Intramolecular Diels–Alder additions to 2-benzopyran-3-ones; *endo*-selective additions and some reactions of the adducts

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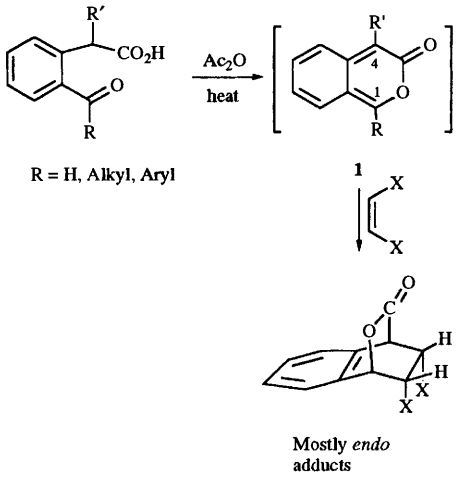
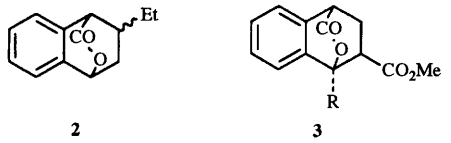
Unlike *o*-quinodimethanes lacking a bridge between the termini of the diene system *e.g.* 18a (*n* = 3 or 4), the 2-benzopyran-3-ones 10a, 10b and 10c undergo *endo*-selective intramolecular Diels–Alder addition of the connecting chain to give *cis*-BC fused ring systems of type 13. The adduct 13b is converted into the ester 21 with methanolic HCl and into the ketol 36 by $LiAlH_4$ reduction followed by oxidation (MnO_2). The ketone 31 is prepared from 21 by epoxidation followed by BF_3·Et_2O-catalysed rearrangement; with NaOMe–CD_3OD it fails to undergo *cis–trans* isomerisation and fails to incorporate deuterium at C-8 probably due to the overwhelming acidity of the C-6 protons. The *cis*-dihydronaphthalene 26 obtained from 21 gives *cis*-27 with KOBu^t–$(CD_3)_2SO$ showing the greater thermodynamic stability of the *cis*-fused ring system in this case.

2-Benzopyran-3-ones **1** are readily generated, reactive Diels–Alder dienes that react efficiently both with simple alkenes like but-1-ene and with conventional dienophiles (Scheme 1).[1]



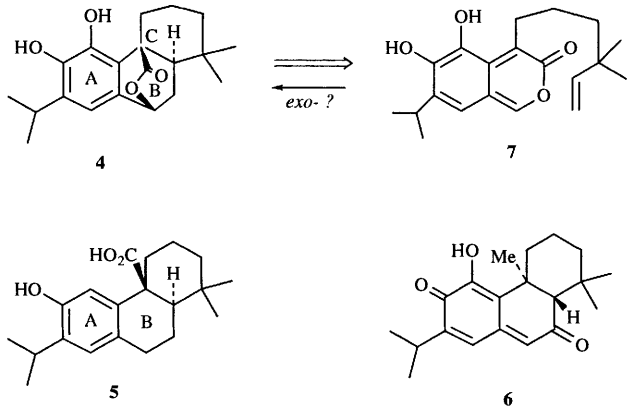
Scheme 1

Additions are usually *endo*-selective but aryl groups at C-1 and C-4 of **1** induce *exo*-selectivity.[2] Although **1** (R = R′ = H) adds non-regioselectively to methyl acrylate,[3] it adds to but-1-ene to give mainly **2**[1] and an aryl group at C-1 of **1** leads to a preference for adducts of type **3**.[4] These characteristics have



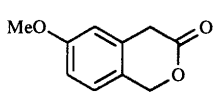
2 **3**

rendered the intermolecular Diels–Alder additions of 2-benzopyran-3-ones useful in the synthesis of ring-A aromatic steroids[1] as well as lignans like (−)-podophyllotoxin[4] and (±)-aklavinone.[5] Despite the possible differences/advantages in stereo- and regio-selectivity shown by intramolecular Diels–Alder (IMDA) reactions this aspect of the chemistry of **1** has remained unexplored. Such additions appeared to be appropriate for the synthesis of diterpenoids such as carnosol **4**,[6] pisiferic acid **5**[7] and taxodione **6**[8] (Scheme 2). The majority of *o*-quinodimethanes undergo *exo*-selective IMDA addition of the connecting chain when the addend is a simple vinyl group and the chain consists of three or four methylene groups.[9] Accordingly **7** might be expected to give the *anti*-stereochemistry present in these natural products (Scheme 2).



Scheme 2

The model compounds required to test this idea were prepared starting with alkylation of the readily available isochroman-3-ones *e.g.* **8**[10] with the iodides **9a** and **9b**. There are



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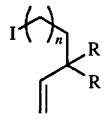
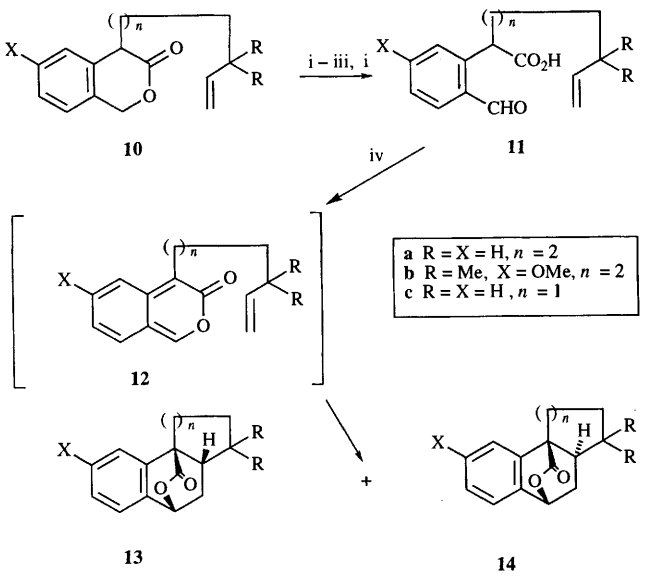


9a R = H, *n* = 2
b R = Me, *n* = 2
c R = H, *n* = 1

varying reports regarding the alkylation of isochroman-3-ones; whilst some authors report no problems in achieving high yields,[11] others found it necessary to resort to the increased acidity of the $Cr(CO)_3$ complexes of the isochroman-3-ones.[12] We found use of $KN(SiMe_3)_2$ in THF–HMPTA at 20 °C (20 h) resulted in efficient alkylation but that some dialkylation product was always formed.

The alkylated products **10a–10c** were readily converted into the *o*-formylphenylacetic acids **11a–11c** as shown in Scheme 3. Upon heating in boiling acetic anhydride these acids produced strong yellow colours consistent with generation of the pyrones

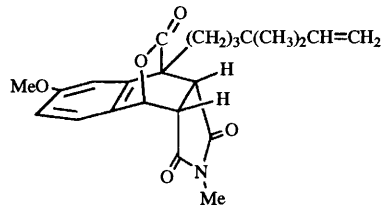


Scheme 3 *Reagents and conditions:* i, Na_2CO_3, H_2O, MeOH or NaOH, H_2O, EtOH, reflux; ii, CH_2N_2–Et_2O, 0 °C; iii, Swern oxidation; iv, Ac_2O, 140 °C

12.† On continued heating the yellow colours faded and isolation gave the *endo*-adducts **13a–c** and *exo*-adducts **14a–c**. In all cases the adduct type **13** resulting from *endo*-addition of the connecting chain predominated: **13a**:**14a** ratio = 4.5:1; **13b**:**14b** ratio = 6.0:1, and **13c**:**14c** ratio = 7.0:1. The stereochemistry of the adducts follows from their ^1H NMR spectra. Thus **13b** and **14b** are distinguished by the presence of a high field methyl resonance for **13b** (δ_H 0.17); for **14b** the highest field methyl resonance appears at δ_H 0.86. As shown in **16** and **17** a methyl is located in the shielding region of the phenyl ring for **13b** (=**16**) and held over the lactone carbonyl in **14b** (=**17**): NMR data is appended to structures **16** and **17** in the form; δ_H value, multiplicity, *J* values. As expected from the spectra of simple adducts of 2-benzopyran-3-one[13] the *exo*-directed methylene hydrogen H_a in **16** is more strongly coupled to the vicinal bridgehead proton (δ_H 5.53) than is its *endo* geminal partner and shows a large (*J* 10.5 Hz) coupling to the *cis* ring junction methine at δ_H 1.80. In contrast the *exo*-directed methylene proton in **17** (δ_H 2.26) shows a smaller coupling (*J* 6 Hz) to the *trans* ring junction methine. Similar NMR evidence allows assignment of the configurations of **13a** and **14a** *e.g.* **13a** shows a strongly shielded methylene proton (δ_H 0.68) not shown by **14a**. In the same way **13c** and **14c** are distinguished by NMR evidence (Experimental section).

The uniform preference for *endo*-chain addition observed in these intramolecular reactions echoes the similar *endo*-preference seen in the intermolecular additions of **1** (R = R′ = H) to alkenes like cyclopentene,[14] but contrasts with the *exo*-chain preference shown for **18a** (*n* = 3) (*exo*:*endo* ratio = 3:1) and **18a** (*n* = 4) (*exo*:*endo* ratio = 5:1).[15] A related example involves addition of dimethyl maleate to **18b** which gives the *exo*-adduct (effect of the phenyl group),[16,17] whereas the same dienophile adds to **19** to give mostly the *endo*-adduct. These results suggest that repulsion involving the C(O)O moiety of the pyrones inhibits *exo*-addition. Another factor favouring *endo*-addition of alkyl groups is indicated by preferred *endo*-addition of cyclopentene to (*E*)-α-methoxycarbonyl-*o*-quinodimethane **20**. This could either be attributed to steric attraction (a form of secondary MO–MO interaction),[14] or to reduced steric interactions in transition structures with *endo*- rather than *exo*-disposed groups.[18]

Since the major adduct **13b** had the *cis* BC ring junction



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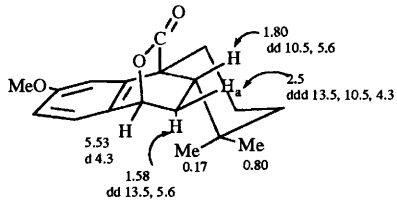
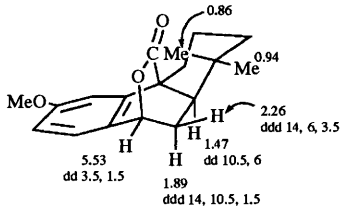
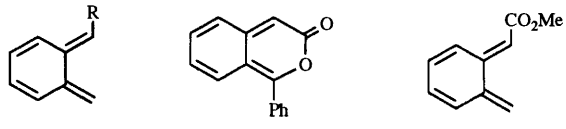


16 (= **13b**)



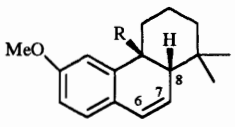
17 (= **14b**)

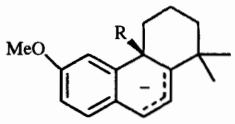


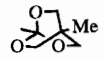
18 a R = $(CH_2)_n CH=CH_2$ **19** **20**
b R = Ph

various attempts were made to convert it into products with the *trans* stereochemistry required for the synthesis of diterpenes like pisiferic acid. Our experiments extend the range of compounds that can be prepared from adducts of 2-benzopyran-3-one and reflect on the relative stability of *cis*–*trans* isomers of compounds like pisiferic acid. Reaction of *endo*-adduct **13b** with methanolic hydrogen chloride gave the methyl ester **21** (90%). With a strong base like potassium *tert*-butoxide literature precedent suggested[19] this would form the 1-aryl substituted allyl anion **22**; α-face protonation might then give the required C-8 epimer of **21**. With potassium *tert*-butoxide in boiling *tert*-butyl alcohol **21** gave the related acid **23**. Despite scrupulous attempts to exclude moisture, formation of **23** could not be avoided. Accordingly the *ortho* ester **24** was prepared using the method developed by Corey and Raju[20] (Experimental section). With potassium *tert*-butoxide in dimethyl sulfoxide at 100 °C (2 h) **24** gave the naphthalene **25** with loss of the *ortho* ester group, and no observable epimerised product. The acid **23** was converted into the oxazoline **26**[21] (Experimental section); **26** remained unchanged upon heating with potassium *tert*-butoxide (12 equiv.) in boiling *tert*-butyl alcohol (18 h). To test if this result was due to our failure to produce the anion of type **22**, or to the greater thermodynamic stability of the *cis* isomer **26**, the latter was treated with potassium *tert*-butoxide in $(CD_3)_2SO$ in a sealed NMR tube. Monitoring the reaction progress by NMR showed a slow build up of the di-deuteriated *cis* compound **27**; the NMR spectrum of the recovered product in $CDCl_3$ was identical to that of the starting material except that the resonances of 6-H and 8-H were absent and that of 7-H had collapsed to a singlet. This result suggests the *cis* isomer is thermodynamically preferred over its *trans* counterpart. The appearance of a shielded methyl resonance (δ_H 0.36) for **21** suggests conformer **28** is preferred to

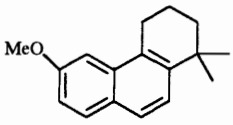
† The intramolecular addition of **12b** is slower than its intermolecular addition to *N*-methylmaleimide to give **15** (80%).





21 R = CO_2Me
23 R = CO_2H
24 R = 
26 R = 

22



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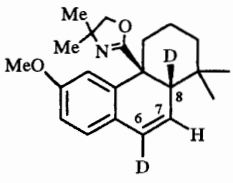

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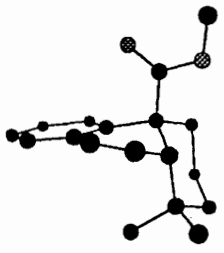

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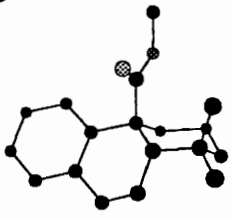

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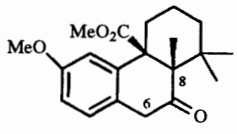
the alternative **30**. The appearance of a high field methyl resonance is a characteristic feature of the *cis* ring fusion in these diterpenoids.[22] Likewise a coupling of 6.0 Hz between 7-H and 8-H of **21** agrees with a conformer of type **28** [dihedral angle (φ), *ca.* 30°] rather than type **30** (φ *ca.* 90°) or a *trans* isomer of type **29** (φ 102°) for both of which $J_{7,8}$ would be near zero.

In a further attempt to epimerise at C-8 the ester **21** was converted into the ketone **31**. Epoxidation of **21** with *m*-chloroperbenzoic acid in the presence of sodium hydrogen carbonate and direct rearrangement of the freshly prepared epoxide with boron trifluoride–ether at 20 °C gave **31** (71%) together with the α-diketone **32** (15%). Treatment of **31** with NaOMe–CD_3OD at 65 °C (6 h, sealed NMR tube) showed complete exchange of the C-6 methylene protons and ester methoxy group, but retention of the C-8 methine proton and *cis* stereochemistry. Several workers have found no evidence for equilibration of *cis* and *trans* 6-ketones of a similar type.[23] The extremely high acidity of the methylene protons in β-decalone (pK_a 12.9)[24] is presumably responsible for the difficulty in ionising the C-8 proton (pK_a > 20). A similar problem of *cis* to *trans* epimerisation confronted Kametani and his collaborators in their synthesis of pisiferic acid.[25] In that work, conversion of **33** (R = β-H) into **33** (R = α-H) was achieved in seven steps *via* the enone **34** which upon catalytic reduction gave mostly **35** (R = α-H) (8α:8β ratio = 4:1). A related route for C-8 inversion of the endo adduct **13b** is in principle possible from the ketone **36** available from **13b** by lithium aluminium hydride reduction followed by selective oxidation at the benzylic alcohol site using manganese dioxide. Somewhat surprisingly the latter reaction gave in addition to **36** (66%) the hemiacetal **37** (15%) resulting from oxidation at the primary alcohol site. This route and other possible ways of effecting epimerisation at C-8 were set aside in favour of a synthesis based upon diverting the stereochemistry of the intramolecular Diels-Alder addition. This was achieved by incorporation of a *trans* phenylsulfonyl group at the dienophile double bond. Subsequent removal of the phenylsulfonyl group in a Julia-like elimination (Na amalgam) provided an effective solution to the stereochemical problem.[26]



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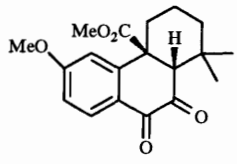

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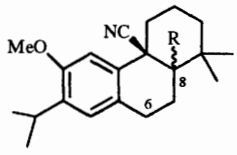

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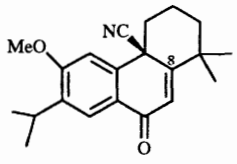

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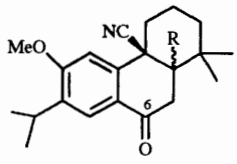

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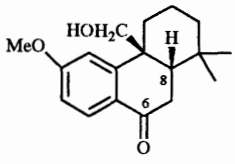

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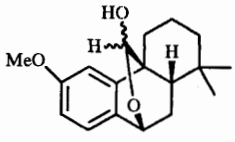

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Experimental

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. Unless otherwise stated IR spectra were recorded as Nujol mulls on a Philips PU 8706 IR spectrophotometer, and referenced to a peak at 1601 cm^{-1} of polystyrene. Unless otherwise stated ^1H NMR spectra were determined in $CDCl_3$, with tetramethylsilane as internal standard with a General Electric QE 300 instrument (300 MHz spectra); 400 MHz spectra were obtained on a Bruker AM 400 spectrometer. *J* Values are given in Hz. Mass spectra are EI spectra recorded on a Kratos MS/50 or a V.G. autospec instrument. Chromatography on silica refers to short-column chromatography over Kieselgel G60 (Merck).[27] Ether refers to diethyl ether and light petroleum to the fraction with bp 60–80 °C.

Alkylation of 6-methoxyisochroman-3-one 8

To a stirred solution of **8**[10] (5.58 g, 0.031 mol), 6-iodo-3,3-dimethylhex-1-ene **9b**[25] (7.6 g, 0.031 mol) and hexamethylphosphoric triamide (HMPTA; 5.5 cm^3) in dry tetrahydrofuran (THF) (100 cm^3), was added *via* syringe potassium bis(trimethylsilyl)amide in toluene (0.5 mol dm^{-3}; 64 cm^3) at 20 °C under argon. The mixture was stirred for 18 h at 20 °C, quenched with water and extracted into ether. The organic

extract was washed with dilute hydrochloric acid (2 mol dm^{-3}; 50 cm^3) and water, dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on silica with dichloromethane to give the *dialkylated lactone* (2.25 g, 18%) (Found: M^+, 498.4231. $C_{26}H_{38}O_3$ requires *M*, 398.4235); ν_{max}(film)/cm^{-1} 1736 and 1619; δ_H 0.89 (12 H, s, 4 × Me), 0.9–1.3 (8 H, m), 1.63–1.78 (2 H, m), 1.95–2.08 (2 H, m), 3.32 (3 H, s, OMe), 4.73–4.86 (4 H, m, 2 × CH=CH_2), 5.31 (2 H, s, benzylic-H), 5.65 (2 H, dd, *J* 19 and 11, 2 × HC=), 6.70 (1 H, d, *J* 2.0), 6.80 (1 H, dd, *J* 9 and 2.0) and 7.02 (1 H, d, *J* 9); *m/z* 398 (M^+), 288, 245, 191, 159, 109 (38.5, 68.1, 20.2, 100, 25.9 and 47.5%).

Further elution of the column gave the *mono-alkylated lactone* **10b** as an oil (4.47 g, 50%) (Found: C, 74.85; H, 8.85. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.3%); ν_{max}(film)/cm^{-1} 1738 and 1611; δ_H 0.97 (6 H, s, 2 × Me), 1.25–1.50 (4 H, m, 2 × CH_2), 1.70–2.00 (2 H, m, CH_2), 3.54 (1 H, apparent t, *J* 7, methine-H), 3.80 (3 H, s, OMe), 4.85–4.94 (2 H, overlapping multiplet, vinyl CH_2), 5.20 (1 H, d, *J* 13.0, $ArCH_2$), 5.39 (1 H, d, *J* 13.0, $ArCH_2$), 5.68–5.80 (1 H, m, vinyl methine), 6.70 (1 H, d, *J* 2.5), 6.80 (1 H, dd, *J* 8.5 and 2.5) and 7.12 (1 H, d, *J* 8.5); δ_C(75 MHz) 22.1, 26.4, 30.6, 36.25, 42.0, 46.0, 55.1, 68.9, 110.3, 111.9, 112.2, 123.0, 125.7, 136.3, 147.8, 159.7 and 172.5; *m/z* 288 (M^+), 260, 219, 178, 109, 69, 41 (100, 22.8, 30.2, 77.8, 38.1, 46.3 and 52.7% respectively). Further elution of the column gave the starting lactone **8** (1.1 g) (NMR spectrum identical with that of the starting material).

Hydrolysis of 6-methoxy-4-(4,4-dimethylhex-5-enyl)isochroman-3-one 10b

A mixture of the title compound (874 mg, 3.03 mmol), aq. sodium hydroxide (2 mol dm^{-3}; 8 cm^3) and ethanol (≈0.5 cm^3) was boiled under reflux for 2.5 h, cooled, transferred to a separating funnel and ice-cold dilute hydrochloric acid (2 mol dm^{-3}; 20 cm^3) added. The precipitated acid was quickly extracted into pre-cooled (0 °C) ether which upon separation was treated with an ethereal solution of diazomethane (10 cm^3) at 0 °C. Evaporation of the mixture left a residue which was chromatographed on silica with dichloromethane to give *methyl 2-(2-hydroxymethyl-5-methoxyphenyl)-6,6-dimethyloct-7-enoate* as an oil (918 mg, 94.6%) (Found: C, 71.2; H, 8.9. $C_{19}H_{28}O_4$ requires C, 71.25; H, 8.75%); ν_{max}($CHCl_3$)/cm^{-1} 3458br (OH), 1735 (CO) and 1608 (C=C); δ_H 0.92 (6 H, s, 2 × Me), 1.10–1.38 (4 H, m), 1.65–1.79 (1 H, m), 2.02–2.1 (1 H, m), 2.15 (1 H, dd, *J* 7.5 and 4, exch. D_2O, CH_2OH), 3.65 (3 H, s, CO_2Me), 3.81 (3 H, s, OMe), 3.95 (1 H, t, *J* 7.0, CHCO), 4.61 (1 H, dd, *J* 12 and 7.5, CH_2OH), 4.76 (1 H, dd, *J* 12 and 4, CH_2OH), 4.82–4.97 (2 H, overlapping multiplet, CH=CH_2), 5.7 (1 H, dd, *J* 17 and 11.5, C*H*=CH_2), 6.78 (1 H, dd, *J* 8.0 and 2.5), 6.92 (1 H, d, *J* 2.5, ArH) and 7.22 (1 H, d, *J* 8.0); δ_C(75 MHz) 22.4, 26.3, 26.3, 33.6, 36.1, 42.0, 45.9, 51.6, 54.7, 62.3, 110.0, 111.6, 112.7, 130.2, 130.8, 139.0, 147.8, 159.1 and 174.3; *m/z* 320 (M^+), 288, 260, 219, 178, 137, 109, 91 and 69 (5.4, 73.6, 20.0, 31.3, 72.6, 100, 47.1, 30.5 and 69.4%).

Oxidation of methyl 2-(2-hydroxymethyl-5-methoxyphenyl)-6,6-dimethyloct-7-enoate

To a stirred solution of oxalyl chloride (0.62 cm^3) in dry dichloromethane (15 cm^3) at −78 °C was added dropwise *via* a syringe dimethyl sulfoxide (1 cm^3). The mixture was stirred for 5 min and a solution of the title hydroxy ester (2.1 g, 6.5 mmol) in dry dichloromethane (5 cm^3) was added dropwise. The mixture was stirred under argon for 0.5 h and then triethylamine (4.5 cm^3) was added. The mixture was allowed to attain room temperature, poured into ice, diluted with ether and the organic layer washed with dilute hydrochloric acid (0.1 mol dm^{-3}; 100 cm^3) and water. The ether extract was separated, dried ($MgSO_4$) and evaporated to give a residue which was chromatographed on silica with dichloromethane to give methyl 2-(2-formyl-5-methoxyphenyl)-6,6-dimethyloct-7-enoate as an oil (2 g, 96.7%) (Found: C, 71.65; H, 8.15. $C_{19}H_{26}O_4$ requires C, 71.7; H, 8.2%); ν_{max}(film)/cm^{-1} 1734 (CO_2Me), 1685 (CHO) and 1598 (C=C); δ_H 0.93 (6 H, s, 2 × Me), 1.20–1.40 (4 H, m), 1.62–1.81 (1 H, m), 2.0–2.18 (1 H, m), 3.62 (3 H, s, CO_2Me), 3.85 (3 H, s, Me), 4.80–4.96 (3 H, overlapping multiplet, methine-H and HC=CH_2), 5.65–5.76 (1 H, m, *H*C=CH_2), 6.91 (1 H, dd, *J* 8.5 and 2.5), 6.98 (1 H, d, *J* 2.5), 7.74 (1 H, d, *J* 8.5) and 10.05 (1 H, s, CHO); δ_C(75 MHz) 22.3, 26.2, 33.8, 36.0, 41.8, 44.7, 51.5, 55.0, 109.9, 111.6, 114.2, 126.6, 136.3, 143.2, 147.7, 163.4, 173.5 and 190.6; *m/z* 318 (M^+), 287, 258, 242, 217, 189, 161, 91 and 69 (60.2, 13.2, 15.5, 18.2, 19.5, 100, 78.5, 13.6 and 42.6%).

Hydrolysis of methyl 2-(2-formyl-5-methoxyphenyl)-6,6-dimethyloct-7-enoate

Method A. A mixture of the title compound (209 mg, 0.65 mmol), 1,4-dioxane (10 cm^3), concentrated hydrochloric acid (10 cm^3) and water (10 cm^3) was boiled under reflux for 1 h. The mixture was cooled, shaken with water and extracted into ether. The organic extract was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give an oily residue which was applied to a column of silica gel. Elution with distilled diisopropylether–acetic acid mixture (100 cm^3 : 4 drops) gave 2-(*2-formyl-5-methoxyphenyl*)-6,6-*dimethyloct-7-enoic acid* **11b** (151.5 mg, 75.8%), mp 60–61 °C (from ether) (Found: C, 70.9; H, 8.1. $C_{18}H_{24}O_4$ requires C, 71.05; H, 7.9%); ν_{max}(film)/cm^{-1} 3700–2300br, 1705, 1601 and 1568; δ_H 0.95 (6 H, s, 2 × Me), 1.10–1.38 (4 H, m, 2 × CH_2), 1.63–1.78 (1 H, m, CH_2), 2.08–2.23 (1 H, m, CH_2), 3.8 (3 H, s, OMe), 4.79 (1 H, apparent t, *J* 7.0), 4.82–4.90 (2 H, overlapping multiplets, CH=CH_2), 5.64–5.78 (1 H, m, *H*C=CH2), 6.92 (1 H, dd, *J* 8.5 and 2.5), 6.98 (1 H, d, *J* 2.5), 7.78 (1 H, d, *J* 8.5), 10.01 (1 H, s, CHO) and 10.35 (1 H, br s, CO_2H); *m/z* 304 (M^+, 287, 242, 207, 189, 175, 161, 149 and 110 (11, 7.9, 7.7, 6.2, 19.6, 7.0, 22.5, 17.6 and 100%).

Method B. A mixture of the ester (2 g, 6.28 mmol), potassium carbonate (1.73 g, 12.54 mmol), methanol (60 cm^3) and water (15 cm^3) was boiled (2 h) under reflux, cooled, acidified with hydrochloric acid (2 mol dm^{-3}; 50 cm^3) and extracted into ether. The ether extract was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude acid which was dissolved in ether and shaken twice with saturated aq. sodium hydrogen carbonate. The sodium hydrogen carbonate extracts were combined and neutralised with concentrated aq. HCl. The acid was extracted into ether and the ether extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the pure acid **11b** (1.87 g, 98%).

Generation and intramolecular Diels–Alder cycloaddition of 4-(4,4-dimethylhex-5-enyl)-6-methoxy-2-benzopyran-3-one 12b

The acid **11b** (47.0 mg, 0.154 mmol) and freshly distilled acetic anhydride (3 cm^3) were boiled under reflux for 1 h, after which the mixture was cooled and evaporated under reduced pressure. The residue was chromatographed on silica with benzene–ether (97:3) to give the *exo*-adduct 6-methoxy-1,1-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4a,9-carbolactone **14b** (5.5 mg, 12.5%), mp 89–90 °C (from light petroleum) (Found: C, 75.8; H, 7.85. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.7%); ν_{max}($CHCl_3$)/cm^{-1} 1740, 1610, 1590 and 1494; δ_H(400 MHz) 0.86 (3 H, s, Me), 0.94 (3 H, s, Me), 1.23 (1 H, apparent td, *J* 13.5 and 3.5), 1.47 (1 H, dd, *J* 10.5 and 6, *endo*-methine-H), 1.55–1.63 (1 H, m), 1.68–1.76 (1 H, m), 1.82 (1 H, apparent td, *J* 13.5 and 4.5), 1.89 (1 H, ddd, *J* 14.0, 10.5 and 1.5, *endo*-methylene-H), 2.07 (1 H, apparent qt, *J* 13.5 and 3.5), 2.26 (1 H, ddd, 14, 6 and 3.5, *exo*-methylene-H), 2.55–2.64 (1 H, m), 3.82 (3 H, s, OMe), 5.53 (1 H, dd, *J* 3.5 and 1.5, bridgehead methine-H), 6.74 (1 H, dd, *J* 8 and 2.5), 6.83 (1 H, d, *J* 2.5) and 7.16 (1 H, d, *J* 8); *m/z* 286 (M^+), 242, 227, 211, 199, 185 and 171 (30.3, 100, 40.4, 5.7, 14.9, 30.0 and 96.7%).

Further elution gave the *endo*-adduct **13b** (32 mg, 72.6%), mp 127–28 °C (from light petroleum) (Found: C, 75.75; H, 7.8%); ν_{max}(film)/cm^{-1} 1745, 1607 and 1491; δ_H(400 MHz) 0.17 (3 H, s,

Me), 0.80 (3 H, s, Me), 1.28 (1 H, apparent dt, *J* 13 and 4.0), 1.47 (1 H, br d, *J* 13), 1.58 (1 H, dd, *J* 13.5 and 5.5, *endo*-methylene-H), 1.80 (1 H, dd, *J* 10.5 and 5.5, *endo*-methine-H), 1.76–1.82 (1 H, m), 1.88 (1 H, apparent qt, *J* 13.5 and 3.0), 2.09 (1 H, apparent dt, *J* 14 and 5), 2.50 (1 H, ddd, *J* 13.5, 10.5 and 4.0, *exo*-methylene-H), 2.53 (1 H, br m), 3.87 (3 H, s, OMe), 5.53 (1 H, d, *J* 4.0, bridgehead methine-H), 6.75 (1 H, dd, *J* 7.5 and 2), 6.98 (1 H, d, *J* 2) and 7.17 (1 H, d, *J* 7.5); *m/z* 286 (M^+), 242, 189, 171, 115, 69 and 55 (15, 100, 10.1, 80.9, 21.6, 18.5 and 22.3%).

Generation and intermolecular Diels–Alder trapping of 4-(4,4-dimethylhex-5-enyl)-6-methoxy-2-benzopyran-3-one 12b with *N*-methylmaleimide

A mixture of acid **11b** (21 mg, 0.069 mmol), *N*-methylmaleimide (15.3 mg, 0.138 mmol), *p*-xylene (15 cm^3) and freshly distilled acetic anhydride was heated for 1 h at 80 °C under argon. A small portion of the reaction mixture was evaporated under reduced pressure. The NMR spectrum of the residue suggested the absence of peaks corresponding to adducts **13b** and **14b**. A further two equivalents of *N*-methylmaleimide (15.3 mg) were added and the reaction mixture was boiled under reflux for 1 h and cooled. The mixture was evaporated under reduced pressure to give the crude adduct **15** which was chromatographed on silica with ethyl acetate–benzene (9:1) to give the pure N-*methylmaleimide adduct* **15** (22 mg, 80%), mp 148–149 °C (from light petroleum) (Found: M^+, 397.1885. $C_{23}H_{27}NO_5$ requires *M*, 397.1889); ν_{max}(KBr)/cm^{-1} 1758, 1703 and 1609; δ_H 1.05 (6 H, s, 2 × Me), 1.50–1.60 (2 H, m), 1.62–1.80 (2 H, m), 2.22–2.36 (1 H, m), 2.38–2.50 (1 H, m), 2.54 (3 H, s, N-Me), 3.42 (1 H, d, *J* 8.5, *exo*-H), 3.80 (3 H, s, OMe), 3.83 (1 H, dd, *J* 8.5 and 4.0, *exo*-H), 4.90–5.02 (2 H, overlapping multiplets, HC=CH_2), 5.80 (1 H, d, *J* 4.0, bridgehead methine-H), 5.82–5.92 (1 H, m, *H*C=CH_2), 6.81 (1 H, dd, *J* 8 and 2.5), 6.83 (1 H, d, *J* 2.5) and 7.22 (1 H, d, *J* 8); *m/z* 397 (M^+), 336, 328, 271, 256, 171, 128, 109 and 63 (18.5, 6.5, 38.8, 100, 16.4, 73, 20.3, 34 and 29%).

Reaction of the *endo*-adduct 13b with methanolic hydrogen chloride

The adduct **13b** (95 mg, 0.33 mmol) was boiled under reflux for 1 h in methanol (5 cm^3) previously saturated with dry hydrogen chloride. The reaction mixture was cooled, diluted with ether and washed with saturated aq. sodium hydrogen carbonate and water. The ether layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure and purification of the residue by chromatography on silica with dichloromethane afforded methyl 6-methoxy-1,1-dimethyl-1,2,3,4,4a,10a-hexahydrophenanthrene-4a-carboxylate **21** (85.5 mg, 90%), mp 54–56 °C (from light petroleum) (Found: C, 75.8; H, 8.15. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.0%); ν_{max}(film)/cm^{-1} 1730, 1610 and 1571; δ_H 0.36 (3 H, s, Me), 0.94 (3 H, s, Me), 1.33–1.45 (2 H, m), 1.54–1.64 (2 H, m), 1.70–1.83 (1 H, m), 2.50 (1 H, br d, *J* 13.0), 2.73 (1 H, d, *J* 6.0, allylic-H), 3.51 (3 H, s, CO_2Me), 3.83 (3 H, s, OMe), 5.98 (1 H, dd, *J* 10.0 and 6.0, olefinic-H), 6.46 (1 H, d, *J* 10.0, olefinic-H), 6.73 (1 H, dd, *J* 8.0 and 2.5, ArH), 6.92 (1 H, d, *J* 2.5) and 6.96 (1 H, d, *J* 8.0); *m/z* 300 (M^+), 241, 225, 218, 197, 185, 171, 159 and 141 (29.4, 57.3, 12.9, 37.9, 5.4, 30.2, 100, 12.6 and 12.6%).

Attempted epimerisation of the ester 21

The ester **21** (48.5 mg, 0.161 mmol), potassium *tert*-butoxide (197.5 mg, 1.76 mmol) and *tert*-butyl alcohol (5 cm^3) were boiled under reflux for 15 h then the mixture was cooled, diluted with ether and washed with dilute hydrochloric acid (2 mol dm^{-3}; 25 cm^3) and water. The ether layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue which was recrystallised from ether to give the acid 6-methoxy-1,1-dimethyl-1,2,3,4,4a,10a-hexahydrophenanthrene-4a-carboxylic acid **23** (39.1 mg, 85%), mp 200–201 °C (from ether) (Found: C, 73.3; H, 7.7. $C_{18}H_{22}O_3 \cdot 0.5H_2O$ requires C, 73.2; H, 7.8%); ν_{max}/cm^{-1} 3400–2400br (CO_2H), 1697 and 1610; δ_H 0.32 (3 H, s, Me), 0.91 (3 H, s, Me), 1.20–1.50 (2 H, m), 1.53–1.88 (3 H, m), 2.56 (1 H, br d, *J* 13.5), 2.62 (1 H, d, *J* 6.0, methine-H), 3.80 (3 H, s, MeO), 5.95 (1 H, dd, *J* 10.0 and 6.0, olefinic-H), 6.46 (1 H, d, *J* 10.0, olefinic-H), 6.76 (1 H, dd, *J* 8.0 and 2.5), 6.92 (1 H, d, *J* 2.5), 6.96 (1 H, d, *J* 8.0) and 11.1 (1 H, br s, CO_2H); *m/z* 286 (M^+), 240, 225, 203, 193, 171, 153 and 128 (19.8, 60.0, 100, 37.25, 38.25, 79.6, 26.6 and 25.6%).

Preparation and attempted epimerisation of ortho ester 24

A solution of the acid **23** (10 mg, 0.035 mmol), in freshly distilled oxalyl chloride (5 cm^3) was stirred for 3 h at 20 °C. The mixture was evaporated under reduced pressure at 20 °C to give the acid chloride, ν_{max}(film)/cm^{-1} 1784 and 1610; δ_H(300 MHz) 0.33 (3 H, s, Me), 0.97 (3 H, s, Me), 1.2–1.8 (5 H, m), 2.66 (1 H, d, *J* 6, methine-H), 2.76 (1 H, br d, *J* 12.5, methylene-H), 3.84 (3 H, s, OMe), 6.02 (1 H, dd, *J* 10.0 and 6, olefinic-H), 6.51 (1 H, d, *J* 10.0, olefinic-H), 6.82 (1 H, dd, *J* 7 and 2) and 7.20 (2 H, overlapping multiplets, ArH). The acid chloride was immediately dissolved in dichloromethane (1 cm^3) and stirred with pyridine (0.5 cm^3) and 3-hydroxymethyl-3-methyloxetane (0.5 cm^3) for 18 h at 20 °C. The reaction mixture was diluted with ether and washed with water. The ether layer was separated, dried ($MgSO_4$) and evaporated to give a residue which was chromatographed on alumina with benzene–ether (9:1) to afford the ester (7 mg, 76%), δ_H 0.37 (3 H, s, Me), 0.95 (3 H, s, Me), 1.05 (3 H, s, Me), 1.22–1.52 (2 H, m), 1.53–1.92 (3 H, m), 2.6 (1 H, br d, *J* 13.0), 2.71 (1 H, d, *J* 6, methine-H), 3.81 (3 H, s, OMe), 3.86 (1 H, d, *J* 11, OCH_2), 4.03 (1 H, d, *J* 11, OCH_2), 4.12 (1 H, d, *J* 4.5, oxetane methylene-H), 4.14 (1 H, d, *J* 4.5, oxetane methylene-H), 4.20 (1 H, d, *J* 4.5, oxetane methylene-H), 4.22 (1 H, d, *J* 4.5, oxetane methylene-H), 5.98 (1 H, dd, *J* 10 and 6, ArCH=C*H*), 6.48 (1 H, d, *J* 10, ArC*H*=CH), 6.75 (1 H, dd, *J* 7 and 2) and 6.99 (2 H, m, ArH).

To this ester (7 mg, 0.018 mmol) in dichloromethane (1 cm^3) stirred at −15 °C, was added *via* a syringe freshly distilled boron trifluoride–ether (5 mm^3).‡ The mixture was stirred under argon for 6 h at −15 °C, quenched with triethylamine (10 mm^3), filtered through a sintered glass funnel and evaporated under reduced pressure by a cold rotary evaporator. The crude product was quickly passed through a short column of alumina with dichloromethane to give the ortho ester **24** (4 mg, 60%); δ_H 0.36 (3 H, s, Me), 0.67 (3 H, s, Me), 0.90 (3 H, s, Me), 1.20–1.87 (5 H, m), 2.45 (2 H, m, methine-H and methylene-H), 3.68 [6 H, s, $CH_3C(CH_2)_3$], 3.80 (3 H, s, OMe), 5.86 (1 H, dd, *J* 10.0 and 6.5, ArCH=C*H*), 6.42 (1 H, d, *J* 10.0, ArC*H*=CH), 6.68 (1 H, dd, *J* 8.0 and 2.5), 6.88 (1 H, d, *J* 8.0) and 6.93 (1 H, d, *J* 2.5).

The *ortho* ester **24** (4 mg, 0.01 mmol) and freshly sublimed potassium *tert*-butoxide (22.4 mg, 20 equiv.) in freshly distilled dimethyl sulfoxide (1 cm^3) were heated for 2 h at 100 °C, cooled and diluted with ether. The mixture was washed with water to remove dimethyl sulfoxide and separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure on a rotary evaporator. The residue was chromatographed on silica with benzene to give the 6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydrophenanthrene **25** (2 mg, 77%), mp 114–116 °C (from light petroleum) (Found: C, 84.75; H, 8.55; M^+, 240.1508. $C_{17}H_{20}O_2$ requires C, 85.0; H, 8.3%; *M*, 240.1514); ν_{max}(CH_2Cl_2)/cm^{-1} 2954, 2920, 1612, 1501, 1031 and 1021; δ_H 1.35 (6 H, s, 2 × Me), 1.76–1.80 (2 H, m), 1.90–2.02 (2 H, m), 3.05 (2 H, apparent t, *J* 6.4, methylene-H), 3.93 (3 H, s, OMe), 7.10 (1 H, dd, *J* 9.0 and 2), 7.25 (1 H, d, *J* 2), 7.37 (1 H, d, *J* 9.0), 7.59 (1 H, d, *J* 9.0) and 7.68 (1 H, d, *J* 9.0); *m/z* 240 (M^+), 225, 196, 171, 165, 152 and 115 (19.1, 37.3, 7.5, 5.3, 12.1, 8.9 and 9.1%).

‡ 1 mm^3 = 1 μl.

Preparation of oxazoline 26

A solution of the acid **23** (52 mg, 0.180 mmol) in oxalyl chloride (1 cm^3) was stirred for 3 h at 20 °C. Oxalyl chloride was evaporated under reduced pressure to give the acid chloride which was dissolved in dichloromethane (5 cm^3). The solution was cooled to 0 °C and 2-amino-2-methylpropan-1-ol (200 mm^3) was added dropwise. The reaction mixture was allowed to attain ambient temperature in 2 h and was diluted with ether. The ether layer was washed with water, separated, dried ($MgSO_4$) and evaporated under reduced pressure to give a residue which was treated with thionyl chloride (0.5 cm^3). The mixture was stirred (0.5 h) at 20 °C, plunged into ice cold aq. sodium hydroxide (2 mol dm^{-3}; 25 cm^3) and extracted into ether. The ether extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give a residue, which was chromatographed on silica with benzene–ether (88:12) to give 4a-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-6-methoxy-1,1-dimethyl-1,2,3,4,4a,10a-hexahydrophenanthrene **26** as an oil (24 mg, 40%) (Found: M^+, 339.2209. $C_{22}H_{29}NO_2$ requires *M*, 339.2198); ν_{max}(film)/cm^{-1} 2980, 2968, 1650 and 1610; δ_H 0.39 (3 H, s, Me), 0.95 (3 H, s, Me), 1.18 (3 H, s, Me), 1.22 (3 H, s, Me), 1.35–1.45 (3 H, m), 1.50–1.70 (3 H, m), 1.70–1.90 (1 H, m), 2.43 (1 H, br d, *J* 13, methylene-H), 2.74 (1 H, d, *J* 5.5, methine-H), 3.71 (1 H, d, *J* 11.0, $=NCMe_2CH_2$), 3.74 (1 H, d, *J* 11.0, $=NCMe_2CH_2$), 3.80 (3 H, s, OMe), 5.98 (1 H, dd, *J* 10.0 and 5.5, olefinic-H), 6.44 (1 H, d, *J* 10.0, olefinic-H), 6.72 (1 H, dd, *J* 8.0 and 2.5) and 6.94 (2 H, m); *m*/*z* 339 (M^+), 324, 308, 282, 268, 256, 240, 225, 184 and 171 (48, 18.5, 65.0, 9.6, 9.9, 24.2, 99.8, 100, 25.2 and 39.2%).

Attempted epimerisation of oxazoline 26 with potassium *tert*-butoxide

A mixture of compound **26** (15 mg, 0.044 mmol), *tert*-butyl alcohol and potassium *tert*-butoxide (60 mg, 12 equiv.) was boiled for 18 h under reflux, cooled and diluted with ether. The ether extract was then washed with water, separated and dried ($MgSO_4$). Evaporation of the mixture under reduced pressure gave the unchanged starting material as indicated by ^1H NMR.

Attempted epimerisation of oxazoline protected acid 26 with potassium *tert*-butoxide in deuteriated dimethyl sulfoxide

A mixture of the protected acid **26** (7 mg, 0.02 mmol), potassium *tert*-butoxide (11.5 mg, 5 equiv.) and deuteriated dimethyl sulfoxide (0.5 cm^3) was placed in an NMR tube and subjected to 5 freeze-pump-thaw cycles to remove any dissolved oxygen in the system. The tube was sealed under vacuum and placed in a thermostat-controlled oil bath. The bath temperature was set at 80 °C whilst the reaction was monitored by NMR spectroscopy. Heating was continued until a change in the nature of the NMR spectrum had occurred. The tube was cooled in liquid nitrogen, opened and the contents emptied into dilute hydrochloric acid (2 mol dm^{-3}; 25 cm^3) and extracted into ether. The ether layer was washed with water, separated and dried ($MgSO_4$). Evaporation of the extract and chromatography of the residue on silica with benzene–ether (88:12) gave the *cis-deuteriated oxazoline protected acid* **27** (5.5 mg, 80.6%) as an oil; (Found: M^+, 341.2320. $C_{22}H_{27}D_2NO_2$ requires *M*, 341.2323); ν_{max}(film)/cm^{-1} 2960, 2928, 1651 and 1606; δ_H 0.39 (3 H, s, Me), 0.95 (3 H, s, Me), 1.18 (3 H, s, Me), 1.22 (3 H, s, Me), 1.35–1.41 (1 H, m), 1.50–1.70 (2 H, m), 1.70–1.90 (1 H, m), 2.43 (1 H, br d, *J* 13), 3.73 (2 H, br s, OCH_2), 3.80 (3 H, s, OMe), 5.99 (1 H, s, C*H*=CDAr), 6.72 (1 H, dd, *J* 8.0 and 2.5) and 6.94 (2 H, overlapping peaks); $\delta_H(C_6D_6)$ 0.58 (3 H, s, Me), 0.92 (3 H, s, Me), 1.04 (3 H, s, Me), 1.06 (3 H, s, Me), 1.15–1.40 (2 H, m), 1.40–1.70 (2 H, m), 1.88–2.0 (1 H, m), 2.61 (1 H, br d, *J* 13.5), 3.32 (3 H, s, OMe), 3.38 (1 H, d, *J* 8, oxazoline methylene-H), 3.45 (1 H, d, *J* 8, oxazoline methylene-H), 6.05 (1 H, s, olefinic-H), 6.54 (1 H, dd, *J* 8.0 and 2.5), 6.85 (1 H, d, *J* 2.5) and 7.24 (1 H, d, *J* 2.5); *m*/*z* 341 (M^+), 326, 310, 284, 270, 258, 241, 226, 186, 173 and 101 (53.5, 14.7, 57.9, 6.0, 6.4, 19.3, 95.7, 80.7, 16.6, 26.0 and 100%).

Preparation of keto ester 31

To a vigorously stirred solution of ester **21** (10 mg, 0.033 mmol), saturated aq. sodium hydrogen carbonate (4 cm^3), solid sodium hydrogen carbonate (50 mg) and dichloromethane (4 cm^3) was added in one portion *m*-chloroperbenzoic acid (100%, 6.3 mg, 0.036 mmol). The mixture was stirred for 12 h at 20 °C, diluted with water and extracted into ether. The ether extract was washed twice with aq. sodium metabisulfite (2 mol dm^{-3}; 25 cm^3) and with water, separated and dried ($MgSO_4$). Evaporation of the extract on a rotary evaporator gave the epoxide; δ_H 0.23 (3 H, s, Me), 1.12 (3 H, s, Me), 1.2–1.8 (5 H, m, methylene-H), 2.52 (1 H, br d, *J* 13), 3.05 (1 H, d, *J* 2.5, methine-H), 3.53 (3 H, s, CO_2Me), 3.76 (1 H, dd, *J* 4 and 2.5), 3.83 (3 H, s, OMe), 3.86 (1 H, d, *J* 4), 6.8 (1 H, dd, *J* 8.0 and 2.5), 6.94 (1 H, d, *J* 2.5) and 7.33 (1 H, d, *J* 8.0). The epoxide without further purification was dissolved in dry ether (5 cm^3), treated with freshly distilled boron fluoride–ether (5 mm^3) and stirred for 0.5 h at 20 °C. The reaction was quenched with water and the mixture was extracted with ether. The ether extract was washed with saturated aq. sodium hydrogen carbonate and water, separated, dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica with benzene–ether (9:1) to give the keto ester **31** (7.5 mg, 71.2%), mp 124–126 °C (from light petroleum) (Found: M^+, 316.1677. $C_{19}H_{24}O_4$ requires *M*, 316.1674); ν_{max}($CHCl_3$)/cm^{-1} 1730 and 1690; δ_H 0.27 (3 H, s, Me), 1.03 (3 H, s, Me), 1.22–1.41 (2 H, m), 1.52–1.75 (3 H, m, 3 × methylene-H), 2.63 (1 H, s, methine-H), 2.85–2.98 (1 H, m), 3.42 (1 H, d, *J* 22, $COCH_2$), 3.55 (3 H, s, CO_2Me), 3.64 (1 H, d, *J* 22, $COCH_2$), 3.84 (3 H, s, OMe), 6.82 (1 H, dd, *J* 8.5 and 2.5), 7.01 (1 H, d, *J* 8.5) and 7.06 (1 H, d, *J* 2.5); *m*/*z* 316 (M^+), 257, 241, 232, 220, 201, 187, 173, 159 and 145 (100, 83.5, 91, 15.6, 15.3, 24.2, 95.9, 15.5, 19.4 and 16.1%). Further elution of the column gave the *diketone* **32** (1.5 mg, 15%), mp 162–163 °C (from light petroleum) (Found: M^+, 330.1478. $C_{19}H_{22}O_5$ requires *M*, 330.1467); ν_{max}($CHCl_3$)/cm^{-1} 1730, 1681 and 1600; δ_H 0.38 (3 H, s, Me), 1.04 (3 H, s, Me), 1.33–1.53 (2 H, m), 1.63–1.80 (3 H, m, 3 × methylene-H), 2.92–3.01 (2 H, m, overlapping peaks, methylene-H and methine-H), 3.54 (3 H, s, CO_2Me), 3.94 (3 H, s, OMe), 6.99 (1 H, dd, *J* 9.0 and 2.5, ArH), 7.03 (1 H, d, *J* 2.5) and 8.18 (1 H, d, *J* 9.0); *m*/*z* 330 (M^+), 302, 270, 255, 243, 227, 220, 201, 187 and 175 (14.2, 14.5, 14.5, 6.2, 29.5, 20.3, 100, 9.2, 24.9 and 18.7%).

Attempted epimerisation of the keto ester 31

Compound **31** (6 mg, 0.018 mmol), freshly prepared sodium methoxide (5 mg, 0.09 mmol) and deuteriated methanol (0.5 cm^3) were placed in an NMR tube and subjected to 5 freeze-pump-thaw cycles to remove any dissolved oxygen in the system. The tube was sealed under vacuum and heated in a thermostat controlled bath set at 65 °C, whilst progress of the reaction was monitored by NMR spectroscopy. After 6 h the benzylic ($ArCH_2$) and the ester (CO_2Me) proton signals of the starting ester **31** had completely disappeared, indicating an exchange by deuterium. However, the signal due to the methine (COCH) remained unchanged. The tube was cooled in liquid nitrogen, opened, the contents poured into water and extracted into ether. The ether extract was washed with dilute hydrochloric acid (2 mol dm^{-3}; 20 cm^3) and water, separated and dried ($MgSO_4$). Evaporation of the extract gave an oily residue which was chromatographed on silica gel. Elution with benzene–ether (9:1) gave the deuteriated keto ester **31** as an oil (4 mg, 69.6%); ν_{max}(film)/cm^{-1} 1730 and 1687; δ_H 0.27 (3 H, s, Me), 1.03 (3 H, s, Me), 1.22–1.41 (2 H, m), 1.52–1.75 (3 H, m, 3 × methylene-H), 2.63 (1 H, s, methine), 2.85–2.98 (1 H, m), 3.84 (3 H, s, OMe), 6.82 (1 H, dd, *J* 8.5 and 2.5), 7.01 (1 H, d, *J* 8.5) and 7.06 (1 H, d, *J* 2.5).

Preparation of hydroxy ketone 36

A solution of the adduct **13b** (15 mg, 0.05 mmol) and lithium aluminium hydride (17 mg, 0.44 mmol) in dry THF (5 cm^3) was

stirred at 20 °C for 45 min. The reaction mixture was filtered through a glass sinter and the filtrate diluted with ether and washed with water. The organic extract was separated and dried ($MgSO_4$). Evaporation of the extract under reduced pressure followed by recrystallisation of the crude product gave a *dihydroxy compound* (11.5 mg, 76%), mp 172–173 °C (from light petroleum) (Found: C, 74.8; H, 9.2. $C_{18}H_{26}O_3$ requires C, 74.5; H, 9.0%); ν_{max}(KBr)/cm^{-1} 3462, 3426, 1611 and 1580; δ_H(C_6D_6) 0.39 (3 H, s, Me), 0.86 (3 H, s, Me), 1.13–1.23 (1 H, m, methylene-H), 1.23–1.50 (6 H, m, obscuring 2 × OHs and CH_2s), 1.79 (1 H, dd, *J* 7.0 and 2.5, $C(CH_3)_2CH$), 2.02–2.18 (2 H, m), 2.30 (1 H, ddd, *J* 15, 8.5 and 2.5), 3.34 (1 H, d, *J* 11.0, CH_2OH), 3.36 (3 H, s, Me), 3.47 (1 H, d, *J* 11.0, CH_2OH), 4.80 (1 H, dd, *J* 8.5 and 7, ArC(OH)*H*), 6.66 (1 H, dd, *J* 8.5 and 2.5), 6.94 (1 H, d, *J* 2.5) and 7.24 (1 H, d, *J* 8.5); *m*/*z* 290 (M^+), 272, 242, 227, 199, 185, 171, 165, 160 and 153 (10.5, 23.8, 100, 14.4, 7.0, 14.0, 74.3, 5.2, 17.0 and 7%).

A mixture of the foregoing dihydroxy compound (20 mg, 0.068 mmol) and freshly prepared active manganese dioxide (9.1 mg, 1.15 mmol) in dry chloroform (5 cm^3) was vigorously stirred for 1 h at 20 °C. The reaction mixture was filtered, diluted with ether and washed with water. The organic layer was separated, dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica in benzene–ether (9:1) gave the *hemiacetal* **37** (3 mg, 15.3%) (Found: M^+, 288.1725. $C_{18}H_{24}O_3$ requires *M*, 288.1738); ν_{max}(film)/cm^{-1} 3408, 1611 and 1590; δ_H 0.15 (3 H, s, Me), 0.77 (3 H, s, Me), 1.2–1.58 (6 H, m, obscuring an OH and CH_2s), 1.68–1.79 (1 H, m), 1.86 (1 H, apparent qt, *J* 13.5 and 3.5, CH_2), 2.28 (1 H, ddd, *J* 14.5, 10 and 4.5, CH_2), 2.51 (1 H, br d, *J* 14.0, CH_2), 3.83 (3 H, s, OMe), 4.72 (1 H, d, *J* 10.5, collapsed to a singlet in dilute solution of trifluoroacetic acid in $CDCl_3$), 4.89 (1 H, d, *J* 4.5), 6.80 (1 H, dd, *J* 8.0 and 2.5), 7.03 (1 H, d, *J* 2.5) and 7.16 (1 H, d, *J* 8.0); *m*/*z* 288 (M^+), 270, 242, 227, 199, 185, 171, 165, 158 and 141 (1.1, 11.9, 68.6, 7.9, 5.6, 16.6, 100, 6.7, 18.1 and 11.9%). Further elution of the column gave the *keto alcohol* **36** (13 mg, 66%) (Found: M^+, 288.1736. $C_{18}H_{24}O_3$ requires *M*, 288.1725); ν_{max}(film)/cm^{-1} 3410, 1660 and 1598; δ_H 0.32 (3 H, s, Me), 0.95 (3 H, s, Me), 1.19–1.62 (6 H, br overlapping multiplets, OH and 5 × CH_2), 2.09 (1 H, d, *J* 7, methine-H), 2.40 (1 H, d, *J* 12), 2.75 (1 H, d, *J* 19.5, $ArCOCH_2$), 2.90 (1 H, dd, *J* 19.5 and 7.0, $ArCOCH_2$), 3.46 (1 H, d, *J* 11.0, OCH_2), 3.54 (1 H, d, *J* 11, OCH_2), 3.88 (3 H, s, OMe), 6.81–6.92 (2 H, m, ArH) and 8.07 (1 H, d, *J* 9); *m*/*z* 288 (M^+), 257, 243, 215, 201, 189, 175, 159, 144 and 128 (28.9, 100, 5.7, 35.2, 16.6, 65.8, 40.9, 22.4, 11.6 and 19.2%).

4-(Hex-5-enyl)isochroman-3-one 10a

To a stirred solution of isochroman-3-one [28] (1.73 g, 0.011 mol), 6-iodohex-1-ene **2a** (2.69 g, 0.012 mol) and HMPTA (1.3 cm^3) in dry THF (85 cm^3) was added *via* a syringe potassium bis(trimethylsilyl)amide solution in toluene (0.5 mol dm^{-3}; 23.5 cm^3) at 20 °C under argon. The mixture was stirred for 18 h at 20 °C, quenched with water and extracted into ether. The organic extract was washed with dilute hydrochloric acid (2 mol dm^{-3}; 50 cm^3) and water, dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on silica with dichloromethane to give the mono-alkylated *lactone* **10a** as an oil (1.25 g, 49.5%) (Found: M^+, 230.1313. $C_{15}H_{18}O_2$ requires M^+, 230.1306); ν_{max}(film)/cm^{-1} 1735; δ_H 0.98–2.20 (8 H, m, methylenes), 3.60 (1 H, apparent t, *J* 7.0, methine-H), 4.82–5.06 (2 H, overlapping multiplets, HC=CH_2), 5.24 (1 H, d, *J* 14.0, benzylic-H), 5.44 (1 H, d, *J* 14.0, benzylic-H), 5.62–5.90 (1 H, multiplet with fine splitting *H*C=CH_2) and 7.29 (4 H, m); *m*/*z* 230 (M^+), 185, 169, 148, 129, 115 and 91 (52.7, 10.7, 5.3, 100, 58.0, 61.5 and 80%).

Methyl 2-(2-hydroxymethylphenyl)oct-7-enoate

The lactone **10a** (695 mg, 3.02 mmol), aq. sodium hydroxide (2 mol dm^{-3}; 7.5 cm^3) and ethanol (3.5 cm^3) were boiled under reflux for 2.5 h, cooled, transferred to a separating funnel and ice-cold dilute hydrochloric acid (2 mol dm^{-3}; 20 cm^3) added. The precipitated acid was quickly extracted into pre-cooled (0 °C) ether and treated with an ethereal solution of diazomethane (10 cm^3) at 0 °C. Evaporation of the mixture left a residue which was chromatographed on silica with dichloromethane to give the *title compound* as an oil (767 mg, 78%) (Found: M^+, 262.1522. $C_{16}H_{22}O_3$ requires M^+, 262.1524); ν_{max}(film)/cm^{-1} 3365 br (OH) and 1729 (CO); δ_H 1.15–1.35 (2 H, m), 1.35–1.50 (2 H, m), 1.72–1.89 (2 H, m), 1.96–2.08 (1 H, m), 2.08–2.23 (1 H, m), 2.54 (1 H, dd, *J* 7.0 and 3.5, exch. D_2O, OH), 3.62 (3 H, s, OMe), 3.98 (1 H, apparent t, *J* 7.5, benzylic methine-H), 4.68 (1 H, dd, *J* 12.5 and 7.0, CH_2OH), 4.81 (1 H, dd, *J* 12.5 and 3.5, CH_2OH), 4.88–5.05 (2 H, overlapping multiplets, CH=CH_2), 5.68–5.85 (1 H, m with fine splitting, C*H*=CH_2) and 7.20–7.45 (4 H, m); *m*/*z* 262 (M^+), 244, 230, 219, 212, 202 and 197 (9.7, 21.2, 100, 5, 10.3, 26.9 and 5.5%).

Methyl 2-(2-formylphenyl)oct-7-enoate

To a stirred solution of oxalyl chloride (0.40 cm^3) in dry dichloromethane (15 cm^3) at −78 °C was added dropwise *via* a syringe dimethyl sulfoxide (0.65 cm^3). The mixture was stirred for 2 min and a solution of the foregoing hydroxy ester (1.08 g, 4.12 mmol) in dry dichlomethane (5 cm^3) was added dropwise within 5 min. The mixture was stirred under argon for 20 min at −78 °C after which triethylamine (2.5 cm) was added. The mixture was allowed to attain room temperature, poured into ice and diluted with ether and the organic layer washed with dilute hydrochloric acid (0.1 mol dm^{-3}; 50 cm^3) and water. The ether extract was separated, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica with dichloromethane to give the *title compound* as an oil (1.03 g, 96%) (Found: M^+, 260.1406. $C_{16}H_{20}O_3$ requires *M*, 260.1412); ν_{max}(film)/cm^{-1} 1730 (CO_2Me), 1692 (CHO) and 1598 (C=C); δ_H 1.10–1.48 (4 H, m), 1.70–1.84 (1 H, m), 1.94–2.04 (2 H, m), 2.04–2.28 (1 H, m), 3.57 (3 H, s, CO_2Me), 4.70 (1 H, apparent t, *J* 7.5, methine-H), 4.86–5.04 (2 H, overlapping multiplets, HC=CH_2), 5.68–5.83 (1 H, m, *H*C=CH_2), 7.40–7.50 (2 H, m), 7.50–7.66 (1 H, m), 7.75 (1 H, d, *J* 7.5) and 10.23 (1 H, s, CHO); *m*/*z* 260 (M^+), 242, 228, 200, 183, 159, 131, 91 and 77 (20.2, 5.0, 21.4, 23.8, 54.2, 62.0, 100, 77 and 38%).

2-(2-Formylphenyl)oct-7-enoic acid 11a

A mixture of the foregoing ester (52 mg, 0.202 mmol), potassium carbonate (50 g, 0.404 mmol), methanol (2 cm^3) and water (1 cm^3) was boiled under reflux for 2 h, cooled, acidified with hydrochloric acid (2 mol dm^{-3}, 25 cm^3) and extracted into ether. The ether layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude acid which was dissolved in ether and shaken twice with saturated aq. sodium hydrogen carbonate. The sodium hydrogen carbonate extracts were combined and neutralised with concentrated HCl. The acid was extracted into ether, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* **11a** as an oil (45 mg, 90%) (Found: M^+, 246.1253. $C_{15}H_{18}O_3$ requires *M*, 246.1255); ν_{max}(film)/cm^{-1} 3500–2400br (CO_2H) and 1690; δ_H 1.10–1.38 (4 H, m), 1.62–1.78 (1 H, m), 1.88–1.98 (2 H, m), 1.98–2.18 (2 H, m), 4.65 (1 H, br s, methine-H), 4.76–4.93 (2 H, m, HC=CH_2), 5.58–5.75 (1 H, m, *H*C=CH_2), 7.33–7.43 (2 H, m), 7.43–7.55(1 H, m), 7.74 (1 H, d, *J* 7.0), 10.23 (1 H, s, CHO) and 10.6 (1 H, br s, CO_2H); *m*/*z* 246 (M^+), 228, 210, 184, 169, 159, 131, 118 and 91 (3.4, 19.3, 6.2, 32.2, 19.6, 47.0, 100, 47.4 and 74.8%).

Generation and intramolecular Diels–Alder cycloaddition of 4-(hex-5-enyl)-2-benzopyran-3-one 12a

The formyl acid **11a** (22.0 mg, 0.089 mmol) and freshly distilled acetic anhydride (1 cm^3) was boiled under reflux for 1 h. The mixture was cooled and acetic anhydride was evaporated off under reduced pressure to give a crude mixture of adducts **13a**

and **14a** (*endo*:*exo* = 4.5:1) which were separated on silica with benzene–ether (97:3) to give the exo-*adduct* 1,2,3,4,4*a*,9,10,10*a*-*octahydrophenanthrene*-4*a*,9-*carbolactone* **14a** (3.2 mg, 16%), mp 79–80 °C (from light petroleum) (Found: C, 78.8; H, 7.15. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1746 (CO); δ_H(400 MHz) 1.14–1.38 (2 H, m), 1.54–1.64 (1 H, m), 1.8–2.05 (7 H, overlapping multiplets), 2.13 (1 H, ddd, *J* 13.5, 10.5 and 1.5, *endo*-methylene-H), 2.54–2.66 (1 H, m), 5.49 (1 H, dd, *J* 3.5 and 1.5, bridgehead methine-H), 7.20–7.30 (3 H, m) and 7.30–7.40 (1 H, m); *m*/*z* 228 (M^+), 184, 169, 155, 141, 128, 115, 103 and 91 (4.3, 100, 9.9, 26.0, 83.9, 36.3, 33.6, 9.5 and 10.8%).

Further elution of the column gave the endo-*adduct* **13a** (15 mg, 74%), mp 108–109 °C (from light petroleum) (Found: C, 78.95; H, 7.2%); ν_{max}(KBr)/cm^{-1} 1744; δ_H(400 MHz) 0.60–0.78 (1 H, apparent qd, *J* 13 and 3), 1.22 (1 H, ddd, *J* 13.5, 4.5 and 0.5, *endo*-methylene-H), 1.34 (1 H, apparent qt, *J* 13.5 and 4), 1.56 (1 H, ddd, *J* 13.5, 3.5 and 1.5), 1.68–1.76 (1 H, m), 1.81 (1 H, qt, *J* 13 and 4), 1.84–1.90 (1 H, m), 1.99 (1 H, dddd, *J* 13.5, 10.5, 5 and 3.5, *exo*-methine-H), 2.13 (1 H, td, *J* 14.5 and 5), 2.57 (1 H, br d, *J* 14.5), 2.68 (1 H, ddd, *J* 13.5, 10.5 and 4.5, *exo*-methylene-H), 5.49 (1 H, d, *J* 4.5, bridgehead methine-H), 7.26 (2 H, overlapping peaks, ArH), 7.37 (1 H, ddd, *J* 7.5, 6 and 3, ArH) and 7.45 (1 H, d, *J* 7.5); δ_C 21.9, 25.7, 26.0, 30.5, 30.95, 35.0, 47.9, 76.7, 122.6, 125.9, 126.85, 128.4, 135.05, 138.5 and 175.8; *m*/*z* 228 (M^+), 184, 169, 155, 141, 128, 115, 103 and 91 (2.7, 100, 6.6, 22.2, 90.8, 34.8, 31.0, 5.8 and 7.2%).

4-(Pent-4-enyl)isochroman-3-one 10c

Prepared from isochroman-3-one and 5-iodopent-1-ene (51% yield) as described above for **10b** (Found: C, 77.75; H, 7.5. $C_{14}H_{16}O_2$ requires C, 77.7; H, 7.4%); ν_{max}(film)/cm^{-1} 1735 and 1640; δ_H 1.45–1.70 (2 H, m), 1.78–1.92 (1 H, m), 1.92–2.05 (1 H, m), 2.05–2.20 (2 H, m), 3.61 (1 H, apparent t, *J* 7.0, methine-H), 4.92–5.10 (2 H, overlapping multiplets, HC=CH_2), 5.24 (1 H, d, *J* 14, benzylic-H), 5.44 (1 H, d, *J* 14, benzylic-H), 5.70–5.88 (1 H, multiplet with fine splitting, *H*C=CH_2) and 7.18–7.40 (4 H, m); *m*/*z* 216 (M^+), 171, 161, 148, 129, 115, 104, 91 and 77 (49.7, 14.1, 56.4, 100, 75.5, 68, 25, 88 and 25.6%).

Methyl 2-(2-hydroxymethylphenyl)hept-6-enoate

A mixture of lactone **10c** (400 mg, 1.85 mmol), aq. sodium hydroxide (2 mol dm^{-3}; 4.5 cm^3) and ethanol (2.0 cm^3) was boiled under reflux for 2 h, cooled, transferred to a separating funnel and ice-cold dilute hydrochloric acid (2 mol dm^{-3}; 10 cm^3) added. The precipitated acid was quickly extracted into pre-cooled (0 °C) ether and treated with an ethereal solution of diazomethane (10 cm^3) at 0 °C. Evaporation of the mixture left a residue which was chromatographed on silica with dichloromethane to give the title compound as an oil (386 mg, 84%) (Found: M^+, 248.1418. $C_{15}H_{20}O_3$ requires *M*, 248.1412); ν_{max}(film)/cm^{-1} 3400 (OH) and 1730 (CO); δ_H 1.22–1.51 (2 H, m), 1.72–1.87 (1 H, m), 2.00–2.20 (3 H, m), 2.94 (1 H, br s, exch. D_2O, OH), 3.61 (3 H, s, CO_2Me), 3.96 (1 H, apparent t, *J* 7.5, methine-H), 4.66 (1 H, d, *J* 12.5, CH_2OH), 4.75 (1 H, d, *J* 12.5, CH_2OH), 4.88–5.04 (2 H, overlapping multiplets, CH=CH_2), 5.68–5.82 (1 H, m with fine splitting, C*H*=CH_2) and 7.19–7.41 (4 H, m); *m*/*z* 248 (M^+), 230, 216, 188, 171, 148, 135, 129, 115 and 91 (2.1, 3.0, 27.3, 11.5, 37.1, 35.5, 8.3, 100, 71.4 and 94.3%).

Methyl 2-(2-formylphenyl)hept-6-enoate

To a stirred solution of oxalyl chloride (1.3 cm^3) in dry dichloromethane (3 cm^3) at −78 °C was added dropwise *via* a syringe dimethyl sulfoxide (1.2 cm^3). The mixture was stirred for 2 min and a solution of the foregoing hydroxy ester (194 mg, 0.782 mmol) in dry dichloromethane (1 cm^3) was added dropwise within 5 min. The mixture was stirred under argon for 20 min at −78 °C after which triethylamine (2.5 cm^3) was added. The mixture was allowed to attain room temperature, poured into ice and diluted with ether and the organic layer washed with dilute hydrochloric acid (0.1 mol dm^{-3}; 50 cm^3) and water. The ether extract was separated, dried ($MgSO_4$) and evaporated to give a residue which was chromatographed on silica with dichloromethane to give the *title compound* as an oil (170 mg, 88%) (Found: M^+, 246.1259. $C_{15}H_{18}O_3$ requires *M*, 246.1255); ν_{max}(film)/cm^{-1} 1745 (CO_2Me), 1700 (CHO) and 1646 (C=C); δ_H 1.25–1.52 (2 H, m), 1.70–1.84 (1 H, m), 2.00–2.10 (2 H, m), 2.20 (1 H, m), 2.10–2.25 (1 H, m), 3.64 (3 H, s, CO_2Me), 4.81 (1 H, apparent t, *J* 7.5, methine-H), 4.88–5.04 (2 H, overlapping multiplet, HC=CH_2), 5.66–5.82 (1 H, m, *H*C=CH_2), 7.41–7.52 (2 H, m), 7.56 (1 H, apparent dt, *J* 7.5 and 1.5), 7.82 (1 H, dd, *J* 7.5 and 1.5) and 10.23 (1 H, s, CHO); *m*/*z* 246 (M^+), 231, 185, 171, 159, 145, 129 and 115 (6.5, 47.1, 17.2, 100, 21.6, 40.7, 68.9 and 67%).

2-(2-Formylphenyl)hept-6-enoic acid 11c

A mixture of the foregoing ester (164 mg, 0.66 mmol), potassium carbonate (184 mg, 1.32 mmol), methanol (7 cm^3) and water (1.5 cm^3) was boiled under reflux for 2 h, cooled, acidified with hydrochloric acid (2 mol dm^{-3}; 25 cm^3) and extracted into dichloromethane. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude acid which was dissolved in dichloromethane and shaken twice with saturated aq. sodium hydrogen carbonate. The sodium hydrogen carbonate extracts were combined and neutralised with concentrated HCl. The acid was extracted into ether, washed with water and dried ($MgSO_4$). Evaporation of the extract under reduced pressure gave the title compound **11c** as an oil (136 mg, 89%) (Found: M^+, 232.1111. $C_{14}H_{16}O_3$ requires *M*, 232.1099); ν_{max}(film)/cm^{-1} 3700–2500br (CO_2H), 1725 and 1695; δ_H 1.22–1.55 (2 H, m), 1.72–1.92 (1 H, m), 1.98–2.25 (3 H, m), 4.69 (1 H, apparent t, *J* 7.5, benzylic methine-H), 4.88–5.02 (2 H, m, HC=CH_2), 5.63–5.82 (1 H, m, *H*C=CH_2), 7.42–7.53 (2 H, m), 7.53–7.65 (1 H, m), 7.81 (1 H, dd, *J* 7.5 and 1.0), 10.18 (1 H, s, CHO) and 10.31 (1 H, br s, CO_2H); δ_C(75 MHz) 26.7, 32.1, 33.35, 45.4, 114.8. 127.7, 128.8, 133.6, 133.9, 134.1, 138.0, 140.2, 178.9 and 193.2; *m*/*z* 232 (M^+), 214, 186, 170, 159, 145, 131, 118, 103 and 91 (9.4, 32.2, 26.8, 52.7, 72.8, 44.7, 100, 75.7, 67.6 and 97.0%).

Generation and intramolecular Diels–Alder cycloaddition of 4-(pent-4-enyl)-2-benzopyran-3-one 12c

The foregoing acid **11c** (25.0 mg, 0.107 mmol) and freshly distilled acetic anhydride (1 cm^3) was boiled under reflux for 1 h. The mixture was cooled and acetic anhydride was evaporated off under reduced pressure to give a crude mixture of adducts **13c** and **14c** (*endo*:*exo* = 7:1) which were separated on silica with benzene–ether (97:3) to give the exo-*adduct* 2,3,3*a*,4,5,9*b*-*hexahydro*-1H-*cyclopenta*[a]*naphthalene*-9*b*,5-*carbolactone* **14c** as an oil (3.0 mg, 10.5%) (Found: M^+, 214.1001. $C_{14}H_{14}O_2$ requires *M*, 214.0993); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1748 (CO); δ_H(400 MHz) 1.29–1.41 (1 H, m), 1.85–1.99 (2 H, m), 2.01–2.15 (5 H, overlapping multiplets, methylenes), 2.62–2.71 (1 H, m), 5.60 (1 H, apparent t, *J* 2.5, methine) and 7.27–7.35 (4 H, m).

Further elution of the column gave the endo-*adduct* **13c** as an oil (17 mg, 74%) (Found: M^+, 214.0999. $C_{14}H_{14}O_2$ requires *M*, 214.0993); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1757; δ_H(400 MHz) 0.65–0.84 (1 H, unresolved multiplet), 1.38 (1 H, dd, *J* 13.5 and 5.5, *endo* methylene-H), 1.82–2.40 (3 H, br multiplet, methylenes), 2.21–2.39 (2 H, m), 2.48–2.65 (2 H, m), 5.60 (1 H, d, *J* 4.5, bridgehead methine-H) and 7.25–7.45 (4 H, overlapping peaks); *m*/*z* 214 (M^+), 170, 155, 141, 128, 115 and 103 (3.3, 100, 17, 93, 39.4, 39.8 and 17%).

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