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The Synthesis of Diterpenoid Intermediates

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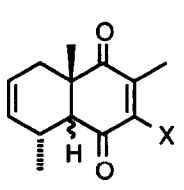
Abstract. Tricyclic cyclohexa-2,4-dienones and methylenecyclohexadienes which are potentially useful for diterpenoid synthesis have been prepared by cyclisation of 1,3,5-hexatriene-1-ones and 1,2,4,6-heptatetraenes.

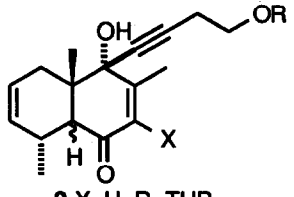
Many of the terpenoids which exhibit interesting biological effects, such as some quassinoids,[1] are highly oxygenated and require the development of new methods for their synthesis. Cyclohexa-2,4-dienones are attractive as precursors for oxygenated cyclohexanes, but have been little used in synthesis. It was first suggested by Stork[2] that a cyclohexa-2,4-dienone could be in thermal equilibrium with the related 1,3,5-hexatriene-1-one and this interconversion was demonstrated by Barton and Quinkert.[3] Detailed studies of the reaction were carried out by Hart[4] and by Chapman;[5] in particular it was shown that E_a for the hexa-1,3,5-trieneone cyclisation was *ca* 18 Kcal lower than that for the 1,3,5-hexatriene cyclisation. In the latter cyclisation difficulties were sometimes encountered in developing it into a synthetic process due to alternative thermal reactions intervening;[6] these could be avoided in the trieneone cyclisation. Since the inception of our work it has been shown that 1,2,3,5-heptatetraenes also undergo facile cyclisation.[7]

After preliminary experiments demonstrated the feasibility of the reaction as a useful synthetic method[8] we decided to examine the stereochemistry of the process for terpenoid synthesis. To this end the acids **8c** and **8t** were synthesised from 2,5-dimethylbenzoquinone. Lewis acid catalysed Diels-Alder reaction of the quinone with *E*-penta-1,3-diene gave the dione **1c** which reacted with the lithio derivative of the tetrahydopyranyl

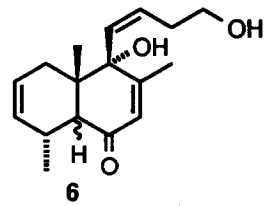
c=*cis* ring junction
t=*trans* ring junction



1 X=H
2 X=OMe



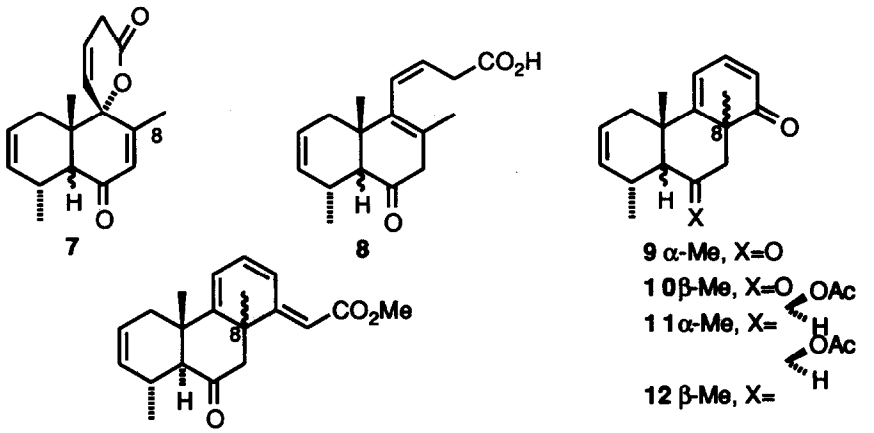
3 X=H, R=THP
4 X=OMe, R=THP
5 X=R=H



6

(THP) ether of but-1-yn-4-ol to form the alcohol **3c** (83%).[9] Removal of the protecting group, followed by Lindlar reduction, produced the diol **6c** (87%) which, on oxidation with Jones' reagent, formed the lactone **7c** (83%).¶ Hydrogenolysis of the lactone **7c** to the acid **8c** proved unexpectedly difficult, but was

¶ The lactone was accompanied by a further oxidation product derived by oxidation of the 2,3-double bond to the 3,4-en-2-one.



eventually achieved with SmI_2[10] (84%). In a similar sequence of reactions‡ the *trans*-dione **1t** (prepared by base catalysed isomerisation of **1c**) was converted into the acid **8t**.#

Reaction of the acid **8c** with oxalyl chloride formed the acid chloride from which the ketene was generated by treatment with Et_3N; spontaneous cyclisation followed to form a 2:1 mixture (81%) of the dienones **9c** and **10c**. Structures were assigned on the basis of spectroscopic evidence and *syn*-stereochemistry established for the methyl groups of **10c** by the demonstration of an n.O.e. between them. Similar cyclisation of the acid **8t** gave a 2:1 mixture of **9t** and **10t**; base catalysed isomerisation of the **9c/10c** mixture gave the **9t /10t** mixture. Bonding of the ketene can occur on the α or β face of the molecule; in the case of **8t** the former leads to **10t** where ring B can adopt a chair conformation, while the latter leads to **9t** with a twist-boat conformation for ring B†. Our original hope that this would provide a stereochemical determinant for the reaction was not fulfilled. MM2 calculations show that there is little differance in steric energy between the isomers **9t** and **10t**; this was confirmed by thermolysis in 1,2-dichlorobenzene which changed the ratio of **9t/10t** from 2:1 to 2:3. However these compounds contain, in ring B, sp^2 hybridised C atoms which usually reduce the energy difference between chair and twist-boat conformations; in accordance with this view thermolysis changed the ratio of acetates **11t /12t**§ from 2:1to 1:10.

It has been shown[11] that allenic esters can be prepared by reaction of ketenes with Ph_3PCHCO_2Me; when the ketene was generated from **8t** in the presence of this reagent the dienones **9t** and **10t** (24%) were formed along with the esters **13** and **14** (54%) (2:1), presumably arising from cyclisation of intermediate 1,2,4,6-tetraenes.

We now sought a more satisfactory method to control the stereochemistry of the cyclisation and following some preliminary work[12] synthesised the acids **22** and **27**.The starting material was 2,6-dimethyl-benzoquinone which was converted into 3,5-dimethyl-2-methoxybenzoquinone by the sequence Thiele reaction to give 1,2,4-triacetoxy-3,5-dimethylbenzene, acid hydrolysis in air, $FeCl_3$ oxidation, and methylation of the hydroxyquinone. Diels-Alder reaction between the quinone and E-penta-1,3-diene

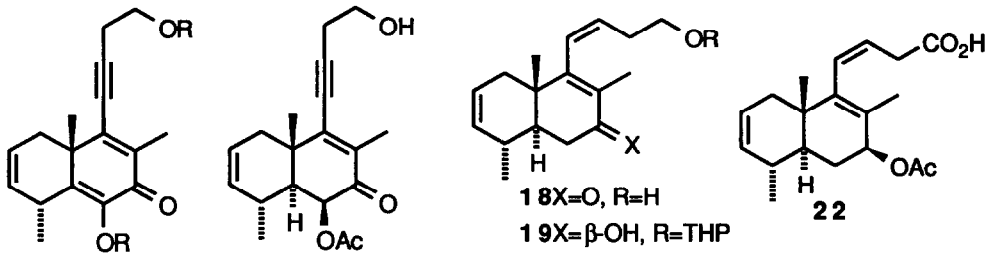
‡ The side-chain stereochemistry in the t series is likely to be the opposite of that in the c series.

The isomer in which the 8,9-double bond had migrated to the 7,8 position was also present.

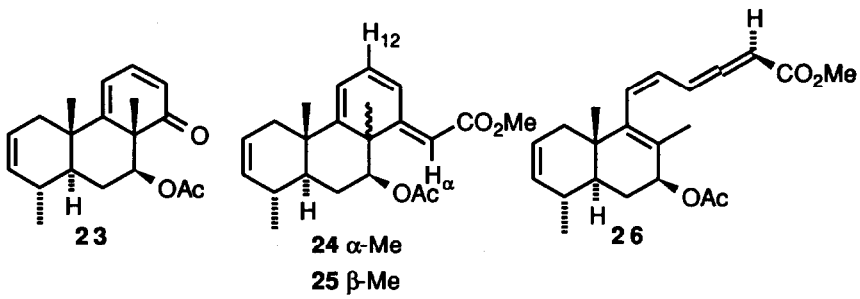
† The ketene derived from **7c** can cyclise in either a 'steriod' or 'non-steriod' conformation. MM2 calculations indicate that the latter are significantly more stable for **8c** and **9c**

§ Prepared by the sequence $LiAlH_4$ reduction of **8t/9t**, MnO_2 oxidation, and acetylation.

catalysed[13] by $AlCl_3$ gave a 1:1 mixture of **2c** and its regioisomer; however changing the Lewis acid to $SnCl_4$ or $TiCl_4$ gave a single regioisomer (85%). A 2D-COSY n.m.r. experiment established the structure. Presumably with the 'smaller' $AlCl_3$ coordination to either carbonyl of the methoxyquinone is possible. The *cis* -dione **2c** was isomerised to the *trans* -compound **2t** with NaOH/MeOH (95%). Reaction of **2t** with the lithio derivative of but-1-yn-4-ol THP ether did not discriminate between the carbonyl groups giving a 1:1 mixture. Reasoning that the C-9 carbonyl, being a vinylogous ester, might be a better Lewis base than the C-6 carbonyl we reacted **2t** with the $RCeCl_2$ reagent[14] which indeed gave the required adduct **4t** (100%). The regiochemistry of the reaction was established by hydrolysis to the dienone **15**, (λ_{max} 224 and 282 nm, shifted to 286 and 405 nm with OH^-; ν_{max} 1615 cm^{-1})which was converted into the diacetate **16** (λ_{max} 256 nm; ν_{max} 1770, 1740, and 1650 cm^{-1}). Reduction of the adduct **4t** with $NaBH_4/CeCl_3/Pr^iOH$, followed by acetylation and methanolysis gave the ketone **17** (53%), δ_H 5.59 (1H, d, *J* 4) , which was reduced with Zn/AcOH forming the trienone **18** (57%).† After protection of the hydroxyl group as the THP ether



reduction with $NaBH_4$/MeOH gave the alcohol **19** (68%). Acetylation produced the ester **20** which, after removal of the THP group, was oxidised to the acid **22** (68%). Reaction of **22** with 2-chloro-1-methylpyridinium iodide/Et_3N gave the dienone **23** (72%), λ_{max} 312 nm; ν_{max} 1735, 1670 cm^{-1} ; δ_H 6.92 (1 H, dd, *J* 6.5 and 10 Hz), 6.09 (1 H, d, *J* 6.5 Hz), 5.86 (1 H, d, *J* 10 Hz), 5.22 (1 H, dd, *J* 12 and 5 Hz), 1.52 (3 H, s), 1.18 (3 H, s); there was a substanial n.O.e. between the angular methyl groups. When the reaction was carried out in the presence of Ph_3PCHCO_2Me a mixture of the esters **24** (38%) and **25** (45%) was obtained. It is likely that both isomers are *E*-alkenes since they exhibit ^5J couplings between

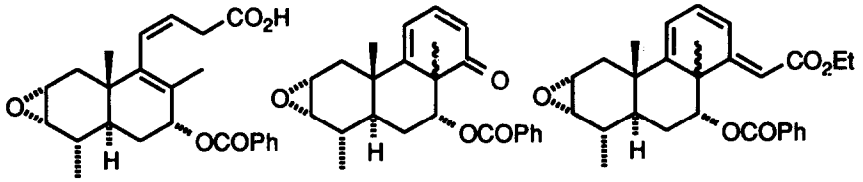


H_α and H_{12}. The major isomer **25** shows large n.O.e.s between the angular methyl groups. In the formation of the allenic ester an additional chiral centre is generated leading to two distereoisomers; the results suggest that each diastereoisomer cyclises in a single mode, ester **26** bonding to the α-face to form **25** and its diastereoisomer bonding on the opposite face to give **24**. The alternative modes of cyclisation would form the

† 10% of the *E*-alkene is also formed.

sterically highly hindered Z-alkenes.

In order to explore the reasons for the selectivities observed in these cyclisations we turned to molecular modelling (MM2 calculations); these showed that the differences in steric energy between both possible cyclisation products were small (*ca* 1.5 Kcal), but in favour of the chair conformations; also there were little differences in steric energies between the starting material conformations when the ketene carbonyl was fixed on the α and β faces within van der Waals' radius relative to the acceptor alkene carbon and orthogonal to it. If this initial α bonding trajectory is accepted then, to form the observed isomer **23**, the initial pyramidilisation is towards a' twist-boat-like' ring B; however to accomodate the developing cyclohexadienone ring (in which the C-CO bond must be equatorial to ring B) the methyl group has to rotate past the allylic acetoxyl group and the carbonyl group past the allylic hydrogen. This also has the consequence of changing the original 'twist-boat-like' ring into a chair. In the unobserved alternative bonding from the β face would be required with formation of a twist-boat ring B by the acetoxy rotating past the carbonyl and the methyl past the hydrogen. Perhaps the selectivity lies in the energetics of these processes in the transition state; however it is difficult to make even a semi-quantitative estimate of their values.



27 **28** **29**

On reaction of the alcohol **19** with $(NCO_2Et)_2/Ph_3P/PhCO_2H$[15] the benzoate **21** was formed. After removal of the THP group, oxidation with Jones' reagent gave the acid **27** where epoxidation of the isolated double bond had occurred in addition to carboxylic acid formation. The acid **27** was cyclised to the dienone **28** (82%), λ_{max} 314 nm; δ_H 5.63 (1 H, dd, *J* 7 and 3). To our surprise cyclisation in the presence of Ph_3PCHCO_2Et gave a single isomer **29** (84%) [(λ_{max} 348 nm; δ_H 5.39 (1H, t, *J* 5)] suggesting that a single diastereoisomer resulted from the allene forming step. At present we are unable to make an unambigous assignment of stereochemistry to the newly created angular methyl groups of **28** and **29**. Their chemical shifts (1.63 and 1.56 ppm) compare favourably with those of **23** and **24**, but the *J* values for the CHOCOPh protons are not those expected for an equatorial hydrogen in a chair cyclohexane; they better fit a twist-boat cyclohexyl ring.

Experimental

All ^1H n.m.r. spectra were measured in $CDCl_3$ at 300MHz, u.v. spectra in EtOH, and i.r. spectra as thin films. *J* values are in Hz. The term 'work-up in the usual way' implies washing the organic extract with brine, drying the solution with $MgSO_4$, filtration and concentration of the extract *in vacuo*.

Alkyne (3c).- 1.6 M n-BuLi in hexane (0.77 cm^3) was added dropwise to a stirred solution of the THP ether of but-1-yn-4-ol (0.189 g) in THF (15 cm^3) at -78°C and the mixture was stirred at this temperature for 2 h. After warming to 0°C the mixture was added dropwise to a stirred solution of the dione (1) (0.12 g) in THF (15 cm^3) at -78°C, stirred for 2 h, and then allowed to warm up to 0°C. Aqueous NH_4Cl was added and the mixture was extracted with Et_2O. Work-up in the usual way, followed by silica gel 60 flash chromatography [EtOAc/light petroleum (b.p. 40 : 60°C), 1:10] gave the dione (1) (15 mg) and the *alkyne* (3c) (165 mg), as an oil, ν_{max} 3410 and 1670 cm^{-1} ; δ_H 5.64 (1 H, s), 5.60 (1 H, m), 5.48 (1 H, m), 4.66 (1 H, s), 3.52 (2 H, m), 2.00 (3 H, s), 1.44 (3 H, d, *J* 7), 1.28 (3 H, s); $^m/_z$ 358.

Diol (5c).- The alkyne (3c) (1.2 g) and toluene-p-sulphonic acid (0.637 g) were stirred at room temperature in Me_2CO:water (8 : 2) (70 cm^3) for 12 h. Me_2CO was removed under reduced pressure and the aqueous residue was extracted with Et_2O. Evaporation of the dried extract gave the *diol* (5c) as a pale yellow oil (0.803 g), ν_{max} 3390 and 1670 cm^{-1} ; δ_H 5.66 (1 H, s), 5.62 (1 H, m), 5.50 (1 H, m), 3.76 (2 H, t), 2.04 (3 H, s), 1.44 (3 H, d, *J* 7), 1.28 (3 H, s); $^m/_z$ 274.

Alkene (6c).- The alkyne (6c) (0.45 g) and Lindlar catalyst (0.1 g) in EtOAc (30 cm^3) were stirred at N.T.P. under an atmosphere of H_2 for 1 h. The catalyst was filtered off and the filtrate was concentrated to give the *alkene* (6c) (0.435 g) as a pale yellow oil, ν_{max} 3390 and 1665 cm^{-1} ; δ_H 5.64 (5 H, m), 3.74 (2 H, t), 1.90 (3 H, s), 1.43 (3 H, d, *J* 7), 1.12 (3 H, s); (Found : M^+ 276.1718. $C_{17}H_{24}O_3$ requires *M* 276.1725).

***cis*-Spirolactone (7c).-** Jones' reagent [freshly prepared from $Na_2Cr_2O_7$ (3 g), conc. H_2SO_4 (4 cm^3) and water (14 cm^3)] was added dropwise over 1 h to a stirred solution of the dihydroxyketone (7c) (2.54 g) in Et_2O (50 cm^3) at 0°C . After 2 h at 20°C the mixture was extracted with Et_2O. Work-up in the usual way, followed by silica gel 60H dry column chromatography [EtOAc/light petroleum (b.p. 40 : 60°C)] gave the *lactone* (7c) (2.07 g), m.p.166-167°C; ν_{max} 1740 and 1675 cm^{-1} ; δ_H 6.12 (1 H, m), 6.01 (1 H, m), 5.78 (1 H, bs), 5.64 (1 H, m), 5.54 (1 H, m), 3.22 (2 H, m), 1.84 (3 H, d, *J* 1), 1.46 (3 H, d, *J* 7.5), 1.08 (3 H, s); (Found: M^+ 272.1412. $C_{17}H_{20}O_3$ requires *M* 272.1413) and a *ketone* (0.147 g), m.p.190-193°C ; ν_{max} 1760 and 1675 cm^{-1} ; δ_H 6.06 (2 H, m), 6.00 (1 H, bs), 5.87 (1 H, m), 3.23 (2 H, m), 2.62 (2 H, s), 2.24 (3 H, s), 1.96 (3 H, s), 1.14 (3 H, s); (Found: M^+ 286.1205. $C_{17}H_{18}O_4$ requires *M* 286.1214).

Acid (8c).- A solution of 1,2-diiodoethane (0.20 g) in THF (5 cm^3) containing a catalytic amount of $FeCl_3$ was added to a slurry of Sm powder (0.11 g) in THF (5 cm^3) at 20°C under a N_2 atmosphere. After 2 h the green slurry had turned blue (SmI_2) and the spirolactone (7c) (100 mg) in THF (5 cm^3) was added. The resulting brown mixture was stirred for 30 min and then poured into saturated aqueous $NaHCO_3$ (50 cm^3). The mixture was extracted with Et_2O, then the aqueous phase was neutralised with 1M HCl and extracted with Et_2O. Concentration of the dried ethereal extracts gave the *acid* (8c) as a colourless oil (0.085 g), ν_{max} 1715 cm^{-1} ; δ_H 5.75 (2 H, m), 5.40 (2 H, m), 1.55 (3 H, s), 1.18 (3 H, d, *J* 7).

Dienones (9c) and (10c).- The acid (8c) (25 mg) in CH_2Cl_2 (3 cm^3) was cooled to 0°C under a N_2 atmosphere and $(COCl)_2$ (0.11 g) added dropwise. After 3 h the volatile components were removed *in vacuo* to give the acid chloride which was dissolved in CH_2Cl_2 (3 cm^3) and cooled to 0°C under a N_2 atmosphere. Et_3N (100 mg) was added dropwise and the reaction mixture was allowed to warm up to room temperature. After 1 h water (15 cm^3) was added and the mixture extracted with CH_2Cl_2. The combined extracts were washed with 20% aqueous $NaHCO_3$. Concentration of the dried extracts gave the *dienones* (9c) and (10c) (2:1) (19 mg) as a yellow oil, ν_{max} 1715 cm^{-1}; δ_H 7.12 (1 H, dd, *J* 10 and 6), 6.28 (1 H, d, *J* 6), 6.04 (1 H, d, *J* 10), 5.52 (2 H, m), 1.63 (3 H, s), 1.43 (3 H, s), 1.20 (3 H, d, *J* 7) and 7.08 (1 H, dd, *J* 10 and 6), 6.41 (1 H, d, *J* 6), 5.96 (1 H, d, *J* 10), 1.44 (3 H, s), 1.36 (3 H, s), 1.20 (3 H, d, *J* 7), (Found: M^+ 256.1463. $C_{17}H_{20}O_2$ requires *M* 256.1470).

Compounds of the trans-AB Series.

These were prepared by the methods described for the *cis*-series.

Dione (1t) (2.1 g) gave *alkyne* (3t) (2.93 g), m.p. 88 - 90°C; ν_{max} 3460 and 1670 cm^{-1} ; δ_H 5.80 (1 H, s), 5.61 (1 H,m), 5.51 (1 H, m), 3.87 (2 H, m), 2.05 (3 H, s),1.17 (3 H, d, *J* 7), 0.92 (3 H, s); (Found: C, 73.8; H, 8.6. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%).

Ether (3t) (1.01 g) gave *alcohol* (5t) (0.71 g), oil, ν_{max} 3390 and 1670 cm^{-1} ; δ_H 5.76 (1 H, s), 5.58 (1 H, m), 5.47 (1 H, m), 3.73 (2 H, t), 2.00 (3 H, s), 1.11 (3 H, d, *J* 7), 0.83 (3 H, s); (Found: M^+ 274.1569. $C_{17}H_{22}O_3$ requires *M* 274.1565).

Alcohol (5t) (1.02 g) gave *alkene* (6t) (0.938 g), solid, ν_{max} 3390 and 1665 cm^{-1} ; δ_H 5.73 (3 H, m), 5.53 (1 H, m m), 5.41 (1H, m), 3.69 (2 H, t), 1.88 (3 H, s), 1.11 (3 H, d, *J* 7), 0.90 (3 H, s); (Found : C, 73.6; H, 8.8. M^+ 276.1731. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.7%. *M* 276.1725).

Diol (6t) (0.82 g) gave *lactone* (7t) (0.63 g), m.p. 205-207°C (EtOAc); ν_{max} 1745 and 1675 cm^{-1} ; δ_H 6.11 (1 H, m), 6.00 (1H, m), 5.86 (1H, s), 5.55 (2 H, m), 3.13 (2 H, m), 1.83 (3 H, d, *J* 1), 1.16 (3 H, d, *J* 7.5), 1.05 (3 H, s); (Found: C, 74.7; H, 7.4; M^+ 272.1408. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%. *M* 272.1413).

Lactone (7t) (90 mg) gave *acids* (8t) (79 mg), oil, (Found: M^+ 274.1543. $C_{17}H_{22}O_3$ requires 274.1568).

Acids (8t) (185 mg) gave the *dienones* (9t) and (10t) (128 mg), oil, ν_{max} 1710 cm^{-1} ; δ_H 7.08 (1 H, dd, *J* 10 and 6), 6.25 (1 H, d, *J* 6), 5.93 (1 H, d, *J* 10), 5.54 (2 H, m), 1.57 (3 H, s), 1.07 (3 H, d, *J* 7), 0.93 (3 H, s) and 7.08 (1 H, dd, *J* 10 and 6), 6.20 (1 H, d, *J* 6), 6.00 (1 H, d, *J* 10), 5.54 (2 H, m), 1.38 (3 H, s), 1.09 (3 H, s), 0.91 (3 H, d, *J* 7) (Found: M^+ 256.1453. $C_{17}H_{20}O_2$ requires *M* 256.1463).

Acetates (11t) and (12t).- $NaBH_4$ (100 mg) (recrystallised from diglyme) in Pr^iOH (10 cm^3) and EtOH (10 cm^3) were added dropwise to a stirred solution of the dienones (9t)/(10t) (93 mg) in EtOH (25 cm^3) at 0°C. After 30 min the temperature was raised to 20°C and, in a further 30 min, water was added and the mixture extracted with Et_2O. Usual work-up

gave a diol mixture (87 mg). MnO_2 (0.12 g) was added to a stirred solution of the diols (37 mg) in $CHCl_3$ (1 cm^3). After 30 min the MnO_2 was filtered off and the filtrate evaporated to give the hydroxyketones (34 mg), ν_{max} 3450 and 1655 cm^{-1} ; δ_H 7.06 (1 H, dd, *J* 10 and 6), 6.21 (1 H, d, *J* 6), 5.88 (1 H, d, *J* 10), 1.31 (3 H, s), 1.18 (3 H, s), 1.10 (3 H, d, *J* 7) and 7.06 (1 H, dd, *J* 10 and 6), 6.12 (1 H, d, *J* 6), 5.92 (1 H, d, *J* 10), 1.64 (3 H, s), 1.43 (3 H, s), 1.03 (3 H, d, *J* 7), which were acetylated to give the *acetates* (**11t**)/(**12t**).

Esters (13) and (14).- The acid (**8t**) was converted into the acid chloride as described previously and dissolved in CH_2Cl_2 (4 cm^3) and added dropwise to a stirred solution of Ph_3PCHCO_2Me (0.36 g) and Et_3N in CH_2Cl_2 (6 cm^3) at 0°C. After 45 min work-up in the usual way, followed by silica gel 60H dry column chromatography [EtOAc/light petroleum (b.p.40 : 60°C), 2 : 1] gave the *ketoesters* (**13**) and (**14**) (0.061 g), ν_{max} 1710 cm^{-1} ; δ_H 7.59 (1 H, d, *J* 10), 6.14 (1 H, d, *J* 6), 3.70 (3 H, s), 1.53 (3 H, s), 1.12 (3 H, d, *J* 7), 0.94 (3 H, s) and 7.63 (1 H, d, *J* 10), 6.10 (1 H, d, *J* 6), 3.70 (3 H, s), 1.40 (3 H, s), 1.08 (3 H, s), 0.93 (3 H, d, *J* 7) and diketones (**9t**) and (**10t**) (0.023 g).

Dione (2c).- $SnCl_4$ (0.75 cm^3) was added dropwise to a solution of 3,5-dimethyl-2-methoxybenzoquinone (1g) in CH_2Cl_2 (10 cm^3) at -20°C. The mixture was stirred for 15 min then *E*-penta-1,3-diene (1.25 cm^3) was added dropwise. The mixture was stirred for a further 2 h then water and CH_2Cl_2 added. Work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2 / hexane,1:1) gave the *dione* (**2c**) (1.2 g) as a solid, m.p. 40-42°C (hexane), (Found C, 72.0; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); $\nu_{max.}$ 1 700, 1 670 and 1 610 cm^{-1}, $\lambda_{max.}$ 28 3 nm; δ_H 5.63 (1 H, m,), 5.55 (1 H, m), 3.94 (3 H, s), 2.94 (1 H, d, *J* 5.5), 2.58 (1 H, m), 2.51 (1 H, bd, *J* 18), 1.87 (3H, s), 1.77 (1 H, bd, *J* 18), 1.30 (3 H, s), 1.12 (3 H, d, *J* 7.5); m/z 234.

Dione (2t).- 10% aqueous NaOH (5 drops) was added to a solution of the dione (**2c**) (1g) in MeOH (50 cm^3). After 48 h the MeOH was removed *in vacuo* and water added. Extraction with CH_2Cl_2 (3 × 10 cm^3) followed by work-up in the usual way gave the *dione* (**2t**) (0.95 g) as a solid, m.p. 25-30°C (Found: C, 71.6; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); $\nu_{max.}$ 1 700, 1 670 and 1 610 cm^{-1}; $\lambda_{max.}$ 284 nm; δ_H 5.61 (1 H, m), 5.48 (1 H, bd, *J* 10), 3.95 (3 H, s), 2.72 (1 H, m), 2.62 (1 H, d, *J* 10), 2.40 (1 H, bd, *J* 18), 2.23 (1 H, dd, *J* 5 and 18), 1.87 (3 H, s), 1.12 (3 H, d, *J* 7) 1.09 (3 H, s) ; m/z 234.

Alkyne (4).- A suspension of $CeCl_3$ (6 g) in dry THF (50 cm^3) was stirred under a N_2 atmosphere at ambient temperature for 18 h. n-BuLi (1.6 M, 20 cm^3) was added to the THP ether of but-1-yn-4-ol (4 g) in THF (50 cm^3) cooled to -78°C. After 2 h the temperature was raised to 0°C over 30 min and then cooled to -78°C and added to the $CeCl_3$ suspension previously cooled to -78°C. The mixture was stirred for 30 min at -78°C then a solution of the dione (**2t**) (3.4 g) in dry THF (50 cm^3) was added. The mixture was stirred at -78°C for 2 h then warmed to 0°C over 30 min when aqueous NH_4Cl was added dropwise. Extraction with CH_2Cl_2 and work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2 / EtOAc, 10:1) gave the *alkyne* (**4t**) (5.05 g) as a pale yellow oil, (Found: C, 71.2; H, 8.4. M^+ 389.2319. $C_{23}H_{33}O_5$ requires C, 71.1; H, 8.3%; $M+H^+$ 389.2328.), $\nu_{max.}$ 3 450, and 1 680 cm^{-1}; $\lambda_{max.}$ 250 nm; δ_H 5.58 (1 H, m), 5.47 (1 H, bd, *J* 9), 4.63 (1 H, m), 3.82 (2 H, m), 3.67 (3 H, s), 3.51 (2 H, m), 2.84 (1 H, bd, *J* 18), 2.54 (2 H, t, *J* 6), 2.41 (1 H, d, *J* 9), 2.01 (3 H, s) , 1.20 (3 H, d, *J* 6), 0.93 (3 H, s).

Hydroxydienone (15).- Toluene-*p*-sulphonic acid (5 mg) was added to the enol ether (**4t**) (100mg) in MeOH (5cm^3). After 1h the MeOH was removed *in vacuo*. The residue was extracted with CH_2Cl_2, worked-up in the usual way , and chromatographed on silica gel 60H (CH_2Cl_2 / EtOAc,10:1) to give the *ketone* (**15**) (61mg) as a colourless oil, (Found, M^+ 272.1415. $C_{17}H_{20}O_3$ requires *M* 272.1412.), $\nu_{max.}$ 3 360, 2 215 and 1 615 cm^{-1}; $\lambda_{max.}$ 282 and 224 nm, (λ_{max} +OH^- 405, 286 and 252 nm); δ_H 6.90 (1 H, s), 5.66 (2 H, m) , 3.87 (2 H, t, *J* 6), 3.30 (1 H, m) , 2.80 (2 H, t, *J* 6), 2.53 (1 H, dd, *J* 5 and 16), 2.12 (3 H, s) , 2.03 (1 H, bd, *J* 16), 1.51 (3 H, d, *J* 7), 1.37 (3 H, s); m/z 272.

Acetate (16) .- The alcohol (**15**) (60mg) was dissolved in Ac_2O (2 cm^3) and pyridine (1 cm^3) containing DMAP (5mg). After 12 h the solvents were removed *in vacuo*, and the residue partitioned between CH_2Cl_2 and water. Work-up in the usual way, followed by chromatography on silica gel 60H (CH_2Cl_2 / EtOAc, 10:1) gave the *acetate* (**16**) (58mg) as a colourless oil, ν_{max} 1 770, 1 740 and 1 650 cm^{-1}; λ_{max} 256 nm.

Acetate (17).- $CeCl_3$ (5 g) was added to a stirred solution of the ketone (4) (3.2 g) in dry Pr^iOH (150 cm^3). The mixture was stirred at 20°C for 30 min then $NaBH_4$ (3 g) was added portionwise over 1 h. After 48 h the mixture was poured into aqueous NH_4Cl and extracted with CH_2Cl_2. Work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2 / EtOAc, 5:1) gave the *alcohol* (2.8 g) as a white crystalline solid, m.p. 96-98°C (Found: C, 70.5; H, 8.8. $C_{23}H_{34}O_5$ requires C, 70.8; H, 8.7%.), $\nu_{max.}$ 3 460 cm^{-1}; δ_H 5.56 (2 H, d, *J* 2), 4.68 (1 H, m), 4.15 (1 H, d, *J* 4), 3.90 (2 H, m), 3.59 (2 H, m), 3.48 (3 H, s), 2.80 (2 H, t, *J* 6), 2.25 (1 H, bd, *J* 18), 2.11 (1 H, dd, *J* 4 and 18), 1.98 (3H, s), 1.32 (3 H, s) , 1.09 (3 H, d, *J* 7). The alcohol (2 g) was added to Ac_2O (5 cm^3) and pyridine (20 cm^3) containing DMAP (50 mg). After 48 h at 20°C the solvents were removed *in vacuo* and the residue partitioned between CH_2Cl_2 and water. Concentration of the dried organic extract gave the *acetate* (2.1 g) as a pale yellow oil, $\nu_{max.}$ 3 465 and 1 725 cm^{-1}; δ_H 5.77

(1 H, dd, *J* 1 and 5), 5.62 (1 H, m), 5.46 (1 H, bd, *J* 11), 4.63 (1 H, m), 3.81 (2 H, m), 3.54 (3 H, s), 2.77 (1 H, bd, *J* 16), 2.50 (2 H, t, *J* 6), 2.09 (3 H, s), 1.84 (3 H, d, *J* 1), 1.03 (3 H, d, *J* 7), 1.01 (3 H, s) ; $^{m}/_{z}$ (FAB) 432. 10M HCl (5 drops) were added to a solution of the acetate (2 g) in MeOH (50 cm^3) . After 1 h at 20°C the MeOH was removed *in vacuo* and the residue extracted with CH_2Cl_2. Work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2 / EtOAc, 10:1) gave the pure *enone* (17) (0.94 g) as a pale yellow gum, (Found M^+ 316.1684. $C_{19}H_{24}O_4$ requires *M* 316.1693.), $\nu_{max.}$ 3 480, 1 745, and 1 665 cm^{-1}; $\lambda_{max.}$ 283 nm; δ_H 5.59 (1 H, d, *J* 4), 5.58 (1 H, m), 5.52 (1 H, bd, *J* 11) 3.82 (2 H, t, *J* 7), 2.78 (2 H, t, *J* 7), 2.06 (3 H, s), 1.97 (3 H, s), 1.81 (1 H, dd, *J* 4 and 10), 1.33 (3 H, s) and 1.06 (3 H, d, *J* 7).

Alkene (18).- Zinc dust (2 g) was added to a stirred solution of the ketone (17) (1 g) in AcOH (30 cm^3) After 18 h the solids were filtered off and washed with CH_2Cl_2. The filtrates were combined and the solvents were removed *in vacuo*. The crude product was purified by chromatography on silica gel 60H (CH_2Cl_2/EtOAc, 10:1) to give the *Z-alkene* (18) containing 10% of the *E-isomer* (0.47 g) (Found: M^+ 260.1771. $C_{17}H_{24}O_2$ requires *M* 260.1765); $\nu_{max.}$ 3 410 and 1 730 cm^{-1}; $\lambda_{max.}$ 261 nm; δ_H 6.12 (1 H, dd, *J* 1 and 12), 5.78 (1 H, dt, *J* 12 and 7), 5.51 (2 H, m) , 3.70 (2 H, t, *J* 6), 2.65 (1 H, dd, *J* 4 and 17), 1.69 (3 H, s) , 1.05 (3 H, s), 1.01 (3 H, d, *J* 7).

Alcohol (19).- The alkene (18) (0.5 g) was dissolved in CH_2Cl_2 (5 cm^3) and dihydropyran (0.3 g) and pyridinium tosylate (50 mg) added. After 1 h water was added and the mixture extracted with CH_2Cl_2. Work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2) gave the *ether* (0.6 g) (Found: M^+ 345.2421. $C_{22}H_{23}O_3$ requires $M+H^+$, 345.2430); $\nu_{max.}$ 1 750 cm^{-1}; $\lambda_{max.}$ 260 nm; δ_H 6.07 (1H, d, *J* 11), 5.76 (1H, dt, *J* 7 and 11), 5.51 (2H, m), 4.58 (1H, m), 3.82 (2H, m), 3.47 (2H, m), 1.70 (3H, s), 1.01 (3H, d, *J* 7), 0.98 (3H, s). $NaBH_4$ (0.25 g) was added to a stirred solution of the ether (0.5 g) in MeOH (15 cm^3) at 0°C. After 30 min aqueous NH_4Cl was added and the mixture extracted with CH_2Cl_2. Work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2/EtOAc, 10:1) gave the *E*-isomer (40 mg) (Found: M^+ 346.2416. $C_{22}H_{34}O_3$ requires *M* 346.2508), ν_{max} 3 455 cm^{-1}; δ_H 5.87 (1 H, d, *J* 15), 5.48 (3H, m), 4.61 (1H, m), 4.12 (1 H, t, *J* 8), 3.84 (2 H, m), 3.47 (2 H, m), 2.42 (2 H, q, *J* 7), 1.75 (3 H, s), 1.00 (3H, d, *J* 7), 0.92 (3H, s) , and then the *Z-alkene* (19) (0.36 g), (Found: M^+ 346.2499), $\nu_{max.}$ 3 405 cm^{-1}; δ_H 5.88 (1 H, bd, *J* 11), 5.63 (1 H, dt, *J* 7 and 11), 5.52 (1 H, m), 5.45 (1 H, bd, *J* 10), 4.58 (1 H, m), 4.12 (1 H, dd, *J* 6 and 7), 1.58 (3H, s), 1.02 (3H, d, *J* 7), 0.91 (3H, s).

Acetate (20).- The alcohol (19) (100 mg) was dissolved in Ac_2O (1 cm^3) and pyridine (1 cm^3) containing DMAP. After 3h the solvents were removed *in vacuo* and the residue chromatographed on silica gel 60H (CH_2Cl_2/EtOAc, 10:1) to give the *acetate* (20) (93 mg) as a pale brown gum, (Found: M^+ 388.2621. $C_{24}H_{36}O_4$ requires *M* 388.2613), ν_{max} 1735 cm^{-1}; δ_H 5.88 (1 H, d, *J* 11), 5.64 (1 H, dt, *J* 11 and 7), 5.53 (1 H, m), 5.46 (1 H, s), 5.40 (1 H, m), 4.60 (1H, m), 3.82 (2 H, m), 3.47 (2 H, m) , 2.09 (3 H, s), 1.00 (3 H, d, *J* 7), 0.95 (3 H, s).

Acid (22).- The ether (20) (50 mg) was dissolved in Me_2CO (1 cm^3) and water (1 cm^3) containing toluene-*p*-sulphonic acid (2 mg). After 4 h the solvents were removed *in vacuo* and water was added. Extraction with CH_2Cl_2 and work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2/EtOAc, 10:1) gave the *alcohol* (30 mg) as a pale brown oil, (Found: M^+ 304.1987. $C_{19}H_{28}O_3$ requires *M* 304.2038.), $\nu_{max.}$ 3 420 and 1 735 cm^{-1}; δ_H 5.93 (1 H, d, *J* 11), 5.62 (1`H, dt, *J* 11 and 7), 5.52 (1 H, m), 5.46 (1 H, s), 5.41 (1 H, m), 3.70 (2 H, t, *J* 7), 2.10 (3 H, s), 1.50 (3 H, s), 1.00 (3 H, d, *J* 7), and 0.93 (3 H, s). Jones' reagent (0.5 cm^3) was added dropwise to a stirred solution of the alcohol (30 mg) in Et_2O (1 cm^3) at 0°C over 30 min. After 2h water was added and the mixture extracted with Et_2O . The extracts were dried and concentrated to give the *acid* (22) (28 mg), $\nu_{max.}$ 3 200, 1 735 and 1 710 cm^{-1}; δ_H 5.82 (2 H, m), 5.43 (2 H, m), 5.26 (1 H, bs), 3.58 (1 H, bs), 2.07 (3 H, s), 1.42 (3 H, s), 0.95 (3 H, d, *J* 7), 0.85 (3 H, s).

Dienone (23).- Et_3N (0.1 cm^3) was added to a stirred solution of the acid (22) (28 mg) in CH_2Cl_2 (5 cm^3) and 2-chloro-1-methylpyridinium iodide (28 mg) at 20°C. After stirring for 15 min water was added and work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2) gave the *dienone* (23) (19 mg) as a yellow oil, (Found: M^+ 300.1716. $C_{19}H_{24}O_3$ requires *M* 300.1725), $\nu_{max.}$ 1 735 and 1 670 cm^{-1}; $\lambda_{max.}$ 312 nm; δ_H 6.92 (1H, dd, *J* 6.5 and 10), 6.09 (1H, d, *J* 6.5), 5.86 (1H, d, *J* 10), 5.58 (1H, m), 5.49 (1H, bd, *J* 10), 5.22 (1H, dd, *J* 5 and 12), 2.21 (1H, dd, *J* 6 and 16), 2.10 (3H, s), 1.52 (3H, s), 1.18 (3H, s), 1.00 (3H, d, *J* 7).

Esters (24) and (25).- Et_3N (0.2 cm^3) was added to a stirred solution of the acid (22) (50 mg) in CH_2Cl_2 (5 cm^3) containing carboethoxyethyltriphenylphosphorane (60 mg) and 2-chloro-1-methylpyridinium iodide (50 mg) at 20°C. After 15 min water was added and the organic layer dried and concentrated to give a mixture which was purified by chromatography on silica gel 60H (CH_2Cl_2) to give the *ester* (25) (26 mg) as a yellow oil, (Found: M^+ 370.2089. $C_{23}H_{30}O_4$ requires *M* 370.2144), $\nu_{max.}$ 1 730 and 1 710 cm^{-1}; λ_{max} 344 nm; δ_H 7.49 (1 H, d, *J* 9), 6.16 (1 H, ddd, *J* 2, 6, and 9), 5.97 (1 H, d, *J* 6), 5.60 (1 H, bs), 5.58 (1 H, m), 5.47 (1 H, bd, *J* 10), 5.04 (1 H, dd, J 5, 11), 4.11 (2 H, m), 2.10 (3 H, s), 1.50 (3 H, s), 1.24 (3 H, t, *J* 7), 1.17 (3 H, s), 1.02 (3 H, d, *J* 7), and the *ester* (24) (22 mg), (Found: M^+ 370.2133), $\nu_{max.}$ 1 735, and 1 710 cm^{-1}; $\lambda_{max.}$ 351 nm; δ_H 7.58 (1 H, d, *J* 9), 6.28 (1 H, ddd, *J* 2, 6 and 9), 6.14 (1 H, d, *J* 6), 5.58 (1H, m), 5.52 (1 H, bs), 5.47 (1 H, bd, *J* 10), 5.32 (1 H, d, *J* 8), 4.13 (2 H, m), 1.93 (3 H, s), 1.28 (3 H, s), 1.26

(3 H, t, *J* 7), 1.15 (3 H, s), 0.99 (3 H, d, *J* 7).

Benzoate (21).- Diethyl azodicarboxylate (120 mg) was added to the alcohol (**19**) (100 mg), $PhCO_2H$ (80 mg) , and Ph_3P (120 mg) in THF (5 cm^3) at 0°C. After 12 h at 20°C the solvent was evaporated to leave an orange oil which was purified by chromatography on silica gel 60H (CH_2Cl_2) to give the *benzoate* (**21**) (84 mg) as colourless oil, (Found: M^+ 450.2774. $C_{29}H_{38}O_4$ requires *M* 450.2770), ν_{max} 1715 cm^{-1}; δ_H 8.07 (2 H, d, *J* 7), 7.54 (1 H, t, *J* 7), 7.43 (2H, t, *J* 7), 5.97 (1 H, d, *J* 11), 5.68 (1 H, dt, *J* 7 and 11), 5.57 (1 H, m), 5.50 (2H, m), 4.60 (1 H, m), 3.82 (2 H, m), 3.47 (2 H, m), 1.62 (3 H, s), 0.95 (3 H, d, *J* 7), 0.89 (3 H, s).

Acid (27).- The ether (**21**) (50 mg) was dissolved in Me_2CO (1 cm^3) and water (1 cm^3) containing toluene-*p*-sulphonic acid (2 mg). After 4 h the solvents were removed *in vacuo* and water was added. Extraction with CH_2Cl_2 and work-up in the usual way, followed by silica gel 60 flash chromatography (CH_2Cl_2/EtOAc, 10:1) gave the *alcohol* (31 mg), (Found: M^+ 366.2203. $C_{24}H_{30}O_3$ requires *M* 366.2195), $\nu_{max.}$ 3 400 and 1 715 cm^{-1}; δ_H 8.04 (2 H, d, *J* 7), 7.55 (1 H, t, *J* 7), 7.44 (2 H, t, *J* 7), 6.01 (1 H, d, *J* 11), 5.67 (1 H, dt, *J* 7 and 11), 5.52 (3 H, m), 3.72 (2 H, t, *J* 7), 2.22 (2 H, q, *J* 7), 1.62 (3 H, s), 0.95 (3 H, d, *J* 7), 0.90 (3 H, s). To a stirred solution of the alcohol (50 mg) in Et_2O (1 cm^3) at 0°C Jones, reagent (0.5 cm^3) was added dropwise over 30 min. The mixture was stirred for a further 1 h then water was added. The Et_2O layer was separated, dried, and concentrated to give the crude acid (**27**) (48 mg).

Dienone (28).- Et_3N (0.2 cm^3)was added to a stirred solution of the acid (**27**) (50 mg) in CH_2Cl_2 (5 cm^3) containing 2-chloro-1-methylpyridinium iodide (50 mg) at 20°C. After 15 min water was added and the organic layer dried and concentrated to give a mixture which was purified by chromatography on silica gel 60H (CH_2Cl_2) to give the *dienone* (**28**) (39 mg) (Found: M^+ 378.1813. $C_{24}H_{26}O_4$ requires *M* 378.1831), $\nu_{max.}$ 1 720 and 1 665 cm^{-1}; λ_{max} 314 nm; δ_H 8.07 (2 H, d, *J* 8), 7.52 (1 H, m), 7.43 (2 H, t, *J* 8), 6.97 (1 H, dd, *J* 6.5 and 10), 6.21 (1 H, d, *J* 6.5), 5.83 (1 H, d, *J* 10), 5.63 (1 H, dd, *J* 3 and 7), 3.29 (1 H, dd, *J* 4 and 6), 1.63 (3 H, s), 1.11 (3 H, s), 1.10 (3 H, d, *J* 7).

Ester (29).- Et_3N (0.2 cm^3) was added to a stirred solution of the acid (**27**) (50 mg) in CH_2Cl_2 (5 cm^3) containing Ph_3CHCO_2Et (60 mg) and 2-chloro-1-methylpyridinium iodide (50 mg) at 20°C. After 15 min water was added and the organic layer dried and concentrated to give a mixture which was purified by chromatography on silica gel 60 (CH_2Cl_2) to give the *ester* (**29**) (49 mg) as a yellow oil, (Found M^+448.2256. $C_{28}H_{32}O_5$ requires *M* 448.2250), $\nu_{max.}$ 1 715 cm^{-1}; $\lambda_{max.}$ 348 nm; δ_H 8.10 (2 H, d, *J* 7.5), 7.61 (1 H, m), 7.53 (1 H, d, *J* 11), 6.97 (2 H, t, *J* 7.5), 6.23 (1 H, ddd, *J* 2, 6.5, and 11), 6.08 (1 H, d, *J* 6.5), 5.63 (1 H, bs), 5.39 (1 H, t, *J* 5), 4.04 (2 H, m), 3.27 (1 H, dd, J 4 and 6), 2.16 (1 H, dd, *J* 6 and 16), 1.98 (1 H, d, *J* 16), 1.56 (3 H, s), 1.13 (3 H, t, J 7.5), 1.09 (3 H, s), 1.05 (3 H, d, *J* 7).

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