# A conjugate addition–radical cyclisation approach to sesquiterpene-phenol natural products

**Barry S. Crombie,[a] Colin Smith,[b] Christalla Z. Varnavas[a] and Timothy W. Wallace*[a]**

[a] *Department of Chemistry and Applied Chemistry, University of Salford, Salford, UK M5 4WT. E-mail: T.W.Wallace@salford.ac.uk*
[b] *Glaxo Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

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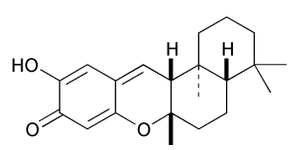
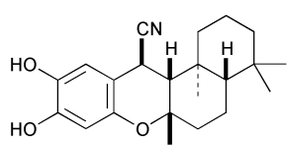
The polycyclic ring system which forms the nucleus of a series of sesquiterpene-phenol natural products, including the antimalarial 15-oxopuupehenol, can be constructed in racemic form in four efficient steps, the last of these being a stereoselective manganese(III) acetate-mediated radical cyclisation reaction.

## Introduction

A series of biologically active natural products, many of marine origin,[1] is based on a fusion of sesquiterpene and phenolic moieties. The series includes the sponge metabolite puupehenone **1**,[2] its congeners 15-cyanopuupehenol **2**,[3] 15-oxopuupehenol **3**[4] and related dimers,[5] 8-epichromazonarol **4**,[6] and ring-opened systems such as hyatellaquinone **5**.[7] The antifungal agent siccanin **6**,[8] which was isolated from the culture broth of a parasitic rye-grass fungus, also belongs in this category although its carbon skeleton, which incorporates a *cis*/*syn*/*cis* fusion of three saturated rings, is unusual.



**1**



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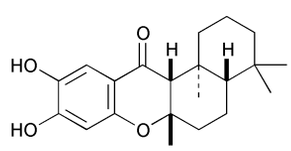

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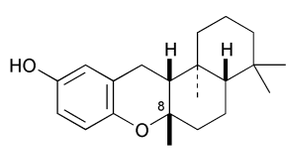

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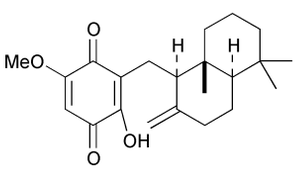

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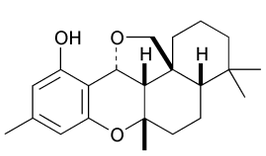

**6**

We have been seeking a synthetic route to compounds of this type, our interest being focused on **2**, which has antiviral properties[3] and activity against tuberculosis,[9] and **3**, which is active against *Plasmodium falciparum* malaria at the micromolar level.[4] Of the world's infectious diseases tuberculosis and malaria are leading killers, accounting for millions of deaths each year, and drug-resistant strains of both continue to emerge.[10] A flexible route to sesquiterpene phenols such as **2** and **3** would offer an alternative source of these interesting materials and might ultimately provide access to biologically active analogues of potential therapeutic use.

Most of the existing approaches to this type of compound are based on a strategy involving the initial formation of a suitably functionalised bicyclic (terpenoid) unit, with the pyran ring being generated late in the sequence. This strategy has provided siccanin **6**,[11] puupehenone **1**,[12] and the methylenedioxy derivative of **3**.[13] More recently a biomimetic cyclisation approach was used to construct chromazonarol (8-*epi*-**4**).[14] In seeking a more flexible route to the tetracyclic nucleus of this type of compound, we devised a convergent strategy based on the sequence shown in Scheme 1. The first step is the conjugate addition of an organocopper species to a chromone-3-carboxylate, a mild and flexible route to 2,2-disubstituted chroman-4-ones.[15] The second step is the generation of a β-ketoester radical, a convenient and relatively clean process under whose oxidative conditions any subsequent cyclisation involving a suitably located olefinic bond can give rise to a functionalised product. This principle has been widely recognised and exploited in a variety of contexts, most notably by Snider and his group.[16] The results of our investigation of the sequence outlined in Scheme 1 are herein described in detail.[17]

## Results and discussion

### Synthesis of chromanones

In the first approach to a radical cyclisation precursor, the ketoester **11** was prepared *via* alkylation of the dianion of methyl acetoacetate with the bromide **10**,[18] and condensed with 2-fluorobenzoyl chloride[19] to obtain the 4-oxochromene-3-carboxylate **12** (Scheme 2). Treatment of the latter with lithium dimethylcuprate gave, *via* conjugate addition at C-2, the anticipated[15] mixture of *cis*-keto, *trans*-keto and enol forms of the chromanone **13**. It was later established that an alternative route to **11**, *via* the methoxycarbonylation of dihydro-β-ionone **14**,[20] readily provided large quantities of the chromanone ester **13**.

The flexibility of the two routes to the ester **13** was briefly investigated. The alkylation route using **10** was used to prepare the *tert*-butyl ester **15** but gave only a modest yield, and a subsequent attempt to convert this into the corresponding chromone **16** using the standard procedure[19] was unsuccessful, presumably due to adverse steric interactions during the cyclisation process. The alkoxycarbonylation route from **14** is compromised by the limited availability of suitably reactive

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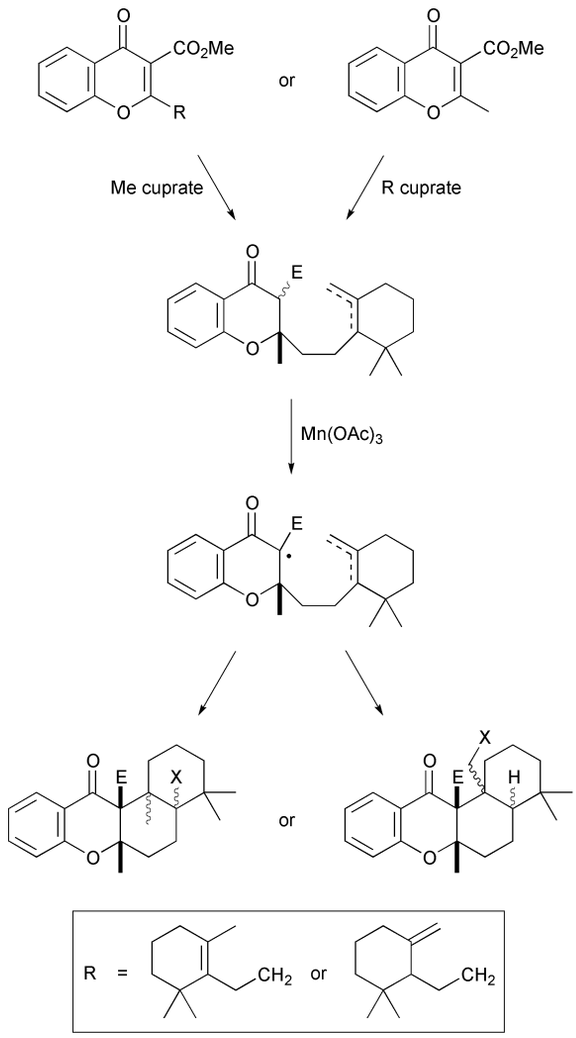
carbonates, but the allyl ester **17** proved accessible by this method. The latter was also prepared in reasonable yield *via* the transesterification of **11** using allyl alcohol and a tin-based solid acid catalyst.[21] An attempt to prepare the *tert*-butyl ester **15** by this method was unsuccessful, delivering only the decarbalkoxylation product **14** (57%).

The conversion of the allyl ester **17** into the corresponding chromone **18** was fairly efficient. The ester **18** possesses two sites with potential reactivity towards organocopper reagents, *viz.* the activated enone and allylic ester moieties, and provided an interesting opportunity to probe the chemoselectivity which might be displayed by such substrates. For example, treating **18** with lithium dimethylcuprate gave rise to a substantial yield of the carboxylic acid **19**, which presumably arose *via* an allylic displacement ($S_N2'$) process.[22] By contrast, the major reaction pathway observed on subjecting the ester **18** to a copper(I)-catalysed methyl Grignard addition[23] in the presence of trimethylsilyl chloride[24] was conjugate addition to the enone unit, which gave rise to the ester **20** in fair yield. These and other chemoselective reactions of allyl enoates are the subject of further investigation and will be described in due course.

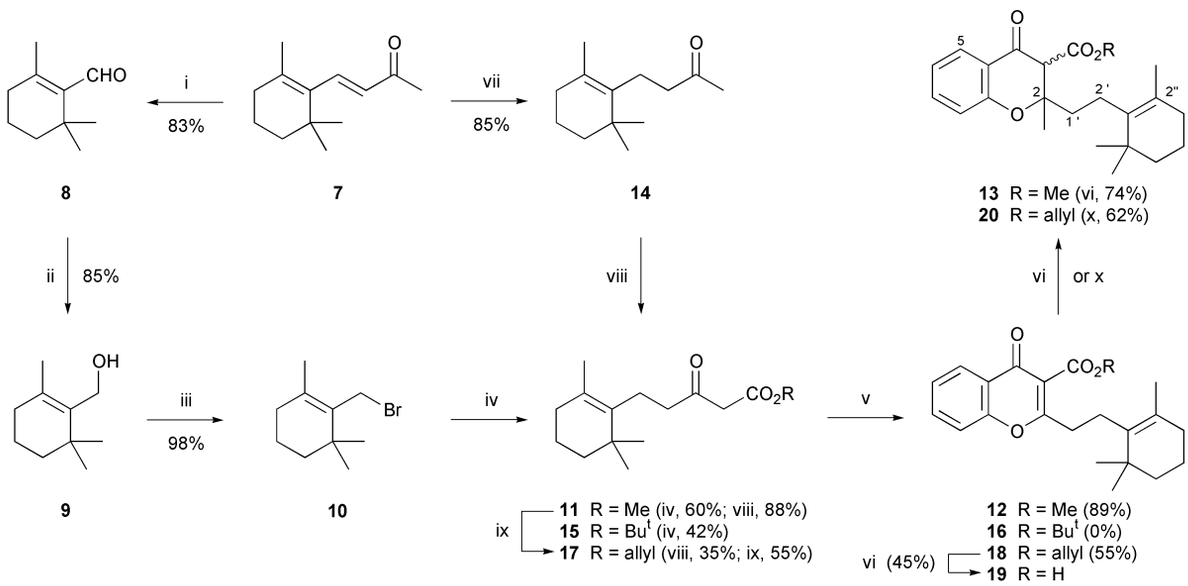
The isomeric chromanone ester **29** was prepared using the sequence shown in Scheme 3. The aldehyde **21**, prepared in three steps from 2,2-dimethylcyclohexanone,[25] was reduced with sodium borohydride and the resultant alcohol **22** transformed into the ester **23** *via* a Claisen rearrangement.[26] Reduction then provided (±)-γ-cyclohomogeraniol **24**[27] which was converted *via* a standard sequence[28] into the iodide **26**. The latter served as the precursor to the mixed thienylcyanocuprate **27**,[29] which underwent conjugate addition to methyl 2-methyl-4-oxochromene-3-carboxylate **28**[19] to give the chromanone ester **29** as a mixture of diastereoisomers in 66% yield. The same mixture was also produced, less efficiently, using reagents derived from copper(I) iodide and lithium imidazol-1-idocyanocuprate.



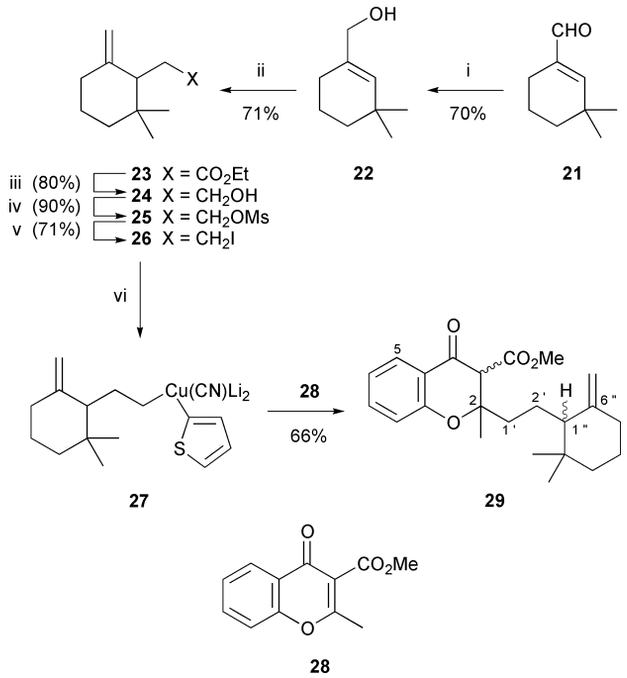

**Scheme 1** (E = $CO_2Me$, X = OAc).

## Oxidative cyclisations

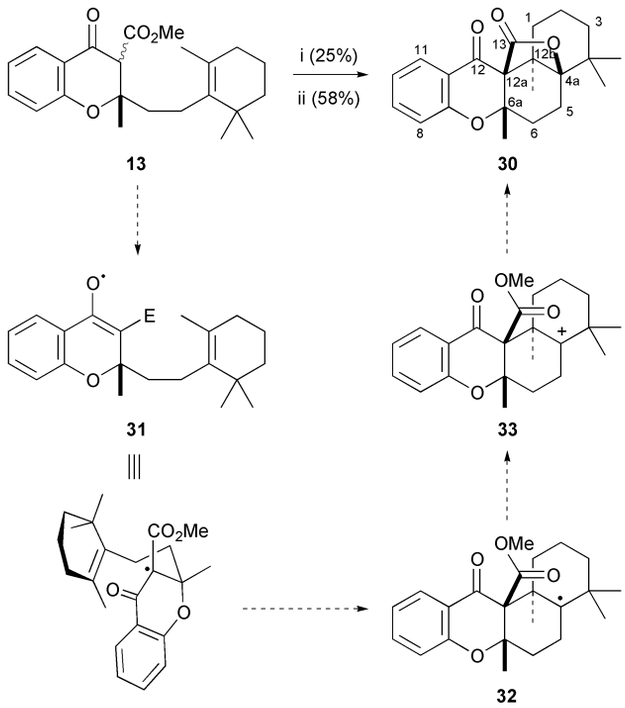
Oxidation of the isomeric mixture of **13** with manganese(III) acetate was attempted under a variety of conditions using copper(II) acetate as a co-oxidant.[30] There was no discernible reaction at 20 °C during one week, but heating at 55–60 °C brought about a reaction in a few hours (higher temperatures tended to lead to a more complex mixture of products so as to make isolation difficult). A reaction was indicated by a colour change, the initial solution of manganese(III) and copper(II) acetates being a dark blue–green, becoming much paler in colour as the reaction proceeded, ending with a



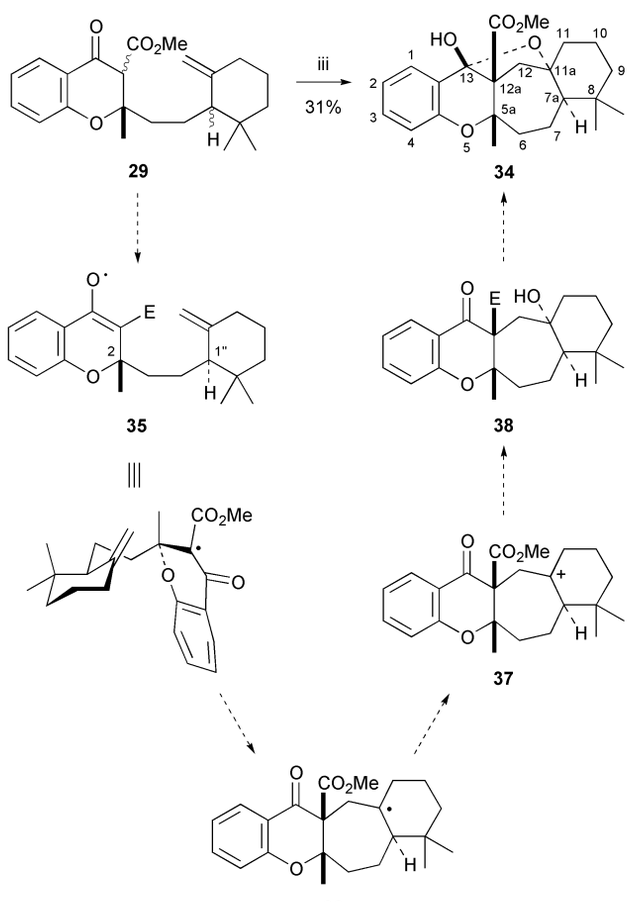

**Scheme 2** *Reagents and conditions*: i, $O_3$, MeOH, −30 °C, then Zn, HOAc; ii, $NaBH_4$, EtOH, $Pr^iOH$, 20 °C, 1 h; iii, $PBr_3$, hexane, $Et_2O$, −30 to +20 °C, 15 h; iv, $MeCOCH_2CO_2Me$, NaH, BuLi, THF, 0 °C, then **10**, 0 to 20 °C, 0.5 h; v, NaH, toluene, 50 °C, 1 h, then 2-$FC_6H_4COCl$, 110 °C, 3 d; vi, $Me_2CuLi$, $Et_2O$, THF; vii, $Bu_3SnH$, AIBN, 80 °C, 15 h, then $SiO_2$; viii, NaH, $(MeO)_2CO$, dioxane, 100 °C, 3.5 h; ix, allyl alcohol, catalyst, toluene, 110 °C; x, TMSCl, cat. CuI, MeMgCl, THF, −10 °C, 5 h, then HOAc, 20 °C.




**Scheme 3** *Reagents and conditions*: i, $NaBH_4$, EtOH, 0 to 10 °C, 2 h; ii, $MeC(OEt)_3$, cat. $EtCO_2H$, 150 °C, 5 h; iii, LAH, THF, 20 °C, 12 h; iv, MsCl, $Et_3N$, DCM; v, NaI, acetone, reflux, 4 h; vi, *t*-BuLi, $Et_2O$–pentane, −30 °C, 15 min, then 2-thienylCu(CN)Li, THF, −50 to −20 °C; then chromone **28**, $Et_2O$, −50 °C, 1 h.




**Scheme 4** (E = $CO_2Me$). *Reagents and conditions*: i, $Mn(OAc)_3$, $Cu(OAc)_2 \cdot H_2O$, HOAc, 58 °C, 5 h; ii, $Mn(OAc)_3$, HOAc, 80 °C, 12 h.




**Scheme 5** (E = $CO_2Me$). *Reagents and conditions*: i, $Mn(OAc)_3$, HOAc, 65 °C, 3 h.

turquoise solution. Aqueous work up followed by chromatography over silica gel gave as a major product the lactone **30**, a colourless crystalline solid, in 25–30% yield. Analysis by $^1H$ NMR spectroscopy and TLC indicated that the balance included starting material and several minor products; none of these was fully characterised. The efficiency of the reaction depended to some extent on the quality of the solvent and the substrates. Initially manganese(III) acetate dihydrate (Aldrich) was used, but it was found that the reaction proceeded more cleanly with the anhydrous material[31] and with dry and degassed acetic acid.

The structure of the lactone **30** was initially deduced by spectroscopic means, especially a $^1H$–$^{13}C$ heteronuclear shift correlation NMR experiment, which indicated the presence of a new oxygenated quaternary carbon adjacent to the *gem*-dimethyl centre. The relative stereochemistry was confirmed by X-ray crystallography[17] as that found in the natural products **1**–**4**, and is presumed to arise *via* an initial 6-*endo*-*trig* cyclisation of the β-ketoester radical **31** derived from **13**, leading to **32** which undergoes further oxidation to a cation **33**, followed by lactonisation (Scheme 4).[32] On the basis that the second oxidation step, from **32** to **33**, should be within the scope of manganese(III) alone,[16] the reaction was repeated in the absence of copper(II) acetate and after some optimisation afforded the lactone **30** in 58% yield.

The chromanone **29** was more easily oxidised than **13**, and gave rise to a large number of products when run at different temperatures, or in the presence or absence of copper(II) acetate. Analysis of the reaction was rendered more complex by the initial presence of up to four diastereoisomers of **29**. Typically, an acetic acid solution of the mixed isomers **29** was treated with dried[33] manganese(III) acetate at 65 °C; the solution became noticeably lighter in colour after 30 min and was worked up after three hours. Chromatography of the product mixture over silica gel yielded as a major product the crystalline hemiacetal **34** (31%) whose structure was established by X-ray crystallography.[17] This product is seen as arising from the 7-*endo*-*trig* cyclisation of the initially-formed ketoester radical **35**, giving **36** which undergoes further oxidation to the cation **37**. The latter is ultimately intercepted by water to give **38** and hence **34** (Scheme 5).[34] Given that the isolated product can only arise from the (rel-2*S*,1″*R*) radical **35**, the overall sequence is a fairly efficient one.

A study of the chemistry of the lactone **30** has been initiated with experiments involving reducing agents. A small-scale

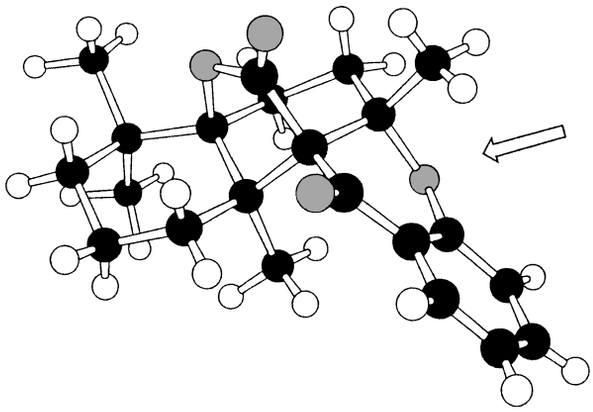
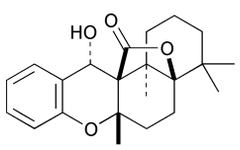
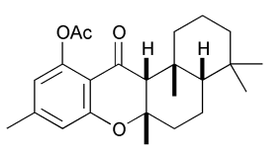


**Fig. 1** X-Ray structure of the lactone **30**.

reaction of **30** with DIBAL-H (3 mol. equiv.) gave as a major product a compound whose UV and IR spectra indicated that aromatic carbonyl function had been reduced (loss of absorptions at 256, 316 nm and 1683 $cm^{-1}$). Comparing models of the starting material **30** and the related ketone **40**, whose reduction with LAH occurs exclusively from the *Si* face of the aromatic carbonyl group,[35] leads us to conclude that the product obtained is the alcohol **39** which would result from reduction of the more open face (Fig. 1, arrowed) of the corresponding carbonyl group in **30**. Treating the lactone **30** with a larger excess of DIBAL-H produced a mixture thought to consist mainly of a lactol **41** and a second product which was partially characterised as the ether-bridged **42**. The reduction of **30** with LAH (2 mol. equiv.) afforded the lactol **41** cleanly but in low yield.



**39**



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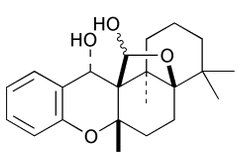
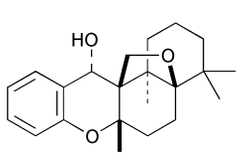


**41**



**42**

The transformation of **13** into **30** generates the tetracyclic nucleus and four contiguous stereogenic centres of the natural products **1**–**4**, and thus offers an efficient and potentially flexible route to polycycles of this type in four steps from commercially available materials. Enantioselective versions of the synthetic sequence, together with further transformations of the lactone **30** (in particular the nett reductive removal of the lactone bridge) are currently under investigation and will be described in due course.

## Experimental

All compounds are racemic. Melting points were recorded using an Electrothermal apparatus and are uncorrected. Unless stated otherwise, IR spectra were recorded as neat films on sodium chloride plates on Perkin-Elmer 1710FT or Nicolet 5SXC FTIR spectrometers. NMR spectra were measured for solutions in deuteriochloroform with tetramethylsilane as the internal reference using Bruker 250, 300 or 400 MHz instruments. Unless otherwise indicated, mass spectra were measured on Finnegan 4500 (low resolution) or Kratos Concept S1 (high resolution) instruments using the ammonia chemical ionisation method; most fragment ions with a relative intensity of less than 20% of the base peak have been omitted. UV spectra were measured for ethanolic solutions using a Hewlett Packard 8452A Diode Array spectrophotometer. Ozone was generated using a Wallace & Tiernan ozonator (type BA.023).

Reactions were usually carried out under a slight overpressure of either argon or nitrogen. Starting materials and solvents were routinely purified by conventional techniques.[36] Acetic acid was dried with acetic anhydride and degassed before use. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL $G/UV_{254}$ plates. Spots were visualised with ethanolic phosphomolybdic acid or acidic vanillin reagents[37] unless otherwise indicated. Preparative (column) chromatography was carried out using silica gel (Merck 9385 and the flash technique[38]) or on Florisil® (Aldrich 28,870-5). Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, bp 40–60 °C, unless otherwise stated. 'Ether' refers to diethyl ether.

**2,6,6-Trimethylcyclohex-1-ene-1-carbaldehyde 8.**[39] A solution of β-ionone† **7** (7.68 g, 0.04 mol) in methanol (70 ml) was cooled to −30 °C. With vigorous stirring, a stream of oxygen–ozone was passed into the solution at a rate of about 50 l $h^{-1}$ (corresponding to 0.052 mol of ozone per hour). After 6 h the reaction was complete by TLC and the solution was flushed with $N_2$ for 5 min. Zinc (4 g) was then added to the cooled solution and, with further cooling, 50% acetic acid (30 ml) was added dropwise. The reduction was noticeably exothermic (−5 to +25 °C) and took 30 min. After stirring for a further 1 h, the reaction mixture was poured into cold water (400 ml) and extracted with DCM (3 × 75 ml). The organic phase was neutralised by washing with saturated aqueous sodium hydrogen carbonate, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was fractionally distilled under reduced pressure to obtain the aldehyde **8** (3.95 g, 65%), bp 70–74 °C at 1 mmHg (lit.,[39] bp 50–51 °C at 0.35 mmHg); $\nu_{max}$ (neat)/$cm^{-1}$ 1715; $\delta_H$ (300 MHz) 1.14 (6 H, s, 6-$Me_2$), 1.34–1.41 (2 H, m, 5-$H_2$), 1.53–1.61 (2 H, m, 4-$H_2$), 2.04 (3 H, s, 1-Me), 2.14 (2 H, t, *J* 6 Hz, 3-$H_2$), 10.07 (1 H, s, CHO); *m*/*z* 170 ($M + NH_4^+$, 100%), 153 ($M + H^+$, 35), 65 (25).

**2,6,6-Trimethylcyclohex-1-ene-1-methanol 9.**[40] A solution of β-cyclocitral **8** (4 g, 26 mmol) in propan-2-ol (7 ml) was added dropwise to an ice-cooled suspension of sodium borohydride (1.47 g, 39 mmol) in ethanol–propan-2-ol (1:1, 10 ml) with stirring. When addition was complete, the mixture was allowed to warm up to ambient temperature and stirring was maintained for 1 h. The reaction mixture was then poured into water (20 ml) and the excess borohydride allowed to decompose. The aqueous phase was saturated with sodium chloride and extracted with ether (3 × 10 ml). The organic extracts were combined, washed with water (10 ml) and brine (10 ml), dried and concentrated *in vacuo*. The resulting viscous, colourless oil was purified *via* column chromatography (petroleum ether–ethyl acetate 4:1) to give the alcohol **9** (3.4 g, 85%) as a colourless waxy solid, mp 32–34 °C (lit.,[40] 40–42 °C); $\nu_{max}$ (Nujol)/$cm^{-1}$ 3345, 1654; $\delta_H$ (300 MHz) 1.01 (6 H, s, 6-$Me_2$), 1.35–1.45 and 1.50–1.60 (both 2 H, m, 4-$H_2$ and 5-$H_2$), 1.72 (3 H, s, 1-Me), 1.94 (2 H, t, *J* 6 Hz, 3-$H_2$), 4.10 (1 H, s, $CH_2O$).

**2-Bromomethyl-1,3,3-trimethylcyclohex-1-ene 10.**[41] Phosphorus tribromide (1.3 g, 4.8 mmol) in hexane–ether (1:1,

† The IUPAC name for β-ionone is 4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one.

10 ml) was added dropwise to a solution of the alcohol **9** (2.0 g, 13 mmol) in hexane–ether (1:1, 25 ml) over 1 h at −30 °C under an inert atmosphere. The reaction mixture was stirred for an additional 2 h at this temperature and then was allowed to warm up to room temperature and stirred for another 12 h. When the reaction was complete saturated aqueous sodium hydrogen carbonate was added dropwise until effervescence was no longer apparent. The solution was extracted with ether (3 × 10 ml) and the combined extracts washed with water (10 ml) and brine (10 ml), dried and concentrated under reduced pressure to obtain the title compound **10** (2.75 g, 98%) as a pale brown liquid which was used without further purification; $\nu_{max}$ ($CHBr_3$)/$cm^{-1}$ 1638, 515; $\delta_H$ (250 MHz) 1.10 (6 H, s, 3-$Me_2$), 1.40–1.65 (4 H, m, 4-$H_2$, 5-$H_2$), 1.74 (3 H, s, 2-Me), 2.02 (2 H, t, *J* 5.5 Hz, 6-$H_2$), 4.08 (2 H, s, $CH_2Br$).

**Methyl 3-oxo-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pentanoate 11.** *Method 1.*[18] A suspension of sodium hydride (60% dispersion in mineral oil, 0.48 g, 12 mmol) in anhydrous THF (20 ml) under an inert atmosphere was stirred with ice-cooling as methyl acetoacetate (1.28 g, 11 mmol) was added dropwise. The reaction mixture was stirred for 10 min and then *n*-butyllithium (1.22 M, 9.4 ml, 11.5 mmol) was added carefully. After a further 10 minutes stirring, the bromide **10** (2.29 g, 10.5 mmol) was added in one portion and the mixture was stirred at room temperature for 30 min. Hydrochloric acid (4 M, 6 ml) was added carefully and the resulting solution diluted with ether (15 ml). The aqueous layer was back-washed with ether (2 × 10 ml) and the combined organic extracts were washed with water (2 × 20 ml) and brine (20 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting yellow oil was purified by chromatography, eluting with petroleum–ethyl acetate (5:1), which gave the title compound **11** (1.66 g, 60%) as an off-white waxy solid, mp 35–37 °C (lit.,[18] bp 118–125 °C at 0.3 mmHg); $\nu_{max}$ ($CHBr_3$)/$cm^{-1}$ 1741, 1712; $\delta_H$ (300 MHz) 0.96 (6 H, s, 6′-$Me_2$), 1.37–1.60 (4 H, m, 4′-$H_2$, 5′-$H_2$), 1.57 (3 H, s, 2′-Me), 1.87 (2 H, t, *J* 6 Hz, 3′-$H_2$), 2.22–2.30 (2 H, m, 4-$H_2$), 2.55–2.63 (2 H, m, 5-$H_2$), 3.42 (2 H, s, 2-$H_2$), 3.71 (3 H, s, OMe); *m*/*z* (peaks > 10%) 270 (M + $NH_4^+$, 100%), 253 (M + $H^+$, 50), 193 (12); $R_f$ 0.45 (DCM, UV active, orange with vanillin). The presence of an enol tautomer was indicated by characteristic peaks in the NMR spectrum at $\delta_H$ 4.97 (s, vinyl) and 11.97 (s, enolic OH).

*Method 2.*[20] Dimethyl carbonate (7.055 g, 6.6 ml, 0.078 mol) and sodium hydride (60% oil dispersion, 3.12 g, 0.078 mol) in dry dioxane (70 ml) under Ar were stirred and heated under reflux. A solution of dihydro-β-ionone ‡ **14**[20] (7.59 g, 0.039 mol) in dry dioxane (10 ml) was then added dropwise over 1.5 h. The reaction was heated under reflux for a further 2 h. Upon cooling the reaction mixture was neutralised with 4 M hydrochloric acid. After vigorous stirring the organic layer was separated, the aqueous layer was extracted with ether, and the combined organics were dried and evaporated. The residue was purified by flash chromatography, eluting with petroleum–ethyl acetate (3:1), to obtain the title compound **11** (8.646 g, 88%) as a yellow oil, identical (NMR, TLC) with material prepared by method 1.

**Methyl 2-[2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl]-4-oxo-4*H*-1-benzopyran-3-carboxylate 12.** A solution of ester **11** (5.90 g, 0.023 mol) in anhydrous toluene (60 ml) was added to a suspension of sodium hydride (60% oil dispersion, 1.40 g, 0.035 mol) in anhydrous toluene (60 ml) under Ar at room temperature. This was then stirred for 1 h at 50 °C. To this yellow suspension was added dropwise a solution of 2-fluorobenzoyl chloride (2.75 ml, 0.023 mol) in dry toluene (60 ml). The reaction was then heated under reflux for 72 h. After cooling the reaction was poured into water (200 ml) and extracted with ether (3 × 100 ml). The combined organics were washed with water (50 ml), brine (50 ml), and dried over sodium sulfate. Concentration gave an orange oil which was purified by flash chromatography, eluting with petroleum–ethyl acetate (2:1), yielding the *title compound* **12** (7.356 g, 89%) as a viscous yellow oil (*M* + $H^+$, 355.1913. $C_{22}H_{27}O_4$ requires 355.1909); $\nu_{max}$ (neat)/$cm^{-1}$ 1736, 1652, 1622, 1575; $\delta_H$ (300 MHz) 1.02 (6 H, s, 6″-$Me_2$), 1.4–1.6 (4 H, m, 4″-$H_2$, 5″-$H_2$), 1.66 (3 H, s, 2″-Me), 1.92 (2 H, t, *J* 6 Hz, 3″-$H_2$), 2.4–2.5 (2 H, m, 2′-$H_2$), 2.7–2.8 (2 H, m, 1′-$H_2$), 3.90 (3 H, s, OMe), 7.35–7.45 (2 H, m, 6-H, 8-H), 7.66 (1 H, ddd, *J* 1.5, 7, 7.5 Hz, 7-H), 8.19 (1 H, dd, *J* 1.5, 7.5 Hz, 5-H); *m*/*z* (CI, MeCN/$NH_3$) 355 (*M* + $H^+$, 100%); $R_f$ 0.55 (petroleum–ethyl acetate 2:1, UV active).

**Methyl 2,3-dihydro-2-methyl-2-[2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl]-4-oxo-4*H*-1-benzopyran-3-carboxylate 13.** To a suspension of copper(I) iodide (6.094 g, 0.032 mol) in dry ether (100 ml) under Ar at −10 °C was added methyllithium in ether (1.5 M, 42.7 ml, 0.064 mol). On addition of a second equivalent of methyllithium, the reaction mixture turned from a yellow suspension to a colourless solution. A solution of **12** (7.356 g, 0.021 mol) in anhydrous THF (100 ml) was added directly to the above solution. The reaction mixture was then cooled down to −42 °C (MeCN–$CO_2$ slush) and stirred for 1 h. The reaction was quenched by stirring with saturated aqueous ammonium chloride (100 ml) for 15 min. The mixture was then extracted with ether (3 × 100 ml) and the combined organics washed with 2 M hydrochloric acid (100 ml), water (100 ml), brine (100 ml) and dried. On concentration, a crude dark orange oil was obtained which was purified by flash chromatography (petroleum–ethyl acetate 2:1) to give the *title compound* **13** (5.960 g, 74%) as an orange oil (*M* + $H^+$, 371.2214. $C_{23}H_{31}O_4$ requires 371.2222); $\nu_{max}$ (neat)/$cm^{-1}$ 1747, 1695, 1609, 1464, 764; $\delta_H$ (300 MHz) 0.72 (minor), 0.85 (major), 0.90 (minor) and 0.95 (major) (total 6 H, 4 × s, 6″-$Me_2$ of diastereoisomers), 1.32 (minor) and 1.45 (major) (total 3 H, 2 × s, 2-Me of diastereoisomers), 1.52 (6 H, br s, 2″-Me of major and minor diastereoisomers), 1.3–1.4 (2 H, m, 5″-$H_2$), 1.45–1.6, 1.65–1.9 and 2.0–2.3 (total 8 H, m, 1′-$H_2$, 2′-$H_2$, 3″-$H_2$, 4″-$H_2$), 3.74 and 3.75 (total 3 H, 2 × s, OMe of diastereoisomers), 3.80 and 3.83 (total 1 H, 2 × s, 3-H of diastereoisomers), 6.9–7.0 (2 H, m, 6-H and 8-H), 7.48 (1 H, br t, *J* 7 Hz, 7-H), 7.84 (1 H, dd, *J* 1, 7 Hz, 5-H); *m*/*z* (peaks > 10%) 388 (*M* + $NH_4^+$, 100%), 371 (*M* + $H^+$, 77), 219 (36); $R_f$ 0.63 (petroleum–ethyl acetate 2:1, UV active). The presence of an enol tautomer was indicated by characteristic peaks in the NMR spectrum, *e.g.* $\delta$ 13.0 ppm (s, enolic OH).

***tert*-Butyl 3-oxo-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pentanoate 15.** A suspension of sodium hydride (60% dispersion in mineral oil, 0.073 g, 1.83 mmol) in dry THF (5 ml) under Ar was stirred with ice cooling as *tert*-butyl acetoacetate (0.290 g, 1.83 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C and then BuLi (1.21 ml, 1.83 mmol, 1.51 M) was added. After a further 15 min of stirring the bromide **10** (0.346 g, 1.59 mmol) in dry THF (3 ml) was added at 0 °C. The reaction was then allowed to reach room temperature overnight. Dilute acetic acid was added until a clear solution resulted. The aqueous layer was separated and extracted with ether (2 × 10 ml). All the organic layers were recombined, washed with water (5 ml), brine (5 ml), dried over sodium sulfate and then evaporated under reduced pressure. Purification by chromatography, eluting with petroleum–ethyl acetate (4:1), gave the *title compound* **15** (0.197 g, 42%) as a pale yellow oil (*M* + $H^+$, 295.2276. $C_{18}H_{31}O_3$ requires 295.2273); $\delta_H$ (300 MHz) 0.95 (6 H, s, 6′-$Me_2$), 1.35–1.45 (4 H, m, 4′-$H_2$, 5′-$H_2$), 1.45 (9 H, s, *t*-Bu), 1.54 (3 H, s, 2′-Me), 1.87 (2 H, t, *J* 6 Hz,

‡ The IUPAC name for dihydro-β-ionone is 4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-one.

3′-$H_2$), 2.2–2.3 (2 H, m, 4-$H_2$), 2.55–2.65 (2 H, m, 5-$H_2$), 3.32 (2 H, s, 2-$H_2$); *m*/*z* (peaks > 10%) 312 ($M + NH_4^+$, 30%), 295 ($M + H^+$, 28), 256 (100), 239 (61), 136 (30).

**Attempted preparation of the ester 15 by transesterification.** A mixture of the ketoester **11** (40 mg, 0.16 mmol), *tert*-butanol (*tert*-butyl alcohol) (0.1 ml, 77.5 mg, 1.05 mmol) and 'sulfated $SnO_2$' catalyst[21] (33 mg) in toluene (5 ml) was heated to 110 °C in a round-bottomed flask fitted with a condenser. The reaction was monitored by TLC (silica, DCM), and after 18 h a new product was visible ($R_f$ 0.52), together with some starting material ($R_f$ 0.45). The mixture was cooled and evaporated under reduced pressure. Chromatography of the residue, eluting with DCM–petroleum (4:1), afforded the ketone **14** (17.8 mg, 57%) as a colourless oil, identical (TLC, NMR) with an authentic sample.[20]

**Attempted preparation of the ester 16.** A solution of **15** (0.160 g, 0.54 mmol) in dry toluene (2 ml) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.025 g, 0.62 mmol) in dry toluene (3 ml) under $N_2$. Effervescence was observed. The reaction mixture was stirred at room temperature for 10 min and then a solution of 2-fluorobenzoyl chloride (0.086 g, 0.54 mmol) in toluene (2 ml) was added. The resulting yellow solution was heated under reflux for 48 h and then quenched by the addition of water (20 ml). This was then extracted with ether (2 × 10 ml) and the organic phases were combined and dried over sodium sulfate. Evaporation under reduced pressure gave an orange oil whose $^1$H NMR spectrum over the aromatic region indicated that the reaction had not proceeded (absence of characteristic signal at $\delta$ > 8.0 ppm expected for 5-H of chromone).

**Prop-2-en-1-yl 3-oxo-5-(2,6,6-trimethylcyclohex-1-en-1-yl)-pentanoate 17.** *Method 1.* A solution of the ketone **14**[20] (0.50 g, 2.57 mmol) and diallyl carbonate (1.10 g, 7.7 mmol) in dry toluene (5 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.206 g, 5.14 mmol) in dry toluene (5 ml) under Ar, and the mixture then heated at 110 °C for 3 h. Upon cooling a mixture of ether (9 ml), conc. hydrochloric acid (1.5 ml) and water (3 ml) was carefully added. After vigorous stirring the organic layer formed was separated and combined with a subsequent ether extract of the aqueous layer. This was then dried, evaporated and chromatographed, eluting with DCM, to give the *title compound* **17** (0.255 g, 35%) as a colourless oil ($M + H^+$, 279.1966. $C_{17}H_{27}O_3$ requires 279.1960); $\nu_{max}$ (neat)/cm$^{-1}$ 2928, 2866, 1748, 1718, 1649, 1625, 1474, 1457, 1411, 1363, 1316, 1226, 1170, 989, 932; $\delta_H$ (300 MHz) 0.95 (6 H, s, 6′-$Me_2$), 1.35–1.40 (2 H, m, 5′-$H_2$), 1.53 (3 H, s, 2′-Me), 1.50–1.60 (2 H, m, 4′-$H_2$), 1.87 (2 H, t, *J* 6 Hz, 3′-$H_2$), 2.20–2.30 (2 H, m, 4-$H_2$), 2.55–2.65 (2 H, m, 5-$H_2$), 3.45 (2 H, s, 2-$H_2$), 4.62 (2 H, dd, *J* 1.5, 6 Hz, 1″-$H_2$), 5.24 (1 H, dd, *J* 1.5, 10.5 Hz, 3″-H), 5.32 (1 H, dd, *J* 1.5, 16 Hz, 3″-H), 5.90 (1 H, tdd, *J* 6, 10.5, 16 Hz, 2″-H); $\delta_C$ ($CDCl_3$, 75 MHz) 19.34, 19.61, 21.91, 28.32 (6′-$Me_2$), 32.66, 34.93, 39.66, 43.71, 49.02, 65.80 (C-1″), 118.74 (C-3″), 128.06 (C-2′), 131.53 (C-2″), 135.57 (C-6′), 166.77 (C-1), 202.38 (C-3); *m*/*z* (peaks > 10%) 296 ($M + NH_4^+$, 80%), 279 ($M + H^+$, 100), 261 (10), 136 (11); $R_f$ 0.54 (DCM, orange with vanillin).

*Method 2.* A mixture of the ketoester **11** (203 mg, 0.80 mmol), allyl alcohol (0.1 ml, 85 mg, 1.46 mmol) and 'sulfated $SnO_2$' catalyst[21] (40 mg) in toluene (10 ml) was heated to 110 °C in a round-bottomed flask fitted with a condenser. The reaction was monitored by TLC (silica, DCM), and after 24 h the ester **17** was visible ($R_f$ 0.54), together with some starting material **11** ($R_f$ 0.45). The mixture was cooled, the catalyst was removed by filtration, the filtrate was evaporated and the residual oil was chromatographed, eluting with DCM–petroleum (4:1), to obtain the ester **17** (130 mg, 58%) as a colourless oil, identical (NMR, TLC) with material obtained by method 1.

**Prop-2-en-1-yl 2-[2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl]-4-oxo-4*H*-1-benzopyran-3-carboxylate 18.** To a solution of sodium hydride (60% dispersion in mineral oil, 0.152 g, 3.8 mmol) in dry toluene (5 ml) was added the ester **17** (0.660 g, 2.37 mmol) in dry toluene (5 ml). Effervescence was observed. The resulting yellow solution was stirred at room temperature for 20 min and then 2-fluorobenzoyl chloride (0.372 g, 2.35 mmol) was added followed by a further addition of dry toluene (10 ml). The reaction was heated under reflux for 24 h and then the cooled suspension was poured into cold water (20 ml). The aqueous layer was extracted with ether (3 × 10 ml) and the combined organics were dried over sodium sulfate and evaporated under reduced pressure. The residual orange oil was purified by chromatography, eluting with DCM, to obtain the *title compound* **18** (0.489 g, 55%) as a yellow oil ($M + H^+$, 381.2061. $C_{24}H_{29}O_4$ requires 381.2066); $\nu_{max}$ (neat)/cm$^{-1}$ 1732, 1651, 1575, 1218, 1127, 1037, 763; $\delta_H$ (300 MHz) 1.02 (6 H, s, 6″-$Me_2$), 1.4–1.6 (4 H, m, 4″-$H_2$, 5″-$H_2$), 1.66 (3 H, s, 2″-Me), 1.92 (2 H, t, *J* 6 Hz, 3″-$H_2$), 2.4–2.5 (2 H, m, 2′-$H_2$), 2.75–2.8 (2 H, m, 1′-$H_2$), 4.82 (2 H, dd, *J ca.* 1, 6 Hz, 1‴-$H_2$), 5.28 (1 H, dd, *J ca.* 1, 10.5 Hz, 3‴-H), 5.45 (1 H, dd, *J ca.* 1, 17 Hz, 3‴-H), 6.00 (1 H, tdd, *J* 6, 10.5, 17 Hz, 2‴-H), 7.39 (1 H, t, *J ca.* 8 Hz, 6-H), 7.44 (1 H, br d, *J* 8.5 Hz, 8-H), 7.66 (1 H, ddd, *J* 1.5, 7.5, 8.5 Hz, 7-H), 8.19 (1 H, dd, *J* 1.5, 8 Hz, 5-H); *m*/*z* (peaks > 10%) 381 (100%); $R_f$ 0.20 (DCM, UV active).

**2-[2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethyl]-4-oxo-4*H*-1-benzopyran-3-carboxylic acid 19.** A solution of lithium dimethylcuprate was prepared by treating a stirred suspension of copper(I) iodide (0.131 g, 0.069 mmol) in ether (3 ml) with methyllithium in ether (1.6 M, 0.87 ml, 1.39 mmol) at −10 °C until the yellow solution turned colourless. The ester **18** (0.175 g, 0.460 mmol) in dry THF (5 ml) was then added dropwise at 0 °C. After 30 min the reaction was quenched by stirring vigorously with saturated aqueous ammonium chloride (3 ml) and the resulting solution extracted into ethyl acetate (3 × 5 ml), dried and evaporated to give a yellow oil. Flash chromatography, eluting with DCM, gave the *title compound* **19** (0.07 g, 45%) which formed colourless needles, mp 110–112 °C (EtOH) ($M + H^+$, 341.1757. $C_{21}H_{25}O_4$ requires 341.1753); $\nu_{max}$ (film)/cm$^{-1}$ 1734, 1610 br, 1573, 1543, 1493, 1460, 1429, 1389, 1137, 1038, 772; $\delta_H$ (300 MHz) 1.07 (6 H, s, 6″-$Me_2$), 1.42–1.46 (2 H, m, 5″-$H_2$), 1.55–1.60 (2 H, m, 4″-$H_2$), 1.74 (3 H, s, 2″-Me), 1.93 (2 H, t, *J* 6 Hz, 3″-$H_2$), 2.45–2.51 (2 H, m, 2′-$H_2$), 3.47–3.53 (2 H, m, 1′-$H_2$), 7.5–7.6 (2 H, m, 6-H, 8-H), 7.82 (1 H, dt, *J ca.* 1.5, 8 Hz, 7-H), 8.27 (1 H, dd, *J* 1.5, 8 Hz, 5-H); $\delta_C$ ($CDCl_3$, 75 MHz) 14.17, 19.49, 19.81, 26.42, 28.54, 33.02, 35.25, 40.05, 117.97, 121.95, 126.40, 126.66, 129.75, 135.45, 135.58, 155.34, 164.43, 180.49, 181.06; *m*/*z* 341 ($M + H^+$, 90%), 300 (29), 279 (53), 205 (45), 156 (100), 137 (20); $R_f$ 0.40 (DCM, UV).

**Prop-2-en-1-yl 2,3-dihydro-2-methyl-2-[2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl]-4-oxo-4*H*-1-benzopyran-3-carboxylate 20.** A solution of the chromone ester **18** (0.40 g, 1.05 mmol) in dry THF (5 ml) was cooled to −10 °C. To this solution was added chlorotrimethylsilane (1 M in THF, 4.2 ml, 4.2 mmol) to give a yellow suspension. Copper(I) iodide (60 mg, 0.3 mmol) was then added followed by methylmagnesium chloride (3 M in THF, 0.77 ml, 2.3 mmol) which resulted in the yellow suspension changing to a yellow solution. After completion of the reaction (*ca.* 5 h, monitored by TLC), cold glacial acetic acid (2 ml) was added and the reaction was allowed to warm up to room temperature overnight. The mixture was extracted with ether (3 × 10 ml), washed with saturated aqueous sodium hydrogen carbonate and dried over sodium sulfate. Evaporation under reduced pressure gave a yellow oil which was purified by chromatography, eluting with DCM, to obtain the *title compound* **20** (0.260 g, 62%) as a yellow oil ($M + H^+$, 397.2382. $C_{25}H_{33}O_4$ requires 397.2379); $\delta_H$ (300 MHz) 0.73 (minor),

0.85 (major), 0.90 (minor) and 0.94 (major) (total 6H, 4 × s, 6″-$Me_2$ of diastereoisomers), 1.31 (minor) and 1.44 (major) (total 3 H, 2 × s, 2-Me of diastereoisomers), 1.53 (6 H, br s, 2″-Me of major and minor diastereoisomers), 1.3–1.4 (2 H, m, 5″-$H_2$), 1.45–1.55, 1.6–1.9 and 2.0–2.3 (total 8 H, m, 1′-$H_2$, 2′-$H_2$, 3″-$H_2$, 4″-$H_2$), 3.82 (minor) and 3.84 (major) (total 1 H, 2 × s, 3-H of keto isomers), 4.55–4.75 (2 H, m, 1‴-$H_2$), 5.19–5.32 (2 H, m, 3‴-$H_2$), 5.80–5.95 (1 H, m, 2‴-H), 6.91–7.00 (2 H, m, 6-H, 8-H), 7.41–7.52 (1 H, m, 7-H), 7.80–7.86 (1 H, m, 5-H); *m*/*z* (peaks > 10%) 415 (14%), 414 ($M$ + $NH_4^+$, 100), 397 ($M$ + $H^+$, 35), 245 (32).

**1-Hydroxymethyl-3,3-dimethylcyclohex-1-ene 22.** To a stirred solution of sodium borohydride (0.753 g, 20 mmol) in ethanol (10 ml) at 0 °C was added dropwise over 0.5 h a solution of 3,3-dimethylcyclohex-1-ene-1-carbaldehyde **21**[25] (2 g, 14.5 mmol) in ethanol (15 ml). The reaction mixture was then warmed to 10 °C, stirred for a further 2 h and then poured into water (15 ml). When the effervescence had ceased the aqueous solution was extracted with ether (3 × 10 ml). The combined organic extract was washed with water (10 ml) and brine (10 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was distilled under reduced pressure, yielding the title compound **22** (1.43 g, 70%) as a colourless viscous oil, bp 76–78 °C at 2 mmHg (lit.,[25] 78–80 °C at 2 mmHg); $\nu_{max}$ (neat)/$cm^{-1}$ 3342, 2930, 2864, 1467, 1454, 1360, 1123, 1066, 1031, 1000, 909, 735; $\delta_H$ (300 MHz) 0.91 (6 H, s, 2 × 3-Me), 1.35 (2 H, m, 4-$H_2$), 1.54–1.63 (2 H, m, 5-$H_2$), 1.88 (2 H, t, *J* 6 Hz, 6-$H_2$), 2.28 (1 H, s, OH), 3.89 (2 H, s, C$H_2$OH), 5.32 (1 H, s, 2-H); *m*/*z* (CI, MeCN/$NH_3$) 141 ($M$ + $H^+$, 30%), 123 (100), 109 (65), 107 (25), 79 (45), 40 (50).

**Ethyl 2-(6,6-dimethyl-2-methylenecyclohexyl)ethanoate 23.** To a mixture of the alcohol **22** (2 g, 14.2 mmol) and freshly distilled triethyl orthoacetate (16.3 g, 100 mmol) was added a catalytic amount of propanoic acid (0.1 g, 1.34 mmol). The mixture was heated to 150 °C and the ethanol formed during the reaction was allowed to distil off.[26] After 1 h of reaction a further portion of propanoic acid (0.1 g, 1.34 mmol) was added and the addition was repeated each hour until the reaction was complete (total 5 h). The triethyl orthoacetate was then distilled off at atmospheric pressure and the brown oily residue was chromatographed, eluting with pentane, to obtain the title compound **23** (2.12 g, 71%) as a colourless oil ($M$ + $H^+$, 211.1695. $C_{13}H_{23}O_2$ requires 211.1698); $\nu_{max}$ (neat)/$cm^{-1}$ 2933, 1735, 1646, 1157, 912, 734; $\delta_H$ (300 MHz) 0.76 (3 H, s, 6′-Me), 0.98 (3 H, s, 6′-Me), 1.18 (3 H, t, *J* 6 Hz, $OCH_2CH_3$), 1.38–1.63 (4 H, m, 4′-$H_2$, 5′-$H_2$), 2.16–2.23 (3 H, m, 1′-H, 3′-H), 2.32–2.41 (2 H, m, 2-$H_2$), 4.07 (2 H, q, *J* 6 Hz, $OCH_2CH_3$), 4.51 (1 H, s, C=CH), 4.76 (1 H, s, C=CH); *m*/*z* 228 ($M$ + $NH_4^+$, 12%), 211 ($M$ + $H^+$, 100), 197 (18).

**2-(6,6-Dimethyl-2-methylenecyclohexyl)ethanol 24.** To an ice-cooled, stirred suspension of lithium aluminium hydride (364 mg, 9.5 mmol) in anhydrous THF (5 ml) under $N_2$ was added dropwise over 0.5 h a solution of the ester **23** (2.0 g, 9.5 mmol) in anhydrous THF (15 ml). The mixture was allowed to warm to room temperature and then stirred for 12 h, after which time the reaction was judged by TLC to be complete. The excess lithium aluminium hydride was destroyed by adding 10% sodium hydroxide dropwise to the cooled reaction mixture, and the precipitated lithium hydroxide was filtered off. The organic solution was washed with water (10 ml) and brine (10 ml), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with pentane–ethyl acetate (10 : 1), which gave the alcohol **24** (1.28 g, 80%) as a colourless oil; $\nu_{max}$ (neat)/$cm^{-1}$ 3325, 2931, 1645, 1464, 1451, 1053, 889 (lit.,[26] 3337, 2929, 1644, 1453, 1052, 889); $\delta_H$ (300 MHz) 0.79 (3 H, s, 6′-Me), 0.86 (3 H, s, 6′-H), 1.1–1.7 (6 H, m, 2-$H_2$, 4′-$H_2$, 5′-$H_2$), 1.8–2.1 (3 H, m, 1′-H, 3′-$H_2$), 2.15 (1 H, br s, OH), 3.4–3.6 (2 H, m, 1-$H_2$), 4.56 (1 H, d, *J* 1.5 Hz, C=CH), 4.71 (1 H, *J* 1.5 Hz, C=CH); *m*/*z* (CI, MeCN/$NH_3$) 169 ($M$ + $H^+$, 20%), 151 (70), 106 (25), 41 (55).

**2-(6,6-Dimethyl-2-methylenecyclohexyl)ethyl methanesulfonate 25.**[28] To a solution of freshly distilled triethylamine (1.82 g, 18 mmol) in anhydrous DCM (35 ml) under Ar at −10 °C was added dropwise the alcohol **24** (2.0 g, 12 mmol). After stirring for 10 min methanesulfonyl chloride (1.60 g, 14 mmol) was added. The reaction mixture was stirred for a further 20 min and then washed with saturated aqueous sodium hydrogen carbonate (20 ml), water (20 ml) and brine (10 ml), dried and concentrated *in vacuo*. The crude mesylate was chromatographed, eluting with petroleum–ethyl acetate (10 : 1), to obtain the title compound **25** (2.68 g, 90%) as an off-white waxy solid, mp 30–32 °C ($M$ + $NH_4^+$, 264.1636. $C_{12}H_{26}NO_3S$ requires 264.1633); $\nu_{max}$ (neat)/$cm^{-1}$ 1626, 1390; $\delta_H$ (300 MHz) 0.83 (3 H, s, 6′-Me), 0.91 (3 H, s, 6′-Me), 1.2–2.0 (7 H, m, 1′-H, 4′-$H_2$, 5′-$H_2$, 2-$H_2$), 2.02 (2 H, t, *J* 6 Hz, 3′-$H_2$), 2.96 (3 H, s, $SO_2Me$), 3.95–4.21 (2 H, m, 1-$H_2$), 4.58 (1 H, s, C=CH), 4.80 (1 H, s, C=CH); *m*/*z* (CI, $NH_3$) 264 ($M$ + $NH_4^+$, 100%).

**2-(2-Iodoethyl)-3,3-dimethyl-1-methylenecyclohexane 26.**[28] To a solution of sodium iodide (0.525 g, 3.5 mmol) in hot anhydrous acetone (30 ml) under Ar was added dropwise a solution of the mesylate **25** (0.5 g, 2 mmol) in anhydrous acetone (25 ml), and the resulting mixture was heated under reflux for 4 h. The acetone was then removed *in vacuo* and the residue dissolved in ether. Water was added to dissolve the remaining sodium iodide and the organic layer was separated, washed with water (50 ml) and brine (50 ml), dried and concentrated *in vacuo*. The residue was chromatographed, eluting with pentane, yielding the title compound **26** (0.396 g, 71%) as a pale brown oil ($M^+$, 278.0536. $C_{11}H_{19}I$ requires 278.0533); $\delta_H$ (300 MHz) 0.81 (3 H, s, 3-Me), 0.91 (3 H, s, 3-Me), 1.20–1.53 (4 H, m, 4-$H_2$, 5-$H_2$), 1.85–2.03 (5 H, m, 2-H, 6-$H_2$, 1′-$H_2$), 2.87–3.21 (2 H, m, 2′-$H_2$), 4.59 (1 H, s, C=CH), 4.81 (1 H, s, C=CH); $\nu_{max}$ (neat)/$cm^{-1}$ 2931, 2866, 1645, 1449, 1366, 1230, 1165, 891; *m*/*z* 296 ($M$ + $NH_4^+$, 34%), 279 ($M$ + $H^+$, 71), 278 (40), 265 (38), 173 (52), 156 (32), 151 (59), 129 (22), 123 (52), 109 (70), 95 (100), 81 (40), 69 (54).

**Methyl 2-methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate 28.** This was prepared from methyl acetoacetate and 2-fluorobenzoyl chloride as described.[19] The product had mp 116–117 °C (lit.,[19] 115–116 °C); $\nu_{max}$ ($CHBr_3$)/$cm^{-1}$ 1725, 1646, 1620; $\delta_H$ ($CDCl_3$) 2.52 (3 H, s, 2-Me), 3.97 (3 H, s, OMe), 7.36–7.44 (2 H, m, 6-H, 8-H), 7.67 (1 H, dt, $J_{6,7}$ 8, $J_{7,8}$ 8, $J_{5,7}$ 1 Hz, 7-H), 8.21 (1 H, dd, $J_{5,6}$ 7.5, $J_{5,7}$ 1 Hz, 5-H).

**Methyl 2,3-dihydro-2-methyl-2-[2-(2,2-dimethyl-6-methylenecyclohexyl)ethyl]-4-oxo-4*H*-1-benzopyran-3-carboxylate 29.** *Method 1.* To a solution of the iodide **26** (250 mg, 0.9 mmol) in anhydrous ether (15 ml) was added *tert*-butyllithium in pentane (1.7 M, 0.53 ml, 0.9 mmol) dropwise under Ar at −35 °C. After stirring for 15 min the pale yellow solution was added to a suspension of copper(I) iodide (96 mg, 0.5 mmol) in anhydrous ether (10 ml) at −50 °C *via* a cannula. The reaction mixture was stirred for another 15 min at −50 °C and the chromone ester **28** (109 mg, 0.5 mmol) in anhydrous ether (10 ml) was then added dropwise. Stirring at −50 °C was continued for a further 1 h, and saturated aqueous ammonium chloride (15 ml) then added. The slurry was stirred for 5 min and the organic layer then separated. The aqueous phase was back-washed with ethyl acetate (2 × 20 ml) and the combined organic extracts were washed with 10% hydrochloric acid (20 ml), water (20 ml) and brine (20 ml), dried and concentrated *in vacuo*. The crude product was chromatographed, eluting with petroleum–ethyl acetate (15 : 1), to obtain the *title compound* **29** (77 mg, 46%; mixture of diastereoisomers) as a pale yellow oil ($M$ + $NH_4^+$,

388.2480; $C_{23}H_{34}NO_4$ requires 388.2488); $\nu_{max}$ (neat)/cm$^{-1}$ 2951, 1742, 1695, 1643, 1609, 1464, 1272, 1241, 763; $\delta_H$ (300 MHz) 0.79, 0.83, 0.87, 0.90 (total 6 H, 4 × s, 2″-$Me_2$ of diastereoisomers), 1.15–2.05 (total 11 H, m, 1′-$H_2$, 2′-$H_2$, 1″-H, 3″-$H_2$, 4″-$H_2$, 5″-$H_2$), 1.48, 1.49 (total 3 H, 2 × s, 2-Me of diastereoisomers), 3.74 (3 H, s, OMe), 3.6–3.85 (1 H, m, 3-H), 4.4–4.8 (total 2 H, 2 × br s, 2 × d, *J ca.* 2 Hz, C=$CH_2$ of diastereoisomers), 6.9–7.0 (2 H, m, 6-H, 8-H), 7.48 (1 H, apparent dt, $J_{7,8}$ 7, $J_{6,7}$ 8, $J_{5,7}$ 1.5 Hz, 7-H), 7.83 (1 H, dd, $J_{5,6}$ 7, $J_{5,7}$ 1.5 Hz, 5-H); *m*/*z* 388 ($M$ + $NH_4^+$, 100%), 371 ($M$ + $H^+$, 30), 322 (25), 219 (30). The presence of enol tautomers was suggested by peaks in the NMR spectrum at $\delta_H$ 6.8 (d, *J* 8 Hz, 6-H), 7.6 (d, *J* 8 Hz, 6-H) and 12.9 (s, enolic OH).

*Method 2.* To a solution of the iodide **26** (250 mg, 0.9 mmol) in anhydrous ether (10 ml) was added *tert*-butyllithium in pentane (1.7 M, 0.53 ml, 0.9 mmol) dropwise under Ar at −30 °C. The solution was stirred for 15 min and then lithium 2-thienylcyanocuprate in THF (0.25 M, 4.0 ml, 1.0 mmol) was added dropwise at −50 °C to give a dark brown suspension. The solution was allowed to warm up to −20 °C and stirred until all the brown solid had dissolved. At this point the reaction mixture was cooled back to −50 °C and a solution of the chromone ester **28** in ether (218 mg, 1 mmol) was added slowly. The resulting deep-red solution was stirred at −50 °C for 1 h and then quenched with saturated aqueous ammonium chloride (25 ml). The ethereal layer was separated, the aqueous phase was back-washed with ethyl acetate (2 × 25 ml), and the combined organic extracts were washed with 10% hydrochloric acid (25 ml), water (25 ml) and brine (25 ml). The extracts were then dried and concentrated *in vacuo*. The residual green oil was chromatographed, eluting with petroleum ether–ethyl acetate (15:1), to obtain the title compound **29** (220 mg, 66%; mixture of diastereoisomers) as a pale yellow oil.

*Method 3.* The procedure described Method 2 was repeated, except that the lithium 2-thienylcyanocuprate was replaced with lithium *N*-imidazol-1-idocyanocuprate. This was made by treating a solution of imidazole (102 mg, 1.5 mmol) in anhydrous THF (6 ml) with *n*-butyllithium in hexanes (1.5 M, 1.0 ml, 1.5 mmol) under Ar at −10 °C to obtain *N*-lithioimidazole. This solution was added to copper(I) cyanide (134 mg, 1.5 mmol), producing the desired cuprate reagent as a pale green solution. This was added to the lithiated iodide (see Method 2) instead of its 2-thienyl analogue. The yield of **29** was 173 mg (52%).

**(±)-(4aα,6aα,12aα,12bβ)-1,3,4,6,6a,12b-Hexahydro-4,4,6a,12b-tetramethyl-2*H*,5*H*-4a,12a-(epoxymethano)benzo[*a*]-xanthene-12,13-dione 30.** *Method 1.* A solution of anhydrous manganese(III) acetate[31] (35 mg, 0.15 mmol) and copper(II) acetate monohydrate (299 mg, 0.15 mmol) in dry degassed acetic acid (10 ml) was heated to 58 °C under an inert atmosphere and treated dropwise with a solution of **13** (50 mg, 0.14 mmol) in dry degassed acetic acid (5 ml). The reaction mixture was stirred at this temperature for a further 5 h, during which the colour of the solution changed from dark blue–green to turquoise, and was then quenched with water (10 ml). The mixture was transferred to a separating funnel and the aqueous phase was extracted with DCM (3 × 10 ml). The organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 × 10 ml), water (10 ml) and brine (10 ml), dried and concentrated. The resulting clear gum was chromatographed, eluting with cyclohexane–ethyl acetate (10:1), which gave several fractions. A major product was crystallised from cold ethyl acetate to give the *title compound* **30** (12 mg, 25%) as colourless crystals, mp 227–228 °C (EtOH) (Found: C, 74.29; H, 7.48. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.39%); $\lambda_{max}$ (EtOH)/nm 256, 316 (end absorption at 217); $\nu_{max}$ (Nujol)/cm$^{-1}$ 1784, 1683, 1605, 1462, 1320, 1302, 1226, 1157, 1032, 926, 756; $\delta_H$ (400 MHz) 1.02 (3 H, s, 4-Me), 1.08 (3 H, s, 4-Me), 1.27 (3 H, s, 12b-Me), 1.42 (3 H, s, 6a-Me), 1.2–1.75 (6 H, m, 1-$H_2$, 2-$H_2$, 3-$H_2$), 1.95 (1 H, ddd, $J_{5β,6β}$ 8 Hz, $J_{5α,6β}$ 12 Hz, $J_{6α,6β}$ 15 Hz, 6β-H), 2.04 (1 H, dd, $J_{5β,6β}$ 8 Hz, $J_{5α,5β}$ 14 Hz, 5β-H), 2.22 (1 H, ddd, $J_{5α,6α}$ 7 Hz, $J_{5α,6β}$ 12 Hz, $J_{5α,5β}$ 14 Hz, 5α-H), 2.36 (1 H, dd, $J_{5α,6α}$ 7 Hz, $J_{6α,6β}$ 15 Hz, 6α-H), 6.90 (1 H, d, $J_{8,9}$ 8 Hz, 8-H), 7.02 (1 H, t, $J_{9,10}$ 8 Hz, $J_{10,11}$ 8.5 Hz, 10-H), 7.48 (1 H, apparent dt, $J_{8,9}$ 8 Hz, $J_{9,10}$ 8 Hz, $J_{9,11}$ 1 Hz, 9-H), 7.92 (1 H, dd, $J_{9,11}$ 1 Hz, $J_{10,11}$ 8.5 Hz, 11-H); $\delta_C$ (100 MHz, $CDCl_3$) 17.13 (2-C), 17.87 (12b-Me), 21.94 (3-C), 23.36 (6a-Me), 23.82 (4-Me), 26.3 (4-Me), 32.86 (1-C), 32.94 (6-C), 35.93 (5-C), 36.04 (4-C), 47.52 (12b-C), 67.30 (12a-C), 78.88 (6a-C), 89.65 (4a-C), 118.07 (8-C), 121.39 (10-C), 121.91 (11a-C), 126.97 (11-C), 136.18 (9-C), 159.38 (7a-C), 171.46 (13-C), 186.51 (12-C); *m*/*z* (FAB) 355 ($M$ + $H^+$, 76%), 327 (81), 303 (30), 300 (100), 283 (65); $R_f$ 0.45 (DCM, UV).

*Method 2.* A solution of anhydrous manganese(III) acetate (387 mg, 1.67 mmol) in acetic acid (dried with acetic anhydride and degassed; 50 ml) was heated to 80 °C under Ar and treated dropwise with a solution of **13** (309 mg, 0.834 mmol) in dry degassed acetic acid (20 ml). The reaction mixture was stirred at 80 °C for 12 h, during which the colour of the solution changed from red–brown to yellow, and then quenched with water (40 ml). The aqueous phase was extracted with DCM (3 × 25 ml) and the organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 × 25 ml), water (25 ml) and brine (25 ml), dried and concentrated. The resulting yellow oil was chromatographed, eluting with petroleum–ethyl acetate (3:1), which gave the lactone **30** (170 mg, 0.48 mmol, 58%) as a colourless solid, identical to the previously characterised sample.

**(±)-Methyl (5aα,7aβ,11aβ,12aα,13β)-5a,6,7,7a,8,9,10,11,12a,13-decahydro-13-hydroxy-5a,8,8-trimethyl-12*H*-11a,13-epoxybenzo[4,5]cyclohepta[1,2-*b*]chromene-12a-carboxylate 34.** To a degassed and dried[33] solution of manganese(III) acetate hydrate (75 mg, 0.28 mmol) in acetic acid (10 ml) at 65 °C under Ar was added a solution of the isomeric chromanones **29** (50 mg, 0.14 mmol) in acetic acid (5 ml). The solution was stirred at 65 °C for 3 h and then quenched by the addition of water (10 ml). The aqueous phase was extracted with DCM (3 × 10 ml) and the combined extract washed with saturated aqueous sodium hydrogen carbonate (3 × 10 ml), water (10 ml) and brine (10 ml), and dried. The solvent was removed under reduced pressure and the residual mixture was chromatographed, eluting with petroleum–ethyl acetate (12:1). The major product, a white solid, was identified as the *title compound* **34** (16 mg, 31%), which formed colourless crystals, mp 158–159 °C (petroleum 60–80 °C) (Found: C, 71.40; H, 7.75. $C_{23}H_{30}O_5$ requires C, 71.46; H, 7.83%); $\delta_H$ (300 MHz) 0.87 (3 H, s, 8-Me), 0.89 (3 H, s, 8-Me), 1.2–1.6 (7 H, m, 7-$H_2$, 7a-H, 9-$H_2$, 10-$H_2$), 1.46 (3 H, s, 5a-Me), 1.7–1.9 (2 H, m, 6-H, 11-H), 2.12 (1 H, dd, *J* 2, 13.5 Hz, 6-H or 11-H), 2.27 (1 H, d, *J* 13.5 Hz, 12-H), 2.34 (1 H, d, *J* 12.5 Hz, 6-H or 11-H), 2.44 (1 H, d, *J* 13.5 Hz, 12-H), 2.88 (1 H, s, exchanges with $D_2O$, OH), 3.66 (3 H, s, OMe), 6.79 (1 H, dd, $J_{2,4}$ 1 Hz, $J_{3,4}$ 8 Hz, 4-H), 6.96 (1 H, apparent dt, $J_{2,4}$ 1 Hz, $J_{2,3}$ 8.5 Hz, $J_{1,2}$ 8.5 Hz, 2-H), 7.20 (1 H, apparent dt, $J_{1,3}$ 1.5 Hz, $J_{3,4}$ 8.5 Hz, $J_{2,3}$ 8.5 Hz, 3-H), 7.56 (1 H, dd, $J_{1,3}$ 1.5 Hz, $J_{1,2}$ 8.5 Hz, 1-H); $\delta_C$ ($CDCl_3$, 100 MHz) 19.57 (10-C), 21.17 (9-C), 21.18 (8-Me), 23.62 (8-Me), 31.74 (5a-Me), 34.85 (8-C), 35.54, 36.66, 41.59, 43.09 (6-C, 7-C, 11-C, 12-C), 50.00 (OMe), 52.08 (7a-C), 63.59 (12a-C), 80.39 (5a-C), 86.54 (11a-C), 97.45 (13-C), 116.86 (4-C), 121.24 (2-C), 124.04 (13a-C), 125.91 (1-C), 129.91 (3-C), 151.62 (4a-C), 172.08 (C=O); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3488, 1728, 1614, 1587, 1486, 1459, 1308, 1262, 1244, 1098, 1060, 1042, 1027, 1006, 757; *m*/*z* (CI, $NH_3$) 404 ($M$ + $NH_4^+$, 2%), 386 ($M$ − $H_2O$ + $NH_4^+$, 2), 369 ($M$ − $H_2O$ + $H^+$, 100).

**(±)-(4aα,6aα,12aα,12bβ)-1,3,4,6,6a,12b-Hexahydro-4,4,6a,12b-tetramethyl-13-oxo-2*H*,5*H*,12*H*-4a,12a-(epoxymethano)-benzo[*a*]xanthen-12-ol 39.** To a solution of lactone **30** (65.5 mg, 0.185 mmol) in dry toluene (2 ml) at −78 °C under Ar

was added dropwise DIBAL-H in toluene (1 M, 0.56 ml, 0.56 mmol). The reaction was held at −78 °C for 1 h and then allowed to warm up to room temperature overnight. Water (4 ml) was added and the reaction mixture was extracted with ether (3 × 5 ml). The organics were washed with water (5 ml) and brine (5 ml), dried and concentrated, yielding the *title compound* **39** (14.6 mg, 23%) as a colourless solid, mp 185–190 °C ($M$ + $H^+$, 357.2065. $C_{22}H_{28}O_4$ requires 357.2066); $\lambda_{max}$ (EtOH) end absorption at 217 nm only; $\nu_{max}$ (Nujol)/$cm^{-1}$ 3495, 1749, 1606, 1583, 1295, 1269, 1228, 1152, 1126, 1067, 1047, 1005, 941, 912, 755; $\delta_H$ (300 MHz) 0.95 (3 H, s, 4-Me), 1.03 (3 H, s, 4-Me), 1.18 (3 H, s, 12b-Me), 1.25 (3 H, s, 6a-Me), 1.2–1.75 (6 H, m, 1-$H_2$, 2-$H_2$, 3-$H_2$), 1.80–1.95 (2 H, m, 5β-H, 6β-H), 2.00–2.20 (2 H, m, 5α-H, 6α-H), 2.84 (1 H, br s, OH), 5.59 (1 H, br s, 12-H), 6.71 (1 H, d, *J* 8 Hz, 8-H), 6.95 (1 H, apparent t, *J* 7.5 Hz, 10-H), 7.16 (1 H, apparent t, *J* 7.5 Hz, 9-H), 7.57 (1 H, d, *J* 7.5 Hz, 11-H); $\delta_C$ ($CDCl_3$, 75 MHz) 17.43, 18.31, 21.75, 24.08, 24.82, 27.00, 34.05, 35.50, 36.01 (quaternary), 36.34, 48.99 (quaternary), 57.60 (C-6a), 66.80 (C-12), 91.35 (C-4a), 116.03 (C-8), 120.93 (C-10), 123.59 (C-11a), 126.42, 128.76, 153.00 (C-7a), 176.95 (C-13) (one peak hidden; assignments tentative); *m*/*z* (peaks > 10%) 374 ($M$ + $NH_4^+$, 100%); $R_f$ 0.30 (DCM, UV active, no colour with vanillin).

**(±)-(4aα,6aα,12aα,12bβ)-1,3,4,6,6a,12b-Hexahydro-4,4,6a,12b-tetramethyl-2*H*,5*H*,12*H*-4a,12a-(epoxymethano)benzo[*a*]xanthene-12,13-diol 41 (±)-(4aα,6aα,12aα,12bβ)-1,3,4,6,6a,12b-hexahydro-4,4,6a,12b-tetramethyl-2*H*,5*H*,12*H*-4a,12a-(epoxymethano)benzo[*a*]xanthen-12-ol 42.** *Method 1.* To a solution of lactone **30** (11.1 mg, 0.031 mmol) in dry THF (3 ml) at 0 °C under Ar was added LAH in ether (1 M, 0.06 ml, 0.06 mmol, 2 mol. equiv.). This was stirred at 0 °C for 3 h and then at room temperature for two days. The reaction was quenched with dilute sulfuric acid (2 M, 5 ml) and extracted with ether (3 × 5 ml). The extract was washed with water (10 ml), and brine (10 ml), dried and concentrated to obtain a crude white solid which by TLC appeared to be a two-component mixture. Flash chromatography, eluting with petroleum–ethyl acetate (3:1), gave the *title compound* **41** (2.8 mg, 25%) as a colourless solid, mp 210–215 °C ($M^+$, 358.2127. $C_{22}H_{30}O_4$ requires 358.2144) ($M$ − $H_2O$ + $H^+$, 341.2112. $C_{22}H_{29}O_3$ requires 341.2117); $\nu_{max}$ (Nujol)/$cm^{-1}$ 3351 (br), 1584, 1226, 1129, 1099, 967, 909, 754; $\delta_H$ (300 MHz) 0.8–1.75 (6 H, m, 1-$H_2$, 2-$H_2$, 3-$H_2$), 0.91 (3 H, s, 4-Me), 0.96 (3 H, s, 4-Me), 1.18 (3 H, s, 12b-Me), 1.27 (3 H, s, 6a-Me), 1.85–2.0 (3 H, m, 5-$H_2$, 6α-$H_{eq}$*), 2.63 (1 H, ddd, *J* 4, 13, 13 Hz, 6β-$H_{ax}$*), 3.45 (1 H, d, *J* 2 Hz, 12-OH), 3.59 (1 H, br s, 13-OH), 5.31 (1 H, d, *J* 3.5 Hz, 13-H), 5.36 (1 H, br s, 12-H), 6.69 (1 H, d, *J* 7.5 Hz, 8-H), 6.94 (1 H, apparent t, *J* 7.5 Hz, 10-H), 7.15 (1 H, apparent t, *J* 7.5 Hz, 9-H), 7.57 (1 H, d, *J* 7.5 Hz, 11-H) [(*) denotes tentative assignment]; *m*/*z* (CI) 358 ($M^+$, 5%), 341 ($M$ − $H_2O$ + $H^+$, 100), 323 (46), 219 (50); $R_f$ 0.15 (DCM, vanillin).

*Method 2.* To a solution of lactone **30** (32.2 mg, 0.091 mmol) in dry toluene (2 ml) at −78 °C under Ar was added dropwise DIBAL-H in toluene (1 M, 1.10 ml, 1.10 mmol, 12 mol. equiv.). The reaction was held at −78 °C for 1 h and then allowed to warm up to room temperature overnight. Water (4 ml) was added and the reaction mixture was extracted with ether (3 × 5 ml). The organics were washed with water (5 ml), brine (5 ml), dried and concentrated, yielding a mixture consisting of the diol **41** and a second compound which was tentatively identified as the alcohol **42** (total 12.8 mg, *ca.* 40%) in which **42** was slightly predominant. The $^1H$ NMR spectrum of **41** appears as described above, with changes in hydroxy signals as follows: $\delta_H$ 3.43 (1 H, d, *J* 2 Hz, disappears on $D_2O$ shake, 12-OH), 3.39 (1 H, d, *J* 3.5 Hz, disappears on $D_2O$ shake, 13-OH), 5.30 (1 H, d, *J* 3.5 Hz, becomes s on $D_2O$ shake, 13-H), 5.36 (1 H, br s, sharpens on $D_2O$ shake, 12-H). Signals attributed to **42** (mixture with **41**): $\delta_H$ 0.8–2.05 (10 H, m, 1-$H_2$, 2-$H_2$, 3-$H_2$, 5-$H_2$, 6-$H_2$), 0.88 (3 H, s, 4-Me), 0.93 (3 H, s, 4-Me), 1.17 (3 H, s, 12b-Me), 1.24 (3 H, s, 6a-Me), 1.62 (1 H, d, *J* 9.5 Hz, disappears on $D_2O$ shake, 12-OH), 3.64 (1 H, d, *J* 9 Hz, 13-H), 4.26 (1 H, d, *J* 9 Hz, 13-H), 4.96 (1 H, d, *J* 9.5 Hz, becomes s on $D_2O$ shake, 12-H), 6.70 (1 H, d, *J* 7.5 Hz, 8-H), 6.92 (1 H, apparent t, *J* 7.5 Hz, 10-H), 7.16 (1 H, apparent t, *J* 7.5 Hz, 9-H), 7.48 (1 H, d, *J* 7.5 Hz, 11-H).

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## References

1 For a review, see D. J. Faulkner, *Nat. Prod. Rep.*, 1996, **13**, 75.
2 B. N. Ravi, H. P. Perzanowski, R. A. Ross, T. R. Erdman, P. J. Scheuer, J. Finer and J. Clardy, *Pure Appl. Chem.*, 1979, **51**, 1893; M. T. Hamann, P. J. Scheuer and M. Kelly-Borges, *J. Org. Chem.*, 1993, **58**, 6565.
3 M. T. Hamann and P. J. Scheuer, *Tetrahedron Lett.*, 1991, **32**, 5671.
4 S. S. Nasu, B. K. S. Yeung, M. T. Hamann, P. J. Scheuer, M. Kelly-Borges and K. Goins, *J. Org. Chem.*, 1995, **60**, 7290.
5 M.-L. Bourguet-Kondracki, C. Debitus and M. Guyot, *Tetrahedron Lett.*, 1996, **37**, 3861 and references cited therein.
6 P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. Arnold and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1435; J. Rodriguez, E. Quiñoa, R. Riguera, B. M. Peters, L. M. Abrell and P. Crews, *Tetrahedron*, 1992, **48**, 6667.
7 R. Talpir, A. Rudi, Y. Kashman, Y. Loya and A. Hizi, *Tetrahedron*, 1994, **50**, 4179; S. Poigny, T. Huor, M. Guyot and M. Samadi, *J. Org. Chem.*, 1999, **64**, 9318.
8 K. Hirai, K. T. Suzuki and S. Nozoe, *Tetrahedron*, 1971, **27**, 6057 and references cited therein.
9 K. A. El Sayed, P. Bartyzel, X. Shen, T. L. Perry, J. K. Zjawiony and M. T. Hamann, *Tetrahedron*, 2000, **56**, 949.
10 For information about the status of these diseases and associated countermeasures, see the World Health Organisation's documentation at ⟨http://www.who.int/inf-fs/en/fact104.html⟩ and ⟨http://www.who.int/health-topics/malaria.htm⟩.
11 M. Kato, Y. Matsumura, K. Heima, N. Fukamiya, C. Kabuto and A. Yoshikoshi, *Tetrahedron*, 1987, **43**, 711 and references cited therein; B. M. Trost, F. J. Fleitz and W. J. Watkins, *J. Am. Chem. Soc.*, 1996, **118**, 5146.
12 G. L. Trammell, *Tetrahedron Lett.*, 1978, 1525; A. F. Barrero, E. J. Alvarez-Manzaneda and R. Chahboun, *Tetrahedron Lett.*, 1997, **38**, 2325.
13 O. Arjona, M. Garranzo, J. Mahugo, E. Maroto, J. Plumet and B. Sáez, *Tetrahedron Lett.*, 1997, **38**, 7249.
14 K. Ishihara, S. Nakamura and H. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 4906.
15 S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 3029.
16 B. B. Snider, *Chem. Rev.*, 1996, **96**, 339 and references cited therein.
17 Preliminary account and X-ray data: B. S. Crombie, A. D. Redhouse, C. Smith and T. W. Wallace, *J. Chem. Soc., Chem. Commun.*, 1995, 403.
18 J. D. White, R. W. Skeean and G. L. Trammell, *J. Org. Chem.*, 1985, **50**, 1939.
19 G. M. Coppola and R. W. Dodsworth, *Synthesis*, 1981, 523.
20 D. Herlem, J. Kervagoret, D. Yu, F. Khuong-Huu and A. S. Kende, *Tetrahedron*, 1993, **49**, 607. Dihydro-β-ionone **20** is also available commercially (Aldrich Flavors & Fragrances, W36260-3).
21 S. P. Chavan, P. K. Zubaidha, S. W. Dantale, A. Keshavaraja, A. V. Ramaswamy and T. Ravindranathan, *Tetrahedron Lett.*, 1996, **37**, 233.
22 For other examples of this process, see I. Fleming, A. K. Sarkar, M. J. Doyle and P. R. Raithby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2023.
23 For a review on copper-catalysed additions of organometallics, see E. Erick, *Tetrahedron*, 1984, **40**, 641.

24 For discussions on the use of silylating agents in conjugate addition protocols, see B. H. Lipshutz, E. L. Ellsworth, T. J. Siahaan and A. Shirazi, *Tetrahedron Lett.*, 1988, **29**, 6677; S. Matsuzawa, Y. Horiguchi, E. Nakamura and I. Kuwajima, *Tetrahedron*, 1989, **45**, 349.
25 T. Kawanobe, K. Kogami, K. Hayashi and M. Matsui, *Agric. Biol. Chem.*, 1984, **48**, 461.
26 T. Eicher, K. Massonne and M. Herrmann, *Synthesis*, 1991, 1173.
27 For an alternative approach to **24**, see R. C. Almanza and A. H. Reyes, *Synth. Commun.*, 1993, **23**, 867.
28 M. J. Kurth and C. J. Soares, *Tetrahedron Lett.*, 1987, **28**, 1031. See also A. Yajima, H. Takikawa and K. Mori, *Liebigs Ann. Chem.*, 1996, 891.
29 For a description and discussion of the methodology used to prepare **27**, see D. S. Dodd and A. C. Oehlschlager, *J. Org. Chem.*, 1992, **57**, 2794 and references cited therein.
30 For related reactions and mechanistic discussions, see S. A. Kates, M. A. Dombroski and B. B. Snider, *J. Org. Chem.*, 1990, **55**, 2427; D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider and M. A. Dombroski, *J. Am. Chem. Soc.*, 1991, **113**, 6607; M. I. Colombo, S. Signorella, M. P. Mischne, M. Gonzalez-Sierra and E. A. Ruveda, *Tetrahedron*, 1990, **46**, 4149. For a pertinent review, see G. G. Melikyan, *Synthesis*, 1993, 833.
31 E. I. Heiba, R. M. Dessau and W. J. Koechl, *J. Am. Chem. Soc.*, 1969, **91**, 138.
32 Lactone formation in this type of reaction is well precedented. For examples and discussions, see B. B. Snider, J. E. Merritt, M. A. Dombroski and B. O. Buckman, *J. Org. Chem.*, 1991, **56**, 5544; B. B. Snider and B. A. McCarthy, *J. Org. Chem.*, 1993, **58**, 6217. See also E. Baciocchi, A. B. Paolobelli and R. Ruzziconi, *Tetrahedron*, 1992, **48**, 4617; E. Baciocchi, B. Giese, H. Farshchi and R. Ruzziconi, *J. Org. Chem.*, 1990, **55**, 5688.
33 P. Breuilles and D. Uguen, *Bull. Soc. Chim. Fr.*, 1988, 705 and references cited therein.
34 For related cyclisations, see A. K. Ghosh, K. Ghosh, S. Pal and U. R. Chatak, *J. Chem. Soc., Chem. Commun.*, 1993, 809, 1176.
35 K. Hirai, K. T. Suzuki and S. Nozoe, *Tetrahedron*, 1971, **27**, 6057. See also S. Oida, Y. Ohashi, A. Yoshida and E. Ohki, *Chem. Pharm. Bull.*, 1972, **20**, 2634.
36 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, 2nd edn., Pergamon, Oxford, 1980.
37 M. Casey, J. Leonard, B. Lygo and G. Procter, *Advanced Practical Organic Chemistry*, Blackie, Glasgow, 1990, p. 114.
38 W. C. Still, M. Khan and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
39 N. Müller and W. Hoffmann, *Synthesis*, 1975, 781.
40 G. Büchi and J. D. White, *J. Am. Chem. Soc.*, 1964, **86**, 2884. See also A. Srikrishna and K. Krishnan, *J. Chem. Soc., Perkin Trans. 1*, 1993, 667.
41 A. G. Andrewes, G. Borch and S. Liaaen-Jensen, *Acta Chem. Scand., Ser. B*, 1984, **38**, 871.