 41.0, 39.7, 38.5, 36.7, 29.0, 28.1, 26.7, 24.9, 20.7; IR, ν_{max} 2951, 2934, 1457, 1380, 1370, 1262, 1206, 1064, 1053, 881, 714 cm^{-1}; MS, *m/z* (EI, 70 eV) 247 [$(M-CH_3\cdot)^+$, 10%], 204 (58), 162 (100), 105 (36), 91 (42).

3.2.12. (3a*S*,4*S*,7*R*,7a*R*,8*S*,9*R*)-2,3,3a,4,7,7a-Hexahydro-2,2,4-trimethyl-4,7-ethano-1*H*-indene-8,9-diol (26). A magnetically stirred solution of acetonide **25** (1.37 g, 5.2 mmol) in acetic acid (20 mL of a 60% v/v solution in water)–THF (5 mL) was heated at 60 °C for 48 h. The cooled reaction mixture was treated with $NaHCO_3$ (18 g, 214 mmol) and water (20 mL). After carbon dioxide evolution had ceased the separated aqueous phase was extracted with ethyl acetate (5×50 mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to flash chromatography (silica, 5:95→30:70 v/v ethyl acetate–hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.7 in 3:7 v/v ethyl acetate–hexane) afforded the starting acetonide **25** (772 mg, 56% recovery) which proved identical, in all respects, with authentic material.

Concentration of fraction B (R_f 0.3 in 3:7 v/v ethyl acetate–hexane) afforded a light-yellow solid. Recrystallization (ethyl acetate) of this material afforded the title *diol* **26** (483 mg, 95% at 44% conversion) as a white crystalline solid, mp 91–92 °C, $[\alpha]_D$=+56 (*c* 0.4, $CHCl_3$) [Found: $(M-C_2H_4O_2)^{+\cdot}$, 162.1410. C, 75.4; H, 9.8. $C_{14}H_{22}O_2$ requires $(M-C_2H_4O_2)^{+\cdot}$, 162.1409, C, 75.6; H, 10.0%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.06 (broad t, *J*=7.8 Hz, 1H), 5.77 (broad d, *J*=8.4 Hz, 1H), 3.76–3.70 (m, 1H), 3.34 (dd, *J*=8.7, 5.4 Hz, 1H), 2.97 (d, *J*=5.1 Hz, 1H), 2.79 (d, *J*=5.7 Hz, 1H), 2.72–2.57 (complex m, 2H), 2.46–2.36 (m, 1H), 1.45–1.33 (complex m, 2H), 1.14 (s, 3H), 1.05–0.94 (m, partially obscured, 2H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 132.5, 70.2, 66.5, 45.6, 44.2, 42.7, 41.9, 40.5, 38.6, 36.1, 29.0, 28.1, 20.4; IR, ν_{max} 3344, 2949, 2930, 1456, 1365, 1053, 1012, 711 cm^{-1}; MS, *m/z* (EI, 70 eV) 162 [$(M-C_2H_4O_2)^{+\cdot}$, 100], 147 (40), 106 (35), 91 (33).

3.2.13. (3a*S*,4*S*,7*R*,7a*R*,9*R*)-2,3,3a,4,7,7a-Hexahydro-9-hydroxy-2,2,4-trimethyl-4,7-ethano-1*H*-indene-8-one (27). A magnetically stirred suspension of diol **26** (457 mg, 2.06 mmol) and *p*-TsOH·H_2O (822 mg, 4.32 mmol) in dichloromethane (40 mL) was cooled to 0 °C and 4-acetamido-TEMPO (922 mg, 4.32 mmol) was added in portions over 1 h. The resulting pale-orange mixture was stirred at 0 °C for 6 h then warmed to 18 °C and stirred at this temperature for 16 h. After this time the reaction mixture was treated with $NaHCO_3$ (20 mL of a saturated aqueous solution) and extracted with dichloromethane (4×20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing orange oil to flash chromatography (silica, 0:1→4:6 v/v ethyl acetate–hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.4 in 3:7 v/v ethyl acetate–hexane) afforded the title *acyloin* **27** (395 mg, 91% at 96%

conversion) as a clear, colourless oil, $[\alpha]_D=-34$ (*c* 0.4, $CHCl_3$) ($M^{+\cdot}$, 220.1464. C, 76.1; H, 9.0. $C_{14}H_{20}O_2$ requires $M^{+\cdot}$, 220.1463. C, 76.3; H, 9.2%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.14–6.05 (complex m, 1H), 3.39 (d, *J*=1.8 Hz, 1H), 3.10–3.07 (m, 1H), 2.70–2.50 (complex m, 3H), 1.68–1.67 (broad m, 1H), 1.54–1.45 (complex m, 2H), 1.25 (s, 3H), 1.17 (dd, *J*=11.7, 9.9 Hz, 1H), 1.10 (dd, *J*=12.6, 10.5 Hz, 1H), 0.99 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.7, 140.3, 127.8, 74.7, 51.3, 45.9, 45.5, 44.8, 44.2, 41.3, 39.9, 28.8, 27.9, 19.1; IR, ν_{max} 3442, 2952, 2931, 1734, 1722, 1456, 1366, 1074, 788, 767, 707 cm^{-1}; MS, *m/z* (EI, 70 eV) 220 ($M^{+\cdot}$, 100%), 205 (43), 163 (64), 161 (70), 105 (47), 91 (61).

Concentration of fraction B (R_f 0.3 in 3:7 v/v ethyl acetate–hexane) afforded the starting diol **26** (18 mg, 4% recovery) which was identical, in all respects, with authentic material.

3.2.14. (3a*S*,4*S*,7*R*,7a*R*,9*R*)-2,3,4,4a,7,7a-Hexahydro-9-[(2-methoxyethoxy)methoxy]-2,2,4-trimethyl-4,7-ethano-1*H*-indene-8-one (28). A solution of acyloin **27** (347 mg, 1.57 mmol) and Hünig's base (690 μL, 3.96 mmol) in dichloromethane (3.5 mL) maintained at 18 °C was treated in a dropwise fashion with MEM-Cl (360 μL, 3.15 mmol) and the resulting mixture stirred at 18 °C for 16 h then treated with $NaHCO_3$ (2 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (5×10 mL) and the combined organic phases then washed with water (1×50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the ensuing light-brown oil to flash chromatography (silica, 0:99:1→20:79:1 v/v/v ethyl acetate–hexane–triethylamine gradient elution) afforded, after concentration of the appropriate fractions (R_f 0.4 in 3:7 v/v ethyl acetate–hexane), the title *ether* **28** (444 mg, 91%) as a clear, colourless oil, $[\alpha]_D=+28$ (*c* 0.4, $CHCl_3$) (Found: $M^{+\cdot}$, 308.1986. C, 69.8; H, 8.8. $C_{18}H_{28}O_4$ requires $M^{+\cdot}$, 308.1988. C, 70.1; H, 9.2%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.10 (dd, *J*=8.4, 6.0 Hz, 1H), 6.03 (broad d, *J*=8.1 Hz, 1H), 5.11 (d, *J*=6.8 Hz, 1H), 4.81 (d, *J*=6.8 Hz, 1H), 3.88–3.75 (m, 2H), 3.59–3.56 (m, 2H), 3.46 (s, 1H), 3.39 (s, 3H), 2.98 (dm, *J*=6 Hz, 1H), 2.71–2.58 (m, 2H), 1.54–1.43 (m, 2H), 1.21 (s, 3H), 1.16–1.08 (m, 1H), 1.04–0.97 (m, partially obscured, 1H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.0, 140.1, 128.4, 96.4, 76.9, 72.0, 67.7, 59.4, 52.5, 45.5, 44.9, 44.2, 43.4, 42.1, 39.6, 28.8, 27.9, 19.6; IR, ν_{max} 2951, 2931, 1736, 1457, 1366, 1110, 1036, 708 cm^{-1}; MS, *m/z* (EI, 70 eV) 308 ($M^{+\cdot}$, 6%), 279 (5), 175 (47), 108 (50), 89 (100), 59 (93).

3.2.15. (1*R*,2a*S*,2b*S*,2c*S*,5a*S*,5b*R*,5c*R*)-Decahydro-1-[(2-methoxyethoxy)methoxy]-4,4,5d-trimethyl-2*H*-cyclopenta[*a*]cyclopropa[*cd*]pentalen-2-one (29). A deoxygenated solution of compound **28** (254 mg, 0.82 mmol) and acetophenone (240 μL, 2.06 mmol) in acetone (120 mL) and contained in a Pyrex™ vessel jacketed by a water-cooled solution of sodium bromide (750 g) and lead(II) nitrate (8 g) in water (1 L) was subject to irradiation from a Philips 125 W HPL-N lamp for 32 h. The reaction mixture was then concentrated under reduced pressure and the resulting clear, colourless oil subject to flash chromatography (silica, 0:1→3:7 v/v ethyl acetate–hexane gradient elution) and thereby yielding two major fractions, A and B.

Concentration of fraction A (R_f 0.2 in 3:7 v/v ethyl acetate–hexane) afforded a white crystalline solid which was recrystallized (ethyl acetate) thus affording *cyclopropane* **29** (145 mg, 80% at 71% conversion) as a white crystalline solid, mp 78–79 °C, $[\alpha]_D=+102$ (*c* 0.2, $CHCl_3$) (Found: $M^{+\cdot}$, 308.1988. C, 70.1; H, 8.9. $C_{18}H_{28}O_4$ requires $M^{+\cdot}$, 308.1988. C, 70.1; H, 9.2%). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.99 (d, *J*=6.9 Hz, 1H), 4.81 (d, *J*=6.9 Hz, 1H), 3.88-3.74 (complex m, 3H), 3.58-3.55 (m, 2H), 3.39 (s, 3H), 2.68 (dt, *J*=12.0 and 7.0 Hz, 1H), 2.38-2.31 (m, 1H), 2.10 (t, *J*=5.4 Hz, 1H), 1.90-1.78 (complex m, 3H), 1.64 (dd, *J*=10.3, 5.6 Hz, 1H), 1.45 (t, *J*=11.9 Hz, 1H), 1.36-1.22 (complex m, partially obscured, 1H), 1.34 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 95.6, 88.1, 72.0, 67.5, 59.4, 53.4, 49.9, 48.9, 43.5, 43.3, 40.8, 36.0, 33.7, 32.1, 29.8, 27.7, 21.4; IR, ν_{max} 2971, 2956, 2933, 2869, 1731, 1110, 1055, 1010 cm^{-1}; MS, (EI, 70eV) *m/z* 308 ($M^{+\cdot}$, 2%), 279 (9), 219 (53), 108 (70), 89 (88), 59 (100).

Concentration of fraction B (R_f 0.4 in 3:7 v/v ethyl acetate–hexane) afforded the starting ether **28** (73 mg, 29% recovery) which proved identical, in all respects, with authentic material.

3.2.16. (3*R*,3a*S*,3b*S*,6a*R*,7a*R*)-Decahydro-3-[(2-methoxyethoxy)methoxy]-3a,5,5-trimethyl-2*H*-cyclopenta[*a*]pentalen-2-one (30). A magnetically stirred solution of compound **29** (145 mg, 0.47 mmol) and AIBN (3.4 mg, 0.021 mmol) in benzene (15 mL) maintained at 18 °C was treated, dropwise, with tri-*n*-butyltin hydride (254 μL, 0.94 mmol) and the resulting mixture allowed to stand for 1 h, then heated at reflux for the same period. The cooled reaction mixture was treated with further aliquots of AIBN (5.9 mg, 0.036 mmol) and tri-*n*-butyltin hydride, then heated at reflux for a further 2 h. This process was repeated twice more and such that the total heating time was 8 h. The cooled reaction mixture was then concentrated under reduced pressure and the ensuing light-yellow oil subject to flash chromatography (silica, 0:1→3:7 v/v ethyl acetate–hexane elution) thus affording two fractions, A and B.

Concentration of fraction A (R_f 0.3 in 3:7 v/v ethyl acetate–hexane) afforded the title *triquinane* **30** (104 mg, 87% at 81% conversion) as a clear, colourless oil, $[\alpha]_D=+20$ (*c* 0.4, $CHCl_3$) (Found: $M^{+\cdot}$, 310.2141. C, 69.6; H, 9.7. $C_{18}H_{30}O_4$ requires $M^{+\cdot}$, 310.2144. C, 69.6; H, 9.7). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.95 (d, *J*=6.9 Hz, 1H), 4.80 (d, *J*=6.9 Hz, 1H), 4.05 (d, *J*=1.8 Hz, 1H), 3.80–3.76 (m, 2H), 3.57–3.53 (m, 2H), 3.38 (s, 3H), 2.78–2.62 (m, 1H), 2.54–2.37 (complex m, 3H), 1.88 (dd, *J*=17.7, 5.4 Hz, 1H), 1.78–1.70 (m, partially obscured, 2H), 1.66–1.50 (complex m, 1H), 1.40–1.24 (complex m, 2H), 1.16 (s, 3H), 1.07–1.00 (m, partially obscured, 1H), 1.04 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.6, 95.6, 88.4, 72.0, 67.3, 59.3, 50.6, 49.2, 47.1, 46.6, 44.8, 43.9, 42.2, 39.4, 37.1, 29.6, 27.4, 22.9; IR, ν_{max} 2949, 2867, 1752, 1466, 1134, 1111, 1098, 1044 cm^{-1}; MS, *m/z* (EI, 70 eV) 310 ($M^{+\cdot}$, 1%), 221 (35), 161 (35), 149 (25), 109 (29), 96 (80), 89 (84), 59 (100).

Concentration of fraction B (R_f 0.2 in 3:7 v/v ethyl acetate–hexane) afforded the starting cyclopropane **29** (27 mg, 19% recovery) which was identical, in all respects, with authentic material.

3.2.17. (3a*S*,3b*S*,4*S*,6a*S*,7a*R*)-Decahydro-4-[(2-methoxyethoxy)methoxy]-2,2,3b-trimethyl-1*H*-cyclopenta[*a*]pentalene (31)

3.2.17.1. Step (i). A magnetically stirred solution of ketone **30** (100 mg, 0.33 mmol) in methanol (15 mL) maintained at 18 °C was treated with $NaBH_4$ (28 mg, 0.73 mmol). After 4 h the reaction mixture was diluted with ethyl acetate (2 mL) then treated with water (15 mL). The separated aqueous phase was extracted with ethyl acetate (5×15 mL) and the combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the ensuing clear, colourless oil to flash chromatography (silica, 1:9 v/v ethyl acetate-hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.2 in 3:7 v/v ethyl acetate–hexane), *(2S,3*R*,3aS,3bS,6a*R*,7a*R*)-decahydro-3-[(2-methoxyethoxy)-methoxy]-3a,5,5-trimethyl-2*H*-cyclopenta[a]pentalen-2-ol* (99.6 mg, 98%) as a clear, colourless oil, $[\alpha]_D$=+12 (*c* 0.6, $CHCl_3$) (Found: $M^{+\cdot}$, 312.2298. C, 69.0; H, 10.1. $C_{18}H_{32}O_4$ requires $M^{+\cdot}$, 312.2301 C, 69.2; 10.3%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.87 (d, *J*=6.9 Hz, 1H), 4.77 (d, *J*=6.9 Hz, 1H), 4.16–4.08 (m, 1H), 3.88–3.81 (complex m, 1H), 3.78–3.71 (complex m, 1H), 3.59–3.52 (complex m, 3H), 3.40 (s, 3H), 3.01 (d, *J*=5.7 Hz, 1H), 2.82–2.66 (complex m, 2H), 2.18–2.08 (m, 1H), 2.01–1.92 (m, 1H), 1.69–1.58 (m, partially obscured, 1H), 1.52–1.04 (complex m, partially obscured, 6H), 1.06 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 97.4, 91.3, 72.9, 72.0, 68.1, 59.4, 53.4, 50.0, 48.4, 47.7, 44.3, 42.8, 42.3, 39.9, 39.2, 30.9, 29.1, 24.9; IR, ν_{max} 3479, 2930, 2865, 1462, 1364, 1170, 1097, 1036, 849 cm^{-1}; MS, *m/z* (EI, 70 eV) 313 [(M+H)$^+$, 1%], 312 ($M^{+\cdot}$, <1), 236 (24), 206 (22), 179 (39), 161 (55), 149 (53), 89 (78), 59 (100).

3.2.17.2. Step (ii). Following the same protocol as employed for the conversion of compound **24** into the corresponding xanthate ester, the abovementioned alcohol was converted into *(2S,3*R*,3aS,3bS,6a*R*,7a*R*)-decahydro-3-[(2-methoxyethoxy)methoxy]-3a,5,5-trimethyl-2*H*-cyclopenta[a]pentalen-2-ol* S-*methyl xanthate* (92%) which was obtained as a clear, colourless oil, $[\alpha]_D$=+45 (*c* 0.4, $CHCl_3$) [Found: $(M-HS\cdot)^+$, 369.2100. C, 59.8; H, 8.7; S, 15.6. $C_{20}H_{34}O_4S_2$ requires $(M-HS\cdot)^+$, 369.2100. C, 59.7; 8.5; S, 15.9%]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87–5.82 (m, 1H), 4.73 (dd, *J*=11.4, 6.9 Hz, 2H), 3.83 (d, *J*=5.1 Hz, 1H), 3.80–3.65 (complex m, 2H), 3.53 (t, *J*=5.1 Hz, 2H), 3.37 (s, 3H), 3.01–2.91 (m, 1H), 2.79–2.65 (m, 1H), 2.56 (s, 3H), 2.38–2.28 (m, 1H), 2.09–2.02 (m, 1H), 1.72–1.58 (complex m, 3H), 1.55–1.45 (m, 1H), 1.37–1.25 (m, 2H), 1.15–1.10 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.4, 96.2, 86.7, 84.3, 72.0, 67.6, 59.3, 53.4, 49.7, 47.7, 44.2, 43.0, 42.8, 40.4, 36.0, 30.6, 28.7, 24.5, 19.3 (one signal obscured or overlapping); IR, ν_{max} 2929, 1730, 1464, 1220, 1062 cm^{-1}; MS, *m/z* (EI, 70 eV) 369 [$(M-HS\cdot)^+$, 7%], 355 (5), 190 (8), 149 (12), 105 (10), 89 (100), 59 (95).

3.2.17.3. Step (iii). Following the same protocol as employed for the conversion of compound **24** into the corresponding hydrocarbon, the abovementioned xanthate was converted into compound **31** (92%) which was obtained as a clear, colourless oil, $[\alpha]_D$=+32 (*c* 0.4, $CHCl_3$) (Found: $M^{+\cdot}$, 296.2337. C, 72.8; H, 11.3. $C_{18}H_{32}O_3$ requires $M^{+\cdot}$, 296.2351. C, 72.9; 10.9%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.75 (d, *J*=6.9 Hz, 1H), 4.70 (d, *J*=6.9 Hz, 1H), 3.72–3.65 (complex m, 3H), 3.57–3.54 (complex m, 2H), 3.40 (s, 3H), 2.69 (q, *J*=9.6 Hz, 1H), 2.62–2.48 (m, 1H), 2.07–2.00 (m, 1H), 1.98–1.86 (m, 1H), 1.76–1.56 (complex m, 4H), 1.49–1.25 (complex m, 4H), 1.10–1.03 (m, partially obscured, 1H), 1.05 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.3, 88.1, 72.1, 66.9, 59.3, 54.2, 51.7, 48.5, 47.9, 44.8, 43.5, 42.5, 40.9, 31.2, 30.5, 28.5, 28.3, 23.8; IR, ν_{max} 2949, 2869, 1464, 1364, 1136, 1111, 1045 cm^{-1}; MS, *m/z* (EI, 70 eV) 296 ($M^{+\cdot}$, <1%), 220 (60), 207 (50), 190 (44), 189 (49), 163 (37), 107 (46), 89 (100).

3.2.18. (3*S*,3a*S*,3b*S*,6a*R*,7a*S*)-Decahydro-3a,5,5-trimethyl-1*H*-cyclopenta[*a*]pentalen-3-ol (32).

A magnetically stirred solution of the MEM-ether **31** (9.5 mg, 0.032 mmol) and PPTS (17 mg, 0.068 mmol) in *t*-butanol (2 mL) was heated at reflux for 4 h. TLC analysis after this time indicated that starting material remained so additional PPTS (4.1 mg, 0.016 mmol) was added and the reaction mixture heated at reflux for a further 4 h. The cooled reaction mixture was then concentrated under reduced pressure. Subjection of the ensuing light-brown oil to flash chromatography (silica, 0:1→1:4 v/v ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.2 in 1:9 v/v ethyl acetate–hexane), the title *alcohol* **32** (5.1 mg, 76%) as a white, crystalline solid, mp 44–46 °C, $[\alpha]_D$=+36 (*c* 0.1, $CHCl_3$) (Found: $M^{+\cdot}$, 208.1830. C, 80.7; H, 11.4. $C_{14}H_{24}O$ requires $M^{+\cdot}$, 208.1827. C, 80.7; H, 11.6%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.78 (t, *J*=6.6 Hz, 1H), 2.66–2.51 (complex m, 2H), 2.12–2.04 (m, 1H), 2.01–1.91 (complex m, 1H), 1.80–1.25 (complex m, 9H), 1.12–1.05 (m, partially obscured, 1H), 1.06 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 83.2, 55.0, 51.7, 48.5, 47.6, 44.9, 43.6, 42.5, 40.9, 33.8, 30.4, 28.3, 28.2, 23.3; IR, ν_{max} 3376, 2949, 2932, 2864, 1464, 1364, 1075 cm^{-1}; MS, *m/z* (EI, 70 eV) 208 ($M^{+\cdot}$, 50%), 190 (14), 149 (100), 123 (30), 107 (54), 93 (38).

3.2.19. (3a*S*,3b*S*,6a*R*,7a*S*)-Decahydro-3a,5,5-trimethyl-3*H*-cyclopenta[*a*]pentalen-3-one (33).

A magnetically stirred solution of alcohol **32** (33.2 mg, 0.159 mmol) in dichloromethane (10 mL) was treated with PCC (68.7 mg, 0.32 mmol). The resulting orange-yellow mixture was stirred at 18 °C for 16 h by which time it had turned red-brown in color. The solvent was removed under a stream of nitrogen and the residue subject to flash chromatography (silica, 5:95 v/v ethyl acetate–pentane elution). Concentration of the appropriate fractions (R_f 0.5) afforded the title ketone **33**[7] (23 mg, 71%) as a white crystalline solid, mp 23–24 °C, $[\alpha]_D$=−56 (*c* 0.4, $CHCl_3$) (Found: $M^{+\cdot}$, 206.1671. C, 81.7; H, 11.1. $C_{14}H_{22}O$ requires $M^{+\cdot}$, 206.1671. C, 81.5; H, 10.8%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84–2.75 (m, 1H), 2.58–2.45 (m, 1H), 2.44–2.21 (complex m, 3H), 2.06–1.93 (complex m, 1H), 1.77–1.55 (complex m, 3H), 1.48–1.34 (complex m, 2H), 1.17 (t, *J*=11.1 Hz, 1H), 1.04 (s, 3H), 1.04–0.94 (m, partially obscured, 1H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 224.8, 59.7, 49.2 (0), 49.1 (8), 47.0,

43.7, 42.2, 41.5, 37.9, 34.6, 29.6, 26.9, 22.7, 17.7; IR, ν_{max} 2933, 2866, 1739, 1464, 1365, 1008 cm^{-1}; MS, *m/z* (EI, 70 eV) 206 ($M^{+\cdot}$, 100%), 191 (10), 162 (46), 150 (39), 149 (36), 107 (56).

3.2.20. (3a*S*,3b*S*,6a*S*,7a*R*)-Decahydro-2,2,3b-trimethyl-4-methylene-1*H*-cyclopenta[*a*]pentalene [(−)-hirsutene, (−)-1]. A magnetically stirred solution of methyl triphenylphosphonium bromide (68.9 mg, 0.19 mmol) in freshly distilled toluene (10 mL) maintained at 0 °C was treated, dropwise, with KHMDS (297 μL of a 15% w/v solution in toluene, 0.197 mmol). The resulting intensely yellow-colored solution was stirred at 0 °C for 1 h then brought to 18 °C over 1 h and immediately re-cooled to 0 °C. A degassed solution of ketone **33** (19.8 mg, 0.096 mmol) in toluene (5 mL) was added, dropwise, to the reaction mixture which was then heated at reflux for 1.5 h. The solvent was removed from the cooled reaction mixture under a stream of nitrogen. Subjection of the ensuing light-yellow oil to flash chromatography (silica, pentane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.6) afforded (−)-hirsutene (−)-**1**] (6.3 mg, 100% at 32% conversion) as a clear, colourless oil, $[\alpha]_D$=−26 (*c* 0.2, $CDCl_3$) (Found: $M^{+\cdot}$, 204.1876. $C_{15}H_{24}$ requires $M^{+\cdot}$, 204.1878). ^1H NMR ($CDCl_3$, 600 MHz) δ 4.83–4.81 (m, 1H), 4.78–4.76 (m, 1H), 2.63–2.58 (m, 1H), 2.53–2.47 (m, 1H), 2.48–2.44 (complex m, 2H), 2.17–2.13 (m, 1H), 1.76–1.70 (m, 1H), 1.63 (ddd, *J*=10.2, 8.4, 1.8 Hz, 1H), 1.48–1.43 (m, 1H), 1.43–1.40 (m, 2H), 1.25 (broad s, 1H), 1.20 (t, *J*=11.4 Hz, 1H), 1.05 (s, 3H), 1.02 (dd, *J*=12.6, 7.8 Hz, 1H), 0.94 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 103.8, 56.3, 53.8, 50.3, 49.3, 44.6, 42.2, 41.3, 39.0, 31.3, 30.1, 27.6, 27.2, 23.6; IR, ν_{max} 2931, 2865, 1649, 1464, 1364, 876 cm^{-1}; MS, *m/z* (EI, 70 eV) 204 ($M^{+\cdot}$, 9%), 189 (3), 94 (100), 79 (34).

Concentration of fraction B (R_f 0.1) afforded ketone **33** (13.5 mg, 68% recovery) which was identical, in all respects, with authentic material.

3.3. Crystallographic studies

3.3.1. Crystal data for 11. $C_{17}H_{26}O_4$, *M*=294.391, *T*=200(1) K, monoclinic, space group $P2_1$, *Z*=2, *a*=9.2853(2), *b*=8.2538(2), *c*=10.7776(3) Å, β=107.9399(10)°, *V*=785.83(3) $Å^3$, *Dx*=1.244 Mgm^{-3}, 1926 unique data ($2\Theta_{max}$=55.06°), 1608 with $I \geq 3.00\sigma(I)$; *R*=0.032, *Rw*=0.030, *S*=1.074.

Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[26] Structure solution was by direct methods (SIR97)[27] and refinement was by full matrix least-squares on F using the CRYSTALS program package.[28] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 213833. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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