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Synthesis of Conformationally Restricted Relatives of the Mevinic Acids

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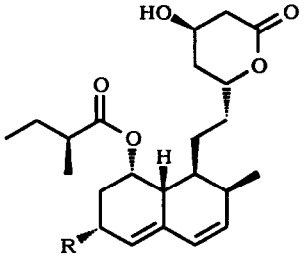
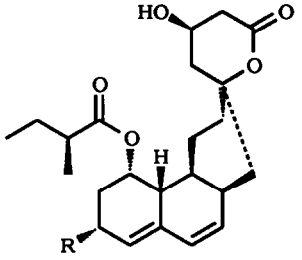
Abstract:- *Condensations between the tricyclic ketones **9**, **19** and **23** and the sodio-lithio dianion of methyl acetoacetate lead to the conformationally restricted Mevinic acid relatives **12b**, **20b** and **26** respectively, following lactonization and selective reduction. The approach of the nucleophile is stereospecific in the first two instances but not in the last; explanations for this behaviour are given. The target compounds showed negligible HMGCoA reductase antagonism.*

The Mevinic acids, represented by Compactin **1**[1] and Mevinolin **2**,[2] the former first isolated from *Penicillium brevicompactum*, have attracted considerable attention due to their ability to interfere with cholesterol biosynthesis in man, by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A [HMGCoA reductase].[3] This has been ascribed to the close structural similarity between the lactone portion of the Mevinic acids and Mevalonic acid, a key intermediate in terpenoid biosynthesis.



1 R = H; (+)--Compactin
2 R = Me; (+)-Mevinolin



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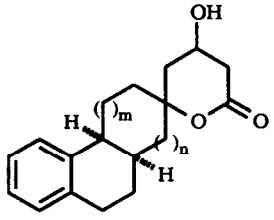

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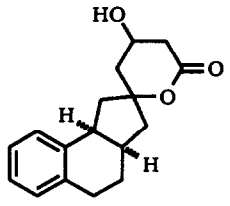
The potential of these compounds as commercial hypocholesterolemic agents is therefore very considerable. However, the complexity of the decalin ring portion of the molecules probably precludes any possibility of a commercially viable synthesis ever being developed.[4] For this reason, as well as to investigate the possibilities of discovering new totally or semi-synthetic analogues with even greater degrees of biological activity than the parent compounds, a diverse range of structures based on compounds **1** and **2** have been prepared for biological evaluation. In many of the more accessible and biologically active derivatives, the complex decalin ring feature

is replaced by simpler aromatic or heteroaromatic groups, while retaining the natural absolute stereochemistry of the hydroxy-lactone ring for maximum activity, and has led to the elaboration of analogues which display enhanced potency as HMGCoA reductase inhibitors, relative to the natural compounds.[5,6] We were intrigued by the possibility that conformationally restricted analogues of the Mevinic acids could show similar bioactivities and, if so, open up a new structural class in this area. This idea is illustrated by structure **3** which, if redrawn, suggests that the *spiro*-hydroxy-lactones **4**, in which this key function is attached to a *cis*-fused tricyclic ring system, represent potentially viable members of this structural type. For ease of synthesis at this early stage, the remainder of the ring system is present as a benzene ring. Herein, we report our efforts in this area.

The first system we chose to examine was that based upon the *cis*-benz[e]linden-2-one **9**.



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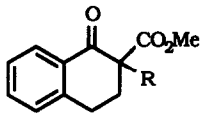
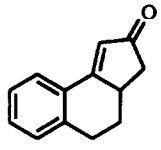


6 a) R = H
b) R = CH_2CCH



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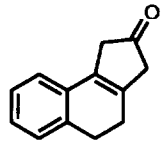

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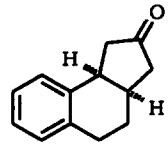
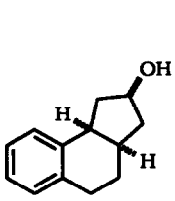


9

Subsequent elaboration of the lactone ring by condensation[7] with a dianion of methyl acetoacetate appeared to offer the most expedient entry into the *spiro*-lactones in general. The *cis*-ketone **9** should be available by hydrogenation[8] of the unsaturated ketone **7**, obtainable[9] from α-tetralone. Initial attempts[9] to prepare the enone **7** by way of the β-formyl derivative of α-tetralone and propargylic bromide proved unsatisfactory apparently due to deformylation prior to alkylation. A much better approach consisted of alkylation of the corresponding methoxycarbonyl derivative **6a** by propargyl bromide leading to the homologue **6b**. Subsequent hydration of the alkyne function with concomitant decarboxylation and aldol cyclisation of the resulting dione then led to the required enone **7**. Use of the methyl ester **6b** has two advantages over the corresponding ethyl ester.[9] Firstly, it is a crystalline solid and secondly, decarboxylation during the alkyne hydration step occurs much more easily. Unfortunately, hydrogenation of the conjugated enone **7** gave the required *cis*-indenone **9**, contaminated by ~10% of the corresponding *trans*-isomer, contrary to a literature report.[8] Although these isomers were separable by column chromatography, a more efficient preparation involved prior base-induced isomerisation of the enone **7** into the β,γ-unsaturated ketone **8**; subsequent hydrogenation then provided only the *cis*-isomer **9**, surprisingly contaminated with the alcohol **10**.[10] This could be oxidised back to the ketone **9** using Jones reagent, in 90% yield.

Condensation of the *cis*-ketone **9** with two equivalents of the sodio-lithio dianion of methyl acetoacetate[11] led to the desired keto-ester **11**, as a single diastereoisomer according to ^{13}C NMR spectroscopy. In line with previous observations,[11] use of only one equivalent of the dianion gave much poorer yields. The stereochemistry of compound **11** was assigned on the well-established preference of relatively small or "linear" nucleophiles to attack cyclic ketones in an axial direction, in the absence of other large steric interactions.[12-15] Explained both

qualitatively[12,13] and computationally,[14,15] examples of such "small" nucleophiles which exhibit high axial selectivity include hydride from lithium aluminium hydride,[13,14] Grignard reagents,[14] cyanomethyl anions[16] and lithium acetylides.[17]



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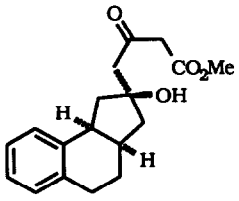

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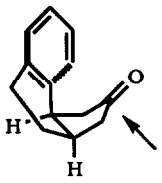

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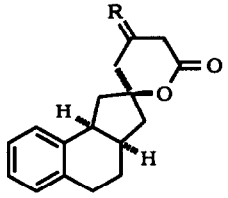
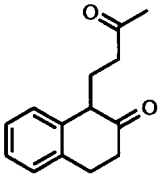


13 a) R = O
b) R = OH,H

It seems reasonable to assume that acetoacetate dianions fall into this class; the stereospecific nature of the present condensation both suggests exclusive axial attack and that the ketone **9** reacts in the highly sterically biased conformation **12**, with the nucleophile approaching the convex face. This is also consistent with the formation of the over-reduction product **10** as a single diastereoisomer[10] and with the chemistry described below.

Completion of the synthesis required lactone formation and selective reduction of the ketone function of keto-ester **11**. The former was readily achieved by saponification of the ester group followed by acidification. However, reduction of the resulting keto-lactone **13a** proved difficult; starting material was recovered when a range of hydride reagents were tested,[18] presumably due to preferential enolisation. Consistent with this was the success achieved when the keto-lactone **13a** was treated with borane-t-butylamine complex followed immediately with aqueous citric acid,[19] which gave the desired hydroxy-lactones **13b** in 52% isolated yield. Not surprisingly, the reduction was not stereoselective, presumably due to the orthogonal orientation of the lactone ring with respect to the remainder of the molecule. On the positive side, this does enable the bioevaluation of two diastereoisomers.



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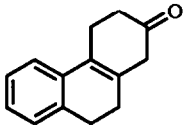

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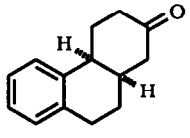

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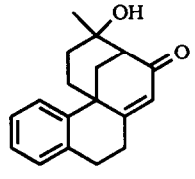

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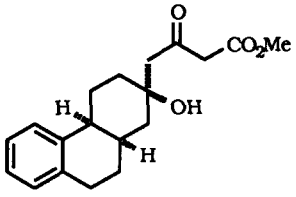
We then proceeded to examine the synthesis of two *spiro*-lactones derived from the *cis*-hexahydro-phenanthrenones **16** and **24**. The *cis*-ketone **16** was prepared by a Robinson annulation of β-tetralone which lead directly to the deconjugated ketone **15**, by way of the dione **14**. In our hands, base-catalysed procedures using either sodium methoxide[21] or potassium hydroxide[22] gave very poor returns, although the latter method, while somewhat capricious, did give a low yield of the desired product **15**, together with the double adduct **17**, apparently as a single diastereoisomer, of undetermined stereochemistry. An acid-catalysed annulation, although slow, was more reliable and gave much better yields of the ketone **15**. The progress of the

reaction could be followed using tlc and the relatively polar dione **14**, isolated from an incomplete reaction. (β-Tetralone and the ketone **15** have similar mobilities on tlc). It was found most efficient to hydrogenate the crude product without further purification, which gave respectable yields of the *cis*-ketone **16**, after chromatography.

Condensation with two equivalents of the dianion of methyl acetoacetate as above then led to a good yield of the desired keto-ester **18**, again as a single diastereoisomer. This was assigned the structure shown on the basis of the expected preference for axial attack by the dianion discussed above and by analogy with the behaviour of imines derived from the hexahydro-naphthalenone **19** in reduction reactions,[23] which are consistent with a reacting conformation based on structure **20** in the present case. Subsequent saponification as before provided the keto-lactone **21a** in excellent yield and reduction using borane-t-butylamine-citric acid then completed the synthesis of the hydroxy-lactones **21b**. Again, the final reduction was non-stereoselective, as expected.



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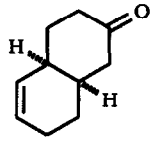

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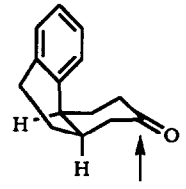

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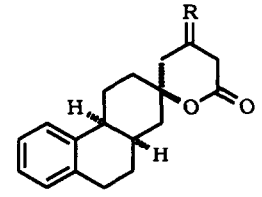
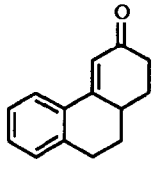


21 a) R = O
b) R = OH,H

The final example was prepared by the method of Brown *et. al.*[9,24] from α-tetralone by sequential Mannich reaction (formaldehyde, piperidine.HCl), quaternisation (MeI) and condensation with methyl acetoacetate to give the conjugated ketone **22**. Direct hydrogenation of the ketone **22** was non-stereoselective, as expected from the foregoing observations.[25] Subsequent base-catalysed deconjugation, leading to ketone **23**, and hydrogenation gave the required *cis*-phenanthrenone **24**.



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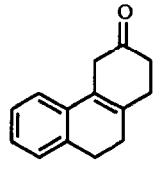

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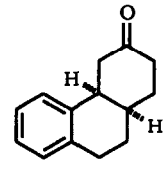

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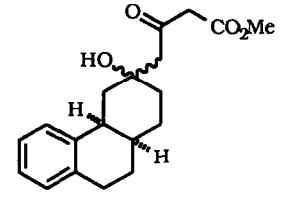

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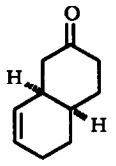
In this case, condensation with methyl acetoacetate dianion was non-stereoselective and gave a good yield of the desired keto-esters **25** as a 58:42 mixture of epimers at the newly created centre. An explanation for this lack of stereoselectivity is based on observations arising from polyene cyclisation studies[26] which strongly suggest that the naphthalenone **26** prefers to react *via* the conformation **27**. In this case, the usual preference for axial attack is in direct competition from equatorial approach by the nucleophile from the less sterically incumbered convex face, as

shown. A consistent feature of all the reactive conformations [**12**, **20** and **27**] implied in this present work, as well as in previous reports, is the propensity for an equatorial position of the ring junction hydrogen nearest to the unsaturated carbon-carbon linkage.



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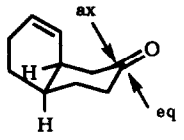

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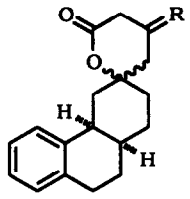
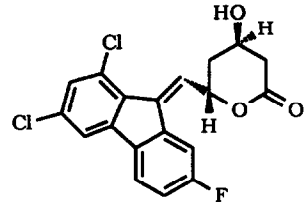


28 a) R = O
b) R = OH,H



29

The epimers **25** were not separated but instead were converted into the *spiro*-keto- and hydroxy-lactones **28a** and **28b** respectively using the methods described above, in good overall yields.
The three *spiro*-hydroxy-lactones **13b**, **21b** and **28b** were assayed for HMGCoA reductase activity using methodology developed by the Merck group.[27] Sadly, the three compounds proved to be inactive and therefore further representatives of this class were not prepared. One piece of evidence consistent with these findings is that the relatively rigid (with respect to the natural Mevinic acids) fluorene analogue **29** also displays poor reductase inhibitory activity.[6]
Of course, more complex analogues in this series could display activity but this model study is hardly encouraging. However, the methodology employed does indicate that reactions between cyclic ketones and acetoacetate dianions can, in suitable cases, be useful for the stereocontrolled synthesis of *spiro*-lactones, given an appropriate degree of planning.

Experimental

General details.- Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infra-red spectra were measured using a Pye-Unicam SP3-100 instrument and chloroform solutions unless otherwise stated. Proton NMR spectra were measured using Bruker instruments operating at 80 MHz (80), 250 MHz (250) or 400 MHz (400), as indicated. ^{13}C NMR spectra were obtained using a Jeol instrument operating at 22.5 MHz. All NMR spectra were obtained using dilute solutions in deuteriochloroform with tetramethylsilane as internal standard. Coupling constants (J) are quoted in Hertz. Mass spectra and molecular weights were measured using either a VG 7070E or an MS 902 instrument, operating in the EI (70 eV) mode.
All reactions were run under an atmosphere of dry nitrogen (except hydrogenations) and all organic solutions from work-ups were dried by brief exposure to anhydrous magnesium sulphate. All chromatography was performed using dry column silica Woelm PharmaTSC and the eluents specified. Petrol refers to light petroleum ether, b.p. 60~80 °C.

2-Methoxycarbonyl-2-(2-propynyl)-3,4-dihydro-1(2H)-naphthone 6b.- 2-Methoxycarbonyl-3,4-dihydro-1(2H)-naphthone **6a**, b.p. 132 at 0.5 mm Hg, was prepared from α-tetralone and dimethyl carbonate (NaH, toluene, reflux), as described for the corresponding ethyl ester.[9] The keto-ester **6a** (20.91 g, 0.1025 mol) was added to a solution of sodium methoxide (6.48 g, 0.12 mol) in dry methanol (70 ml), then most of the solvent was evaporated. A solution of propargyl

bromide (20.91 g, 0.18 mol) in dry toluene (350 ml) was added and the resulting mixture heated at 80 °C for 16h, then cooled and treated with water (50 ml). The separated organic layer was washed with brine (50 ml) then dried and evaporated. Crystallisation of the residue from ether-hexane gave the *keto-ester* **6b** (20.20 g, 83%) as colourless hexagonal plates, m.p. 109-110 °C, ν_{max} 3285, 1738 and 1682 cm^{-1}, δ_H (80) 2.02 (1H, t, *J* 3.0, CCH), 2.37-2.66 (2H, m), 2.88 (2H, d, *J* 3.0, CH_2CC), 2.90-3.17 (2H, m), 3.68 (3H, s, OMe), 7.07-7.62 (3H, m) and 8.02 (1H, dd, *J* 7.2 and *ca.* 1, 8-H), m/z 242 (M^+, 1%), 210 (100), 203 (21), 183 (33), 171 (51), 115 (28) and 91 (13) [Found: C, 74.3; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%].

3,3a,4,5-Tetrahydro-2H-benz[e]inden-2-one 7.- A solution of the keto-ester **6b** (9.85 g, 41 mmol) in methanol (5 ml) was added to a mixture of acetic acid (100 ml), concentrated hydrochloric acid (50 ml) and water (50 ml) and the resulting mixture refluxed for 2h then cooled, neutralized using excess solid sodium bicarbonate and finally extracted with ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to give crude 2-(2-oxopropyl)-3,4-dihydro-1(2H)-naphthone (6.43 g, ~78%) as a brown oil, δ_H (80) 1.68-2.68 (2H, m), 2.25 (3H, s, MeCO), 2.69-3.36 (5H, m), 7.08-7.57 (3H, m) and 7.87-8.12 (1H, m).
Aqueous potassium hydroxide (20%, 100 ml) was added dropwise to a vigorously stirred emulsion of the foregoing, crude, dione (6.43 g) in freshly boiled water (500 ml) and the resulting mixture refluxed for 5h, then cooled and extracted with benzene (3 x 100 ml). The combined extracts were washed with 2M aqueous hydrochloric acid (2 x 50 ml) and water (50 ml) then dried and evaporated. Crystallisation of the residue from ether-hexane gave the enone **7** (5.16 g, 88%) as orange rhombi, m.p. 71-72 °C [lit. m.p.[28] 74-75 °C], λ_{max} 212 (4.407), 224 (4.357) and 265 (4.509) nm., ν_{max} 1693, 1673 and 1597 cm^{-1}, δ_H (200) 1.48-1.80 (2H, m), 2.10-2.39 (2H, m), 2.52-3.16 (3H, m), 6.40 (1H, d, *J* 2.0, :CH), 7.00-7.42 (3H, m) and 7.59-7.72 (1H, m) [Found: C, 84.5; H, 6.5. Calc for $C_{13}H_{12}O$, C, 84.8; H, 6.7%].

1,3,4,5-Tetrahydro-2H-benz[e]inden-2-one 8.- A solution of the foregoing enone **7** (0.84 g, 5 mmol) in dry t-butanol (40 ml) was added to potassium t-butoxide (3.90 g, 35 mmol) at 0 °C. The resulting suspension was stirred at this temperature for 0.5h then quenched by the rapid addition of aqueous acetic acid (10%, 130 ml). The mixture was then neutralized using solid sodium bicarbonate and extracted with ether (3 x 40 ml). The combined extracts were washed with water (2 x 50 ml) then dried and evaporated to give the *deconjugated enone* **8** (0.74 g, 88%) as a colourless powder, m.p. 79-81 °C (from hexane), λ_{max} 218 (4.467) and 276 (3.983) nm., ν_{max} (KBr) 1744 cm^{-1}, δ_H (200) 2.37-2.63 (2H, m), 2.98 (2H, app. t, *J* 7.2), 3.12 (2H, br s), 3.23 (2H, br s), 6.88-7.00 (1H, m) and 7.09-7.23 (3H, m), δ_C 24.00, 27.80, 44.00, 47.08 (all CH_2), 123.20, 126.76, 127.32, 127.88 (all CH), 131.76, 131.92, 134.72, 135.84 (all C) and 214.36 (CO), m/z 184 (M^+, 82%), 156 (100), 155 (38), 141 (85), 128 (37) and 115 (35) [Found: C, 84.7; H, 6.8%].

***Cis*-1,3,3a,4,5,9b-Hexahydro-2H-benz[e]inden-2-one 9**.- The enone **8** (2.26 g, 12.3 mmol) in ethyl acetate (100 ml) containing 5% Pd-C (100 mg) was shaken under hydrogen (1 atmos.) at ambient temperature for 16h, then filtered through kieselguhr. The solids were washed thoroughly with ethyl acetate and the combined filtrates evaporated. Chromatography of the residue [ether-petrol (1:5)] gave the *cis*-ketone **9** (1.89 g, 83%)[29] which showed ν_{max} 1738 cm^{-1}, δ_H (400) 1.44-2.96 (9H, m), 3.54 (1H, ddd, *J* 9.7, 9.6 and 6.2, 9b-H) and 6.96-7.16 (4H, m), δ_C

25.55 (CH_2), 28.78 (CH_2), 34.88 (CH), 38.67 (CH), 44.93 (CH_2), 45.75 (CH_2), 126.20 (2 x CH), 129.18 (CH), 129.42 (CH), 135.67 (C), 137.93 (C) and 218.53 (CO), m/z 186 (M^+, 67%), 143 (100), 129 (61), 128 (31), 115 (13) and 91 (8) [Found: C, 83.8; H, 7.7. Calc. for $C_{13}H_{14}O$, C, 83.8; H, 7.6%], and the alcohol **10** (0.22 g, 9%),[10] essentially as a single diastereoisomer, ν_{max} 3370 cm^{-1}, δ_H (400) 1.17-2.84 (10H, m), 3.13 (1H, ddd, *J* 10.9, 7.9 and 7.9, 9b-H), 4.39 (1H, app. p, *J* 7.0, 2-H) and 6.94-7.19 (4H, m), δ_C 28.01 (CH_2), 28.83 (CH_2), 35.69 (CH), 39.93 (CH), 41.54 (CH_2), 43.98 (CH_2), 72.97 (CHOH), 125.37, 125.93, 128.63, 128.79 (all CH), 137.23 (C) and 139.83 (C), m/z 188 (M^+, 11%), 170 (100), 142 (47), 141 (49), 129 (80), 128 (27), 115 (16) and 91 (16).

The latter alcohol **10** could be oxidised back to the ketone **9** using Jones reagent (0 °C, 0.5h) in ~90% isolated yield.

(2SR,3aRS,9bSR)-2-(3-Methoxycarbonyl-2-oxopropyl)-1,3,3a,4,5,9b-hexahydro-2H-benz[e]inden -2-ol 11.- Methyl acetoacetate (0.52 g, 4 mmol) was added dropwise to a stirred suspension of sodium hydride (0.21 g of a 50% dispersion in oil, 4 mmol) in dry tetrahydrofuran (10 ml) maintained at 0 °C. The resulting mixture was stirred for 10 min, then butyl lithium (3.3 ml of a 1.42M solution in hexanes, 5 mmol) was added dropwise and the mixture stirred for a further 10 min.[11] The ketone **9** (0.46 g, 2 mmol) in dry tetrahydrofuran (2 ml) was then slowly added and the solution stirred overnight without cooling. 2M Hydrochloric acid (3 ml) was then carefully added and the product extracted into ether (2 x 30 ml). Evaporation of the dried extracts left a residue which was chromatographed [ether-petrol (1:1)] to give the *keto-ester* **11** (0.45 g, 61%), as a colourless oil, ν_{max} (film) 3520 and 1725 cm^{-1}, δ_H (80) 1.26-3.45 (11H, m), 2.95 (2H, s, C(OH)C*H*$_2$CO), 3.56 (2H, s, $COCH_2CO$), 3.80 (3H, s, OMe) and 7.19 (4H, s), δ_C 27.25 (CH_2), 28.71 (CH_2), 36.57 (CH), 40.74 (CH), 46.27, 48.43, 50.11 (all CH_2), 52.33 (OMe), 52.93 (CH_2), 78.99 (C), 125.47 (CH), 125.96 (CH), 128.66 (2 x CH), 137.06 (C), 139.55 (C), 167.35 (CO_2) and 204.02 (CO), m/z 284 (M^+-H_2O, 2%), 186 (64), 144 (20), 143 (100), 129 (81), 128 (51), 115 (26) and 91 (15) [Found: C, 71.6; H, 7.6. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%].

***Spiro*-Keto-lactone 13a**.- The foregoing hydroxy-ester **11** (0.18 g) was dissolved in aqueous sodium hydroxide (0.1M, 20 ml) and the solution stirred at ambient temperature overnight then acidified to pH 2 using 2M hydrochloric acid and extracted with chloroform (3 x 30 ml). The combined extracts were dried and concentrated and the residue chromatographed [ether] to give the *keto-lactone* **13a** (0.16 g, 100%) as a colourless powder, m.p. 77-78 °C, ν_{max} 1749, 1724 and 1631 cm^{-1}, δ_H (80) 1.63-3.40 (10H, m), 2.82 (2H, s, CCH_2CO), 3.42 (2H, s, $COCH_2CO$) and 7.15 (4H, br s), δ_C 26.60, 28.82, 36.78, 40.74, 45.18, 45.34, 46.92, 49.24, 86.79 (C), 126.12 (2 x CH), 128.61 (CH), 128.99 (CH), 136.57 (C), 137.66 (C), 167.24 (CO_2) and 200.34 (CO), m/z 270 (M^+, 27%), 169 (70), 168 (100), 167 (23), 166 (46), 143 (17), 142 (17), 141 (27), 130 (13), 129 (77), 128 (40), 115 (20) and 91 (14) [Found: C, 75.4; H, 6.9. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7%].

***Spiro*-Hydroxy-lactones 13b**.- To a stirred solution of the keto-lactone **13a** (0.092 g, 0.3 mmol) in methanol (7 ml) was added borane-t-butylamine complex (0.077 g, 0.8 mmol) followed by aqueous 1M citric acid (1.8 ml). The resulting solution was stirred at ambient temperature for 1h then poured into water (10 ml). The mixture was extracted with ether (2 x 100 ml) and the combined extracts dried and evaporated. Chromatography of the residue [ether] gave the

alcohols **13b** (0.048 g, 52%) as a colourless oil, ν_{max} 3430 and 1720 cm^{-1}, δ_H (250) 1.68-3.27 (15H, m), 4.17-4.33 (1H, m, CHOH) and 6.91-7.18 (4H, m), δ_C 26.64, 26.73, 28.91, 28.96, 29.68 (all CH_2), 36.23 (CH), 36.80 (CH), 39.39 (CH_2), 40.16 (CH), 40.84 (CH), 42.02, 42.26, 45.66, 46.92, 47.20, 48.40 (all CH_2), 62.28 (CH), 62.55 (CH), 89.35 (2 x C), 125.77 (2 x CH), 125.98 (2 x CH), 128.57, 128.71, 128.80, 128.87 (all CH), 136.68, 136.80, 138.44, 138.53 (all C), 170.83 and 170.97 (CO_2), m/z 272 (M^+, 33%), 254 (33), 195 (36), 184 (16), 169 (64), 168 (40), 167 (50), 143 (20), 142 (25), 141 (33), 130 (17), 129 (100), 115 (18) and 91 (15) [Found: M^+, 272.1416. $C_{17}H_{20}O_3$ requires M, 272.1412]. The ^{13}C NMR data indicates an epimer ratio of ~1:1.

3,4,4a,9,10,10a-Hexahydro-2(1H)-phenanthrenone 16. *Method A.*- β-Tetralone (2.92 g, 20 mmol), methyl vinyl ketone (1.6 g, 1.15 eq) and *p*-toluenesulphonic acid (~30 mg) in benzene (50 ml) were refluxed together until tlc showed that none of the intermediate dione **14** was present (~ 50h). After cooling, the reaction mixture was diluted with ether (100 ml) and washed with water (70 ml) then dried and evaporated to leave a yellow oil (4.1 g) containing the ketone **15**. This was dissolved in ethyl acetate (60 ml) containing 10% Pd-C (0.8 g) and the resulting suspension shaken under hydrogen (1 atmos.) at ambient temperature for 48h. Work-up as in the foregoing hydrogenation [**9**] and chromatography [ether-petrol (1:10)] gave the cis-*ketone* **16** (2.17 g, 56% overall) as a yellow oil, ν_{max} 1705 cm^{-1}, δ_H (400) 1.65-1.91 (2H, m, 4-CH_2), 2.02-2.38 (2H, m, 10-CH_2), 2.32-2.45 (2H, m, 1-CH_2), 2.47-2.67 (2H, m, 3-CH_2), 2.68-2.80 (1H, m, 10a-H), 2.84-3.02 (2H, m, 3-CH_2), 3.17-3.28 (1H, ddd, *J* 10.4, 5.0 and 5.0, 4a-H) and 6.90-7.54 (4H, m), δ_C 24.82, 28.69, 32.21 (all CH_2), 36.85 (CH), 38.86 (CH), 40.59 (CH_2), 46.39 (CH_2), 125.94, 126.31, 128.66, 129.31 (all CH), 135.57 (C), 139.23 (C) and 211.63 (CO), m/z 200 (M^+, 44%), 182 (27), 143 (37), 142 (37), 130 (100), 129 (40), 128 (30) and 91 (12) [Found: C, 84.1; H, 8.1. $C_{14}H_{16}O$ requires C, 84.0; H, 8.1%].

The intermediate dione **14** could be isolated after a shorter period of reflux and chromatography [ether-petrol (1:3)] as a yellow oil which showed ν_{max} 1725 cm^{-1}, δ_H (400) 2.25 (3H, s, $COCH_3$), 2.30-3.30 (8H, m), 3.42 (1H, t, *J* 7.0, 1-H) and 7.27 (4H, br s), m/z 216 (M^+, 70%), 159 (72), 158 (100), 146 (23), 131 (74), 130 (74), 129 (37), 128 (21), 117 (40), 116 (24), 115 (55) and 91 (55) [Found: M^+, 216.1132. Calc. for $C_{14}H_{16}O$: M, 216.1151].

Method B.- β-Tetralone (10.0 g, 68 mmol), potassium hydroxide (0.5 g) and methyl vinyl ketone (6.0 g) in ethanol (100 ml) were refluxed together for 0.5h.[22] The cooled mixture was acidified to pH 2 using 10% hydrochloric acid and concentrated under reduced pressure. The residue was diluted with ether (100 ml) and the solution washed with water (50 ml) then dried and evaporated to leave a red oil (11.20 g) and a white solid (0.51 g) which were separated by filtration. Hydrogenation of the red oil as described above followed by chromatography gave recovered β-tetralone (3.70 g), R_f ~0.3 and the desired ketone **16** (2.10 g, 15%), R_f ~0.2, identical to material obtained in method A. The white solid was purified by washing with ether and was the "double" adduct **17**, according to the following data:- m.p. 204-207 °C, ν_{max} (KBr) 3385 and 1650 cm^{-1}, δ_H (200) 1.29 (3H, s, Me), 1.44-1.62 (2H, m), 1.82-2.68 (8H, m), 3.00-3.34 (2H, m), 6.02 (1H, s, C:CH) and 7.04-7.34 (4H, m), δ_C 28.02 (CH_3), 32.15, 32.76, 34.49, 35.42, 38.20 (all CH_2), 50.52 (C), 52.00 (CH), 75.15 (C), 124.04, 124.61, 126.72, 127.06, 127.92 (all CH), 135.44, 140.79, 167.82 (all C) and 198.90 (CO), m/z 268 (M^+, 3%), 250 (22), 198 (31), 197 (100) and 196 (69) [Found: C, 80.3; H, 7.5. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%].

2RS,4aSR,10aRS-2-(3-Methoxycarbonyl-2-oxopropyl)-1,2,3,4,4a,9,10,10a-octahydrophenanth-ren-2-ol 18.- Following the procedure described above for the preparation of keto-ester **11**, reaction between the foregoing *cis*-ketone **16** (5 mmol) and the dianion of methyl acetoacetate (2 eq) gave the *keto-ester* **18** (0.97 g, 62%) as a colourless oil and a single diastereoisomer which showed ν_{max} 3520, 1745 and 1705 cm^{-1}, δ_H (80) 1.40-3.10 (15H, m), 3.49 (2H, s, $COCH_2CO$), 3.76 (3H, s, OMe) and 7.00-7.30 (4H, m), m/z 316 (M^+, 2%), 298 (44), 201 (11), 182 (77), 143 (30), 142 (31), 130 (100), 129 (46), 128 (35), 115 (25) and 91 (23) [Found: C, 72.4; H, 7.6. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.7%].

***Spiro*-Keto-lactone 20a**.- 1M Aqueous sodium hydroxide (50 ml) was added to the keto-ester **18** (0.95 g, 3 mmol) and the resulting mixture stirred at ambient temperature for 18h then acidified by the addition of 10% hydrochloric acid and extracted with chloroform (3 x 30 ml). The combined extracts were dried and evaporated and the residue chromatographed [ethyl acetate-hexane (1:1)] to give the *keto-lactone* **20a** (0.82 g, 96%) as a colourless foam, m.p. 78-81 °C, ν_{max} 1725 cm^{-1}, δ_H (400) 1.67-2.89 (14H, m), 3.43 (2H, s, $CHCH_2CO$) and 7.08-7.21 (4H, m), δ_C 25.80, 26.80, 29.71 (all CH_2), 33.18 (CH), 36.44 (CH_2), 38.89 (CH), 40.88, 44.53, 50.54 (all CH_2), 80.15 (C), 125.97, 126.22, 128.85, 129.42 (all CH), 136.33 (C), 139.95 (C), 167.73 (CO) and 200.76 (CO), m/z 284 (M^+, 15%), 183 (15), 182 (67), 143 (28), 142 (24), 141 (31), 130 (100), 129 (34), 128 (33), 117 (13), 115 (17) and 91 (15) [Found: C, 76.0; H, 7.1. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%].

***Spiro*-Hydroxy-lactones 20b**.- The foregoing keto-lactone **20a** (0.52 g, 1.8 mmol) was reduced as described above using borane-t-butylamine complex to give, after chromatography [ethyl acetate-hexane (1:1)], the *hydroxy-lactones* **20b** (0.35 g, 66%) as a colourless foam, m.p. 140-144 °C, ν_{max} 3450 and 1710 cm^{-1}, δ_H (80) 1.55-2.45 (13H, m), 2.68-2.98 (4H, m), 4.26-4.39 (1H, m, CHOH) and 7.05-7.20 (4H, m), δ_C 25.96, 26.14, 26.88, 26.93, 29.75 (2x) (all CH_2), 33.35 (2 x CH), 36.75 (CH_2), 38.25 (CH_2), 39.22 (CH), 39.31 (CH), 39.52 (2x), 41.54, 42.68, 42.82, 43.00 (all CH_2), 62.26 (2 x CH), 81.76 (C), 82.02 (C), 125.82 (2x), 126.00 (2x), 128.56, 128.63, 129.34 (2x) (all CH), 136.45, 136.64, 140.00 (2x) (all C) and 170.05 (2 x CO), m/z 286 (M^+, 22%), 268 (24), 198 (21), 183 (14), 182 (38), 181 (17), 143 (32), 142 (41), 141 (51), 130 (100), 129 (50), 128 (51), 117 (28), 115 (31) and 91 (28) [Found: C, 75.7; H, 8.0. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.7%]. The ^{13}C NMR data indicated a ~1:1 mixture of epimers at the lactone hydroxyl position.

1,9,10,10a-Tetrahydro-3(2H)-phenanthrenone 22.- This compound was prepared by the method of Brown *et. al.*[9] from α-tetralone by sequential Mannich reaction (formaldehyde, piperidine.HCl), quaternisation (MeI) and condensation with methyl (rather than ethyl[9]) acetoacetate. The final product **22** showed m.p. 78-80 °C [lit.[30] m.p. 80 °C; lit. m.p.[9] 76 °C], λ_{max} 297 (4.296) nm., ν_{max} 1655 cm^{-1}, δ_H (80) 1.40-3.10 (9H, m), 6.60-6.64 (1H, m, 4-H), 7.17-7.55 (3H, m) and 7.78-7.95 (1H, m), m/z 198 (M^+, 72%), 170 (100), 142 (33), 141 (33), 128 (9) and 115 (13) [Found: C, 84.6; H, 7.3. Calc. for $C_{14}H_{14}O$, C, 84.8; H, 7.1%].

1,4,9,10-Tetrahydro-3(2H)-phenanthrenone 23.- The ketone **22** (2.01 g, 10 mmol) in t-butanol (58 ml) was added to potassium t-butoxide (8.75 g) and the resulting mixture stirred at

ambient temperature overnight then quenched by the rapid addition of 10% aqueous acetic acid (290 ml). Excess solid sodium bicarbonate was then added and the whole extracted with ether (3 x 40 ml). The combined ethereal extracts were dried and evaporated and the residue chromatographed [ether-petrol (1:10)] to give the *deconjugated ketone* **23** (1.72 g, 86%) as a yellow oil, ν_{max} (film) 1714 cm^{-1}, δ_H (80) 2.13-2.48 (2H, m, 10-CH_2), 2.59 (4H, br s, 1- and 2-CH_2), 2.81 (2H, app. t, *J* 9, 9-CH_2), 3.20 (2H, m, 4-CH_2) and 6.91-7.30 (4H, m), δ_C 28.12, 28.66, 31.15, 38.52, 39.66 (all CH_2), 121.46 (CH), 124.71 (C), 126.50, 126.71, 127.42 (all CH), 133.27, 134.66, 135.00 (all C) and 209.82 (CO), m/z 198 (M^+, 100%), 170 (7), 156 (53), 155 (22), 154 (9), 142 (27), 141 (72), 129 (14), 128 (23) and 115 (21) [Found: M^+, 198.1052. $C_{14}H_{14}O$ requires M, 198.1044].

***Cis*-1,4,4a,9,10,10a-Hexahydro-3(2H)-phenanthrenone 24**.- The foregoing enone **23** (1.24 g) was hydrogenated as described above to give, after chromatography [ether-petrol (1:5)], the *cis*-ketone **24** (1.00 g, 80%) as a colourless solid, m.p. 67-68 °C [lit.[24,25] m.p. 68-69(70) °C], ν_{max} 1704 cm^{-1}, δ_H (400) 1.65-2.43 (7H, m), 2.48 (2H, app. d, *J* 9, 4-CH_2), 2.90 (2H, m, 9-CH_2), 3.16 (1H, ddd, *J* 10.4, 7.0 and 4.6, 4a-H) and 7.05 (4H, br s), δ_C 23.35, 29.20, 30.77, 32.72 (all CH_2), 37.43 (CH), 41.28 (CH_2), 46.70, 126.01, 126.33, 128.34, 129.21 (all CH), 135.48 (C), 139.12 (C) and 211.23 (CO), m/z 200 (M^+, 100%), 182 (16), 172 (32), 143 (77), 142 (82), 130 (47), 129 (64), 128 (46), 115 (44) and 91 (26) [Found: C, 83.8; H, 8.1. Calc. for $C_{14}H_{16}O$, C, 84.0; H, 8.1%].

***3SR,RS,4aSR,10aRS*-3-(3-Methoxycarbonyl-2-oxopropyl)-1,2,3,4,4a,9,10.10a-octahydrophenan thren-3-ol 25**.- By the foregoing procedure, condensation between the ketone **24** (0.96 g, 5 mmol) and the sodio-lithio dianion of methyl acetoacetate (2 eq) followed by chromatography [ether-petrol (1:1)] gave a 58:42 mixture of the 3-epimers of the *keto-esters* **25** (1.18 g, 77%), as a pale yellow oil, which was not further separated and which showed ν_{max} (film) 3505, 1740 and 1705 cm^{-1}, δ_H (250) 1.38-3.38 (15H, m), 3.45 (1.15H, s, $COCH_2CO$), 3.58 (0.85H, s, $COCH_2CO$), 3.72 (1.72H, s, OMe), 3.80 (1.27H, s, OMe) and 7.13 (4H, m), δ_C 22.46, 23.32, 26.35, 28.38, 29.52, 29.85, 31.53 (all CH_2), 32.44 (CH), 32.61 (CH), 33.58 (CH_2), 35.14 (CH), 37.96 (CH), 42.50, 43.20, 48.83, 50.55, 50.76 (all CH_2), 52.38 (2 x OMe), 54.26 (CH_2), 71.05 (C), 72.49 (C), 125.73 (2x), 125.86, 128.86, 129.04, 129.12 (2x) (all CH), 135.92, 136.05, 140.33, 141.59 (all C), 167.20 (OCO), 167.57 (OCO), 203.99 (CO) and 204.11 (CO), m/z 298 (M^+-H_2O, 8%), 201 (11), 200 (62), 182 (33), 172 (11), 143 (100), 142 (82), 130 (35), 129 (64), 128 (39), 115 (32) and 91 (15) [Found: M^+-H_2O, 298.1556. $C_{19}H_{22}O_3$ requires M, 298.1568].

***Spiro*-Keto-lactones 28a**.- Saponification of the foregoing keto-esters **25** (0.95 g) using 1M aqueous sodium hydroxide (95 ml) as described above followed by chromatography [ether] gave the spiro-*keto-lactones* **28a** (0.86 g, 89%) as a colourless foam, m.p. 153-157 °C, ν_{max} (film) 1730 cm^{-1}, δ_H (250) 1.34-3.10 (14H, m), 3.48 (2H, s, $COCH_2CO$) and 7.16 (4H, br s), m/z 284 (M^+, 65%), 225 (19), 184 (15), 183 (100), 182 (77), 181 (20), 180 (23), 179 (12), 143 (53), 142 (56), 141 (54), 130 (35), 129 (51), 128 (32), 117 (24), 115 (22) and 91 (16) [Found: C, 76.0; H, 7.3. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%].

***Spiro*-Hydroxy-lactones 28b**.- The foregoing keto-lactone **28a** (0.67 g, 2.4 mmol) was reduced using borane-t-butylamine complex (0.47 g, 5.0 mmol) as described above. The crude product was

purified by chromatography [ethyl acetate-hexane (1:1)] to give the *alcohols* **28b** (0.50 g, 73%) as a viscous oil, ν_{max} 3395 and 1720 cm^{-1}, δ_H (250) 1.27-3.52 (17H, m), 4.12-4.62 (1H, m, C*H*OH) and 7.18 (4H, br s), m/z 286 (M^+, 27%), 268 (100), 209 (91) 184 (18), 183 (88), 182 (23), 181 (51), 143 (91), 142 (56), 141 (60), 130 (52), 129 (72), 128 (60), 117 (41), 115 (38) and 91 (30) [Found: M^+, 286.1571. $C_{18}H_{22}O_3$ requires M, 286.1569].

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