Synthetic Investigations on Illudinine: A New Synthesis of Methyl 8-Methoxy-2,2-dimethyl-7-oxo-1,2,3,5,6,7-hexahydro-*s*-indacene-4-carboxylate

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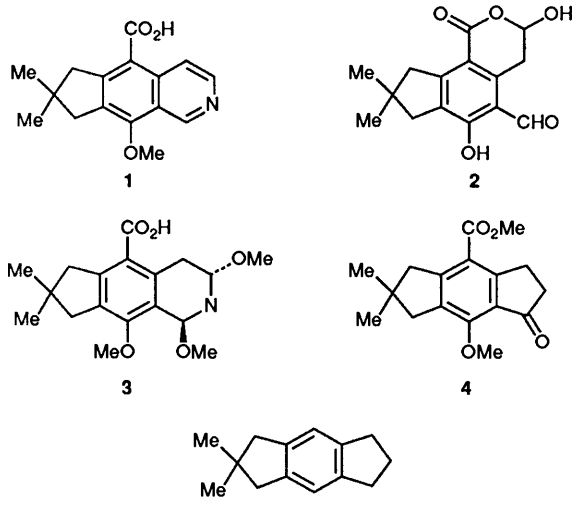
A new strategy for the total synthesis of methyl 8-methoxy-2,2-dimethyl-7-oxo-1,2,3,5,6,7-hexahydro-*s*-indacene-4-carboxylate **4**, a key intermediate in the synthesis of illudalanes, is reported. The key step in this strategy is a new method of preparation of indanones from tetralones. Thus, the furfurylidene derivative of 6-methoxy-3,4-dihydronaphthalen-1-(2*H*)-one is oxidised to the dicarboxylic acid **9a** which is cyclodehydrated to methyl 7-methoxy-1-oxoindan-4-carboxylate **10**. Similar reactions on the tetrahydronaphthalenone **25**, obtained from 6-methoxy-1,2,3,4-tetrahydronaphthalene-7-carbaldehyde **11** by sequential transformations including a regiospecific benzylic oxidation resulted in the hexahydro-*s*-indacenone **4**, thus completing a formal synthesis of illudinine **1**.

The Basidiomycete, *Clitocybe illudens* (Syn: *Omphalotus olearius*), when grown in liquid culture, produces several toxic metabolites possessing antibacterial and antifungal properties. These metabolites are classified as (a) illudalanes (b) protoilludanes and (c) illudanes. Among these, the illudalanes consist of illudinine **1**, illudalic acid **2** and illudacetalic acid **3** (Scheme 1). The isolation and structure elucidation of these compounds was described by Anchel and co-workers[1] and confirmed by synthesis by Woodward and Hoye.[2] In view of their interesting biological activities and unique carbon frame work with diversity of functional groups, these molecules and their analogues[3] have become targets for total synthesis.

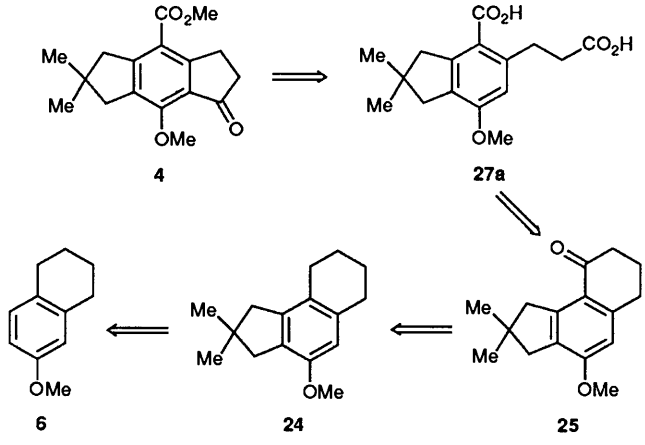


Scheme 1

Woodward and co-workers recognised that these metabolites can be constructed from a common precursor **4** which can be readily made from 2,2-dimethylhexahydro-*s*-indacene[4] **5** by appropriately substituting the aromatic ring. They have successfully realised[2] their objective and, in turn, were able to revise the structure of illudacetalic acid **3**. Our own interest in this area of investigation is to develop a new synthetic strategy for the construction of the substituted hexahydro-*s*-indacenes from readily available aromatic compounds and to elaborate them further into illudinine. We now report our results leading to a new total synthesis of the ketone **4** which has been transformed into illudalanes.

Results and Discussion

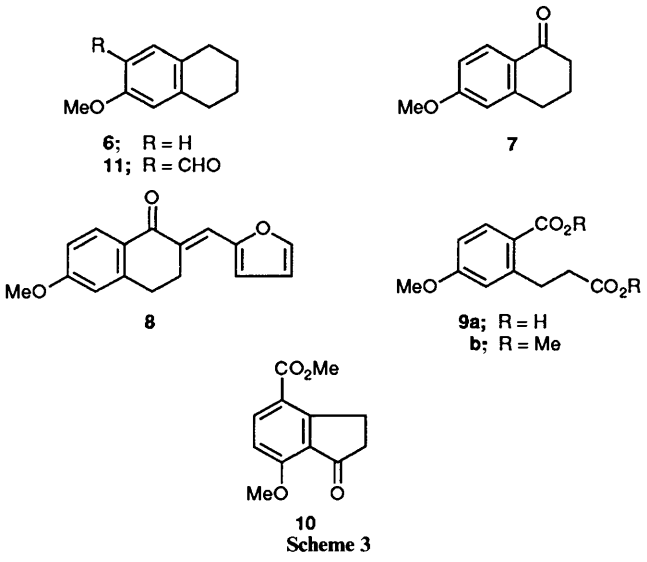
The retrosynthetic protocol of the key intermediate **4** is shown in Scheme 2. The ketone **4** can, in principle, be made



Scheme 2

by the cyclisation of the diacid **27a** which is prepared by the oxidation of the tetralone **25**. This compound can be obtained by the regiospecific oxidation of the tetralin **24** which is derived from the tetralin **6** through a sequential transformation. Thus our main objective in this exercise is to develop working conditions for (i) regiospecific oxidation of the tetralin **24** to tetralone **25**; (ii) oxidation of the tetralone **25** to the dicarboxylic acid **27a** and finally (iii) cyclisation of the diacid **27a** into the hexahydro-*s*-indacene **4**. In order to realise this objective, model experiments were carried out with the tetralin **7** (Scheme 3).

Preparation of 4-Methyl 7-Methoxy-1-oxo-2,3-dihydroindene-4-carboxylate **10**.—Reaction of 1-tetralone **7**, obtained by the oxidation[5] of the tetralin **6**, with 2-furaldehyde in the presence of aqueous sodium hydroxide yielded[6] the furfurylidene derivative **8** (98%). Ozonolysis of **8**, followed by oxidative work-up with 30% hydrogen peroxide in acetic acid gave the dicarboxylic acid **9a** (82%) which was purified *via* its methyl ester **9b**. The acid chloride generated *in situ* from the dicarboxylic acid **9a** was cyclised[7] with anhydrous aluminium chloride in methylene dichloride to give the keto acid which was characterised as its methyl ester **10** (45%).



Scheme 3

Synthesis of the Hexahydro-s-indacenes **4**, **20**, **21** *and* **22**.—Having devised a simple methodology for the conversion of 6-methoxy-1-tetralone **7** into the indenone **10**, we next turned our attention to the synthesis of the hexahydro-*s*-indacenone system as shown in Scheme 4.

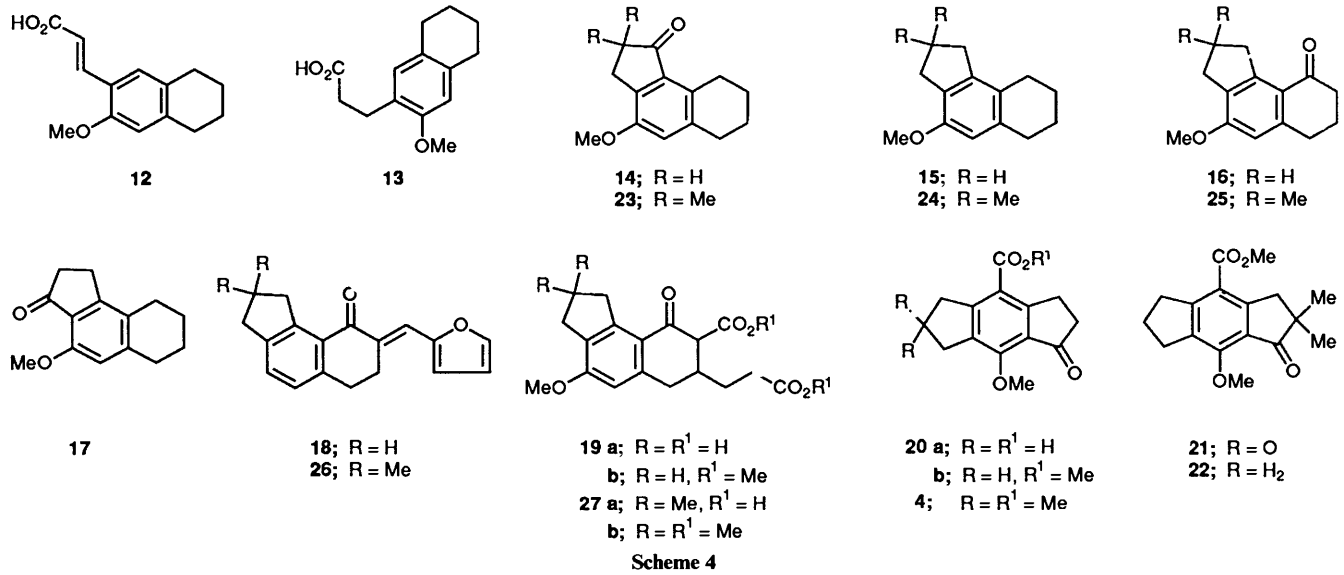
Vilsmeier reaction on the tetralin **6** gave[8] tetrahydronaphthalene **11** (45%) which with malonic acid in pyridine containing a trace of piperdine at 70 °C yielded the cinnamic acid **12** (89%); the latter was reduced with sodium in liquid ammonia[9] to give the propionic acid derivative **13** in quantitative yield. The acid chloride, derived from the acid **13**, was smoothly cyclised with $AlCl_3$–CH_2Cl_2 to afford the benz[*e*]indenone **14**. Clemmensen reduction of the latter with an excess of amalgamated zinc in an ethanolic solution of conc. HCl gave compound **15** (90%) which upon oxidation with anhydrous sodium chromate in acetic acid containing acetic anhydride afforded a mixture of the ketones **16** (53%) and **17** (5%); the former was easily separated by chromatography. The isomeric ketone **17**, was readily distinguished from **16** by significant differences in the ^1H NMR spectrum: thus two benzylic protons at C-1 in **16** appeared at δ 3.32 and were markedly deshielded due to the influence of the carbonyl group.

Reaction of the ketone **16** with 2-furaldehyde in the presence of aqueous sodium hydroxide afforded the furfurylidene derivative **18** (87%). Ozonolysis of the latter followed by oxidative work-up with aqueous hydrogen peroxide (30%) in acetic acid gave cleavage of **18** to the dicarboxylic acid **19a**; this was purified and characterised through its dimethyl ester **19b**. The dicarboxylic acid **19a** was readily cyclised with polyphosphoric acid at 60 °C for 1 h to give the keto acid **20a**, which was esterified with ethereal diazomethane to the methyl ester **20b**. The overall yield of the methyl ester **20b** from **18** amounted to 38%. Other reagents such as aluminium chloride, phosphorus pentoxide, sulphuric acid, hydrofluoric acid and methanesulphonyl chloride were used under a variety of conditions in attempts to effect the cyclisation of the diacid **19a**. In all these cases, either the diacid was recovered unchanged or resulted in poor yield of the keto acid **20a**. The keto ester **20b** was converted into its 2,2-dimethyl derivative **21** by alkylation with methyl iodide–potassium *tert*-butoxide (68% yield). Clemmensen reduction of the ketone **21** afforded the hexahydroindacene **22** (78%), the physical properties and spectral data of which were identical with those reported[2] in the literature. This compound was regiospecifically oxidised to the ketone **4** which was subsequently transformed into the illudalanes by Woodward and Hoye.[2] Hence the above reaction sequence from 6-methoxytetralin constituted a formal synthesis of illudalanes.

Having established a workable procedure for the construction of the hexahydro-*s*-indacenes **20**, **21** and **22**, an alternative and efficient route to the ketone **4** has been devised and is detailed below.

Alkylation of the indanone **14** with an excess methyl iodide and sodium hydride in DMF (dimethylformamide) afforded the 2,2-dimethyl derivative **23** in 86% yield which was reduced to the compound **24** (92%) under Clemmensen reduction conditions. Regiospecific oxidation of **24** exclusively proceeded at the benzylic position *para* to the electron rich methoxy group and resulted in the ketone **25** in 58% yield. The compound **25** readily formed the furfurylidene derivative **26** which was subjected to the oxidative cleavage resulting in the dicarboxylic acid **27a**, purified and characterized through its dimethyl ester **27b**. PPA (polyphosphoric acid) cyclisation of the diacid **27a** proceeded smoothly to afford the hexahydro-*s*-indacene **4** (51%), identical with the compound obtained by the oxidation of the hexahydro-*s*-indacene **22**.

Indanones are converted[11] into the corresponding lactams by the Schmidt reaction using NaN_3–H_2SO_4. These lactams are reduced and finally dehydrogenated to the isoquinolines. We have investigated this reaction on some indanones including the ketone **4** and obtained the lactams. The transformation of these compounds into isoquinolines is currently under progress. This



Scheme 4

methodology will complete the total synthesis of illudinine **1** and these results will be reported elsewhere.

Experimental

M.p.s and b.p.s are uncorrected. IR spectra were recorded as liquid films or Nujol mulls on a Perkin-Elmer model 781 and Hitachi 750–50 spectrometer; ^{1}H NMR spectra were recorded on a Varian T-60, and JEOL FX-90Q spectrometers in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in ppm using TMS (tetramethylsilane) as an internal standard. *J* values are given in Hz. Mass spectra were recorded on a JEOL MS-DX 303 with a built in direct inlet system. ^{13}C NMR spectra were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer in $CDCl_3$ solutions. Microanalyses were carried out using a Carlo Erba 1106 instrument. All anhydrous solvents were prepared by standard procedures. Analytical TLC was performed on glass plates coated with Acme's silica gel G (containing 13% calcium sulphate as the binder) and various combinations of hexane and ethyl acetate were used as eluents. Visualisation of the spots was accomplished by exposure to iodine vapour. Acme's silica gel (60–120 mesh) was used for column chromatography. Work-up usually involved dilution of the reaction mixture with water, extraction with ether, washing of the extract with water, brine and water followed by drying (Na_2SO_4) and evaporation under reduced pressure. The residue was purified by chromatography on silica gel and the product was eluted with hexane containing ethyl acetate (5%).

2-Furfurylidene-6-methoxy-3,4-dihydronaphthalen-1(2H)-one **8**.—To an ice cooled solution of 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **7** (800 mg, 4.5 mmol) in 95% ethanol was added, under nitrogen, aqueous sodium hydroxide (20%; 0.9 cm^3, 4.5 mmol). The mixture was then stirred whilst 2-furaldehyde (0.37 cm^3, 4.5 mmol) in water (3.7 cm^3) was added; stirring was then continued for 3 h. The product was filtered off and recrystallised from ethanol to give the furfurylidene derivative **8** (1.09 g, 95%); m.p. 112–14 °C (Found: M$^+$, 254.0924. $C_{16}H_{14}O_3$ requires *M*, 254.0943) (Found: C, 75.7; H, 5.5; $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.6%); ν_{max}/cm^{-1} 1650, 1600 and 1580; δ_H 2.89–3.03 (2 H, m, allylic), 3.25–3.39 (2 H, m, $ArCH_2$), 3.87 (3 H, s, OCH_3), 6.48–7.5 (6 H, m, C=CH, ArH, furan-H) and 8.08 (1 H, d, *J* 8.8, ArH).

3-(2-Carboxy-5-methoxyphenyl)propionic Acid **9a**.—Ozone was bubbled through a cold (−70 °C) solution of the furfurylidene derivative **8** (250 mg, 1 mmol) in dry ethyl acetate (5 cm^3) until the solution turned blue. Excess of ozone was removed by bubbling nitrogen through the reaction mixture. The ozonide was stirred with glacial acetic acid (10 cm^3), 30% H_2O_2 (2 cm^3) and water (5 cm^3) for 12 h, after which the solution was concentrated under reduced pressure and the residue was worked up with ethyl acetate (3 × 50 cm^3) to afford **9a** (182 mg, 82%), m.p. 195–197 °C (lit.,[6] m.p. 196 °C).

The above acid **9a** was esterified with ethereal diazomethane (200 mg) affording the methyl ester **9b** as a viscous liquid (Found: M$^+$, 252.1002. $C_{13}H_{16}O_5$ requires *M*, 252.0998); ν_{max}/cm^{-1} 1735, 1605, 1565 and 1495; δ_H 2.47–2.67 (2 H, m, $CH_2CO_2CH_3$), 3.13–3.3 (2 H, m, $ArCH_2$), 3.6 (3 H, s, $CH_2CO_2CH_3$), 3.74 (3 H, s, $ArCO_2CH_3$), 3.77 (3 H, s, OCH_3), 6.64–6.74 (2 H, m, *o*-CH_3OArH) and 7.85 (1 H, d, *J* 8, *m*-CH_3OArH).

Methyl 7-Methoxy-1-oxoindan-4-carboxylate **10**.—To an ice cooled solution of the acid chloride, prepared from the acid **9a** (224 mg, 1 mmol) and thionyl chloride, in dry CH_2Cl_2 (20 cm^3) at 5–10 °C, aluminium chloride (147 mg, 1.1 mmol) was slowly added with stirring. The resulting orange coloured solution was stirred at room temperature for 30 min, and poured into ice cold water. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were worked up to yield the keto acid which was esterified with ethereal diazomethane (100 mg). The methyl ester **10** was purified by chromatography using ethyl acetate–hexane (2:3) and crystallised from ethyl acetate–hexane (1:9) to afford white crystals (100 mg, 45%), m.p. 126–129 °C (Found: C, 65.0; H, 5.5. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.5%); ν_{max}/cm^{-1} 1710, 1602, 1584 and 1494; δ_H 2.6–2.76 (2 H, m, CH_2CO), 3.37–3.53 (2 H, m, $ArCH_2$), 3.93 (3 H, s, CO_2CH_3), 4.03 (3 H, s, OCH_3), 6.87 (1 H, d, *J* 8, *o*-CH_3OArH) and 8.23 (1 H, d, *J* 8, *m*-CH_3OArH).

6-Methoxy-1,2,3,4-tetrahydronaphthalene-7-carbaldehyde **11**.—The Vilsmeier reagent was prepared by the slow addition of phosphoryl chloride (6.5 g, 42.5 mmol) to dry DMF (2.98 g, 39.7 mmol) at 0 °C. A stirred mixture of the above reagent and 6-methoxy-1,2,3,4-tetrahydronaphthalene **6** (5.9 g, 36.4 mmol) was heated at 90–100 °C for 5 h and then cooled. Saturated aqueous sodium acetate was then added to the reaction mixture which was boiled for 5 min. Work-up with ether (3 × 100 cm^3) followed by purification by column chromatography (ethyl acetate–hexane 1:20) afforded the aldehyde **11** (2.9 g, 42%) which after recrystallisation from hexane gave white crystals, m.p. 52–54 °C (Found: C, 76.1; H, 7.6. Calc. for $C_{12}H_{14}O_2$; C, 75.8; H, 7.4%); ν_{max}/cm^{-1} 2856, 1688, 1612 and 1500; δ_H 1.78 (4 H, m, $ArCH_2CH_2$), 2.72 (4 H, m, $ArCH_2$), 3.87 (3 H, s, OCH_3), 6.65 (1 H, s, *o*-CH_3OArH), 7.52 (1 H, s, *o*-CHOArH) and 10.37 (1 H, s, CHO).

E-3-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)prop-2-enoic Acid **12**.—A mixture of the aldehyde **11** (12 g, 62.5 mmol), malonic acid (10 g, 115 mmol) and piperdine (0.5 cm^3) in dry pyridine (20 cm^3) was heated at 70 °C for 6 h. The reaction mixture was cooled and poured onto crushed ice (100 g) containing conc. HCl (20 cm^3). The precipitate was filtered off, washed with cold dilute HCl and ice cold water and dried. The product was crystallised from acetone to yield the *acid* **12** (13.1 g, 89%), m.p. 195–197 °C (Found: C, 72.5; H, 7.0; $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%); ν_{max}/cm^{-1} 3300, 1695, 1605 and 1505; δ_H 1.77 (4 H, m, $ArCH_2CH_2$), 2.47–2.97 (4 H, m, $ArCH_2$), 3.8 (3 H, s, OCH_3), 6.37 (1 H, d, *J* 17, =C*H* CO_2H), 6.6 (1 H, s, *o*-CH_3OArH), 7.17 (1 H, s, *m*-CH_3OArH) and 7.83 (1 H, d, *J* 17, C*H*=$CHCO_2H$).

3-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)propionic Acid **13**.—Sodium metal (5 g) was added in small pieces to a stirred solution of the unsaturated acid **12** (13.5 g,) in liquid ammonia (300 cm^3) as rapidly as the metal dissolved. After the addition of the metal was complete, stirring was continued for an additional period of 30 min and the reaction mixture was quenched with solid ammonium chloride. Ammonia was allowed to evaporate from the reaction mixture and the residue was worked up by cautious addition of water followed by extraction with ether to remove any neutral products. The aqueous extract was cooled and acidified with 2 mol dm^{-3} HCl. The precipitated acid was filtered off, washed with water and dried. Recrystallisation from water gave the pure *acid* **13** (12.9 g, 95%) m.p. 109 °C (Found: C, 71.4; H, 8.0. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); ν_{max}/cm^{-1} 3300, 1710 and 1505; δ_H 1.77 (4 H, m, $ArCH_2CH_2$), 2.4–2.97 (8 H, m, $ArCH_2$ and CH_2CO_2H), 3.78 (3 H, s, OCH_3), 6.5 (1 H, s, *o*-CH_3OArH) and 6.8 (1 H, s, *m*-CH_3OArH).

4-Methoxy-2,3,6,7,8,9-hexahydrobenz[e]inden-1-one **14**.—Cyclisation of the acid chloride, prepared from the acid **13** (1.86 g, 7.9 mmol) and thionyl chloride (0.62 cm^3), 8.5 mmol), with $AlCl_3$ (1.08 g, 8.08 mmol) as described above for **9a** yield the *ketone* **14** (1.02 g, 60%). Recrystallisation of this from hexane gave an analytically pure sample, m.p. 96–98 °C (Found: C, 77.9; H, 7.4. $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.5%); ν_{max}/cm^{-1} 1695,

1605 and 1500; $\delta_H(CCl_4)$ 1.72 (4 H, m, $ArCH_2CH_2$), 2.33–3.17 (8 H, complex, $ArCH_2$ and CH_2CO), 3.78 (3 H, s, OCH_3) and 6.5 (1 H, s, ArH).

4-*Methoxy*-2,3,6,7,8,9-*hexahydro*-1H-*benz*[e]*indene* **15**.—A solution of the ketone **14** (7.82 g, 36.2 mmol) in 95% ethanol (40 cm^3) was added to a mixture of freshly prepared amalgamated zinc dust (40 g), water (12 cm^3), conc HCl (40 cm^3) and ethanol (8 cm^3). The mixture was heated under reflux for 20 h, cooled, decanted from insoluble zinc and the residue was worked up with ether. Chromatographic purification gave the *hydrocarbon* **15** (6.55 g, 90%). This was crystallised from hexane to afford white crystals, M.p. 97–98 °C (Found: C, 83.6; H, 9.1. $C_{14}H_{18}O$ requires C, 83.1; H, 9.0%); ν_{max}/cm^{-1} 2920, 1599, 1494 and 1464; δ_H 1.7 (4 H, m, $ArCH_2CH_2$), 2.0 (2 H, m, $ArCH_2CH_2CH_2$), 2.3–2.95 (8 H, m, $ArCH_2$), 3.7 (3 H, s, OCH_3), and 6.3 (1 H, s, ArH); δ_C 23.57 (2 × CH_2), 24.65, 26.38, 29.42, 30.07, 31.48, 55.21, 108.84, 125.09, 128.88, 136.14, 144.81 and 153.91; *m/z* 202 (M^+, 100%).

4-*Methoxy*-2,3,6,7,-*tetrahydro*-1H-*benz*[e]*inden*-9(8H)-*one* **16**.—Anhydrous sodium chromate (500 mg, 3.09 mmol) was added to a solution of the hydrocarbon **15** (170 mg, 0.84 mmol) in glacial acetic acid (1.4 cm^3) and acetic anhydride (0.75 cm^3) and the mixture stirred at 30 °C for 24 h. It was then diluted with water, neutralised with aqueous sodium carbonate and worked up to yield the *ketone* **16** (96 mg, 53%) which crystallised from hexane as white crystals, m.p. 112 °C (Found: C, 77.8; H, 7.5 $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.5%); ν_{max}/cm^{-1} 1662, 1590 and 1464; δ_H 1.84–2.3 (4 H, m, $ArCOCH_2CH_2$, $ArCH_2CH_2CH_2Ar$), 2.56 (2 H, m), 2.8 (2 H, m), 2.92 (2 H, m), 3.32 (2 H, m), 3.88 (3 H, s, OCH_3) and 6.52 (1 H, s, ArH); δ_C 23.1, 24.27, 28.04, 30.51, 34.67, 39.61, 54.7, 107.37, 122.46, 130.91, 146, 148.47, 158.62 and 197.37; *m/z* 216 (M^+, 100%).

Further elution with 1:4 ethyl acetate–hexane yielded the isomeric *ketone* **17** (10 mg, 6%) as a crystalline solid, m.p. 147 °C (Found: C, 77.7; H, 7.5. $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.5%); ν_{max}/cm^{-1} 1692, 1602 and 1590; δ_H 1.84 (4 H, m, $ArCH_2CH_2$), 2.4–3.0 (8 H, m, $ArCH_2$ and $ArCOCH_2$), 3.92 (3 H, s, OCH_3) and 6.5 (1 H, s, ArH); *m/z* 2.16 (M^+, 65%).

8-*Furfurylidene*-4-*methoxy*-2,3,6,7-*tetrahydro*-1H-*benz*[e]*inden*-9(8H)-*one* **18**.—Condensation of the ketone **16** (1.58 g, 7.3 mmol) with 2-furaldehyde (0.6 cm^3, 7.3 mmol) as described above for **7** yielded the crystalline *furfurylidene derivative* **18** (1.87 g, 87%) which recrystallised from ethanol as an yellow solid, m.p. 140 °C (Found: C, 77.5; H, 6.1. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%); ν_{max}/cm^{-1} 1656, 1596 and 1464; δ_H 2.0 (2 H, m, $ArCH_2CH_2CH_2$) 2.45–3.4 (8 H, m, allyic and $ArCH_2$), 3.75 (3 H, s, OCH_3) and 6.2–7.4 (5 H, m, >=C–H, ArH and furan-H); δ_C 24.66, 26.87, 28.43, 29.21, 34.8, 55.09, 107.79, 111.29, 115.18, 121.16, 123.37, 131.56, 133.12, 143.66, 145.22, 149.51, 152.5, 158.88 and 186.58; *m/z* 294 (M^+, 100%).

5-(2-*Carboxyethyl*)-7-*methoxyindan*-4-*carboxylic Acid* **19a**.—Ozonolysis of the furfurylidene derivative **18** (0.457 g, 1.55 mmol) was carried out as described above for **8** to afford, the crude dicarboxylic *acid* **19a** which was crystallised from acetone, m.p. 111 °C, ν_{max}/cm^{-1} 1697, 1677, 1587 and 1458, $\delta_H([^2H_6]$-Acetone) 1.8–2.24 (2 H, m, $ArCH_2CH_2CH_2$) 2.4–3.4 (8 H, complex, $ArCH_2$ and CH_2CO_2H) 3.88 (3 H, s, OCH_3) and 6.8 (1 H, s, ArH). The crude dicarboxylic acid **19a** was esterified with ethereal diazomethane (300 mg), chromatographed on silica gel and eluted with ethyl acetate–hexane (1:20) to yield the *diester* **19b** (0.303 g, 66.74%) as a colourless liquid (Found: M^+ 292.1310. $C_{10}H_{20}O_5$ requires *M*, 292.1311); ν_{max}/cm^{-1} 1735, 1716 and 1593; δ_H 2.06 (2 H, m, $ArCH_2CH_2CH_2$), 2.56–3.32 (8 H, m, $ArCH_2$ and $CH_2CO_2CH_3$), 3.72 (3 H, s, CO_2CH_3), 3.88 (3 H, s, CO_2CH_3), 3.9 (3 H, s, OCH_3) and 6.6 (1 H, s, ArH); *m/z* 292 (M^+, 15%).

8-*Methoxy*-7-*oxo*-1,2,3,5,6,7-*hexahydro*-s-*indacene*-4-*carboxylic Acid* **20a** *and Methyl* 8-*Methoxy*-7-*oxo*-1,2,3,5,6,7-*hexahydro*-s-*indacene*-4-*carboxylate* **20b**.—A mixture of polyphosphoric acid, prepared from phosphorus pentoxide (200 mg) and orthophosphoric acid (*d* 1.8; 0.2 cm^3), was maintained at 80–90 °C for 1 h. It was then cooled to room temp. when the crude acid **19a** (53 mg, 0.2 mmol) was added to it and the whole stirred at 60 °C for 0.5 h. Ice was added to the mixture which was then worked up with ether (3 × 30 cm^3) to yield the keto acid **20a**. This was treated with ethereal diazomethane (100 mg). The product, after work-up, was chromatographed on silica gel (5 g) and eluted with 1:9 ethyl acetate–hexane to afford the keto *ester* **20b** as a solid (25 mg, 38% from **18**) which was recrystallised from hexane, m.p. 100 °C (Found: C, 68.8; H, 6.1; $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2%); ν_{max}/cm^{-1} 1713, 1593 and 1464; δ_H 2.1 (2 H, m, $ArCH_2CH_2CH_2$), 2.52–2.84 (2 H, m, $ArCOCH_2$), 2.96 (2 H, m, *o*-CH_3OArCH_2) 3.12–3.52 (4 H, m, $ArCH_2$), 3.92 (3 H, s, CO_2CH_3) and 4.06 (3 H, s, OCH_3); *m/z* 260 (M^+, 100%).

Methyl 8-*Methoxy*-2,2-*dimethyl*-1-*oxo*-1,2,3,5,6,7-*hexahydro*-s-*indacene*-4-*carboxylate* **21**.—To a mixture of the ketone **20b** (260 mg, 1 mmol) and potassium *tert*-butoxide [prepared from potassium (100 mg, 2.5 mmol) and *tert*-butyl alcohol (3 cm^3)] under nitrogen was added methyl iodide (0.19 cm^3, 3 mmol) in dry benzene (2 cm^3); the mixture was then stirred for 12 h at room temp. The product, obtained after ether work-up, was chromatographed on silica gel and eluted with ethyl acetate–hexane (1:30) to give the dimethylated *ketone* **21** (197 mg, 68%) as a white solid which was recrystallised from hexane, m.p. 88–90 °C (Found; M^+, 288.1332. $C_{17}H_{20}O_4$ requires *M*, 288.1362); ν_{max}/cm^{-1} 1713, 1590 and 1470; δ_H 1.14 (6 H, s, 2 × CH_3), 2.04 (2 H, m, $ArCH_2CH_2CH_2$), 2.9 (2 H, m, *o*-$CH_3O_2CArCH_2$), 3.16 [2 H, s, $ArCH_2C(CH_3)_2$], 3.22 (2 H, m, *o*-$CH_3O_2CArCH_2$), 3.82 (3 H, s, CO_2CH_3) and 4.00 (3 H, s, OCH_3); *m/z* 288 (M^+, 2%).

Methyl 8-*Methoxy*-2,2-*dimethyl*-1,2,3,5,6,7-*hexahydro*-s-*indacene*-4-*carboxylate* **22**.—The keto ester **21** (350 mg, 1.215 mmol) was added to a mixture of freshly prepared amalgamated zinc dust (1.5 g), water (0.5 cm^3) and conc. HCl (1.5 cm^3), and heated under refluxed for 5 h at 100 °C. The reaction mixture was then cooled, decanted from zinc residue and worked up with ether (3 × 50 cm^3). Evaporation of the solvent followed by elution with ethyl acetate–hexane (1:50) in a silica gel column afforded the pure ester **22** (260 mg, 78%), m.p. 48–52 °C (lit.,[2] 50.5–56 °C) (Found M^+, 274.1577. Calc. for $C_{17}H_{22}O_3$: *M*, 274.1569); ν_{max}/cm^{-1} 1716, 1575 and 1470; δ_H 1.08 (6 H, s, 2 × CH_3), 2.0 (2 H, m, $ArCH_2CH_2CH_2$), 2.68 [2 H, s, *o*-$CH_3OArCH_2C(CH_3)_2$], 2.86 (2 H, m, *o*-$CH_3OArCH_2CH_2$), 2.94 [2 H, s, *o*-$CH_3O_2CArCH_2C(CH_3)_2$], 3.12 (2 H, m, *o*-$CH_3O_2CArCH_2CH_2$) and 3.80 (6 H, s, CO_2CH_3 and OCH_3); *m/z* 274 (M^+, 100%).

4-*Methoxy*-2,2-*dimethyl*-2,3,6,7,8,9-*hexahydro*-1H-*benz*[e]-*inden*-1-*one* **23**.—A mixture of sodium hydride (50% dispersion; 1.74 g, 40 mmol) freed from mineral oil and the ketone **14**, (2.16 g, 10 mmol) in dry DMF (12 cm^3) was stirred at room temp. for 30 min; it was then cooled to 0 °C. To this mixture, a solution of methyl iodide (1.4 cm^3, 22.5 mmol) in dry DMF was added. After being stirred for 12 h the reaction mixture was worked up to yield the dialkyl *ketone* **23** (2.09 g, 86%) as colourless crystals which were recrystallised from ethyl acetate–hexane (1:50); m.p. 86–88 °C (Found: C, 78.7; H, 8.3. $C_{16}H_{20}O_2$ requires C, 78.6; H, 8.3%); ν_{max}/cm^{-1} 1695, 1605 and 1495;

$\delta_H(CCl_4)$ 1.16 (6 H, s, 2 × CH_3), 1.78 (4 H, m, $ArCH_2CH_2$), 2.5–3.23 (6 H, m, $ArCH_2$), 3.8 (3 H, s, OCH_3) and 6.66 (1 H, s, ArH).

4-*Methoxy*-2,2-*dimethyl*-2,3,6,7,8,9-*hexahydro*-1H-*benze*[e]-*indene* **24**.—Reduction of the ketone **23** (6 g, 24.6 mmol) with amalgamated zinc dust and HCl as described above for **14** gave the *hydrocarbon* **24** (5.2 g, 92%) which recrystallised from hexane as white crystals; m.p. 75–77 °C (Found: C, 83.4; H, 9.8. $C_{16}H_{22}O$ requires C, 83.4; H, 9.6%); ν_{max}/cm^{-1} 1600 and 1495; δ_H 1.2 (6 H, s, 2 × CH_3), 1.8 (4 H, m, $ArCH_2CH_2$), 2.64 (8 H, m, $ArCH_2$), 3.8 (3 H, s, OCH_3) and 6.4 (1 H, s, ArH).

4-*Methoxy*-2,2-*dimethyl*-2,3,6,7,8,9-*hexahydro*-1H-*benz*[e]-*inden*-9-*one* **25**.—A solution of the above hydrocarbon **24** (1.436 g, 6.24 mmol), glacial acetic acid (7.5 cm^3) and acetic anhydride (4 cm^3) was stirred with anhydrous sodium chromate (3 g, 18.5 mmol) at 30 °C for 24 h. Work-up yielded the *ketone* **25** (876 mg, 58%) as a yellow solid, which was recrystallised from hexane–ether, m.p. 79–81 °C (Found M^+ 244.1443. $C_{16}H_{20}O_2$ requires *M*, 244.1463) (Found: C, 78.5; H, 8.2. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.3%); ν_{max}/cm^{-1} 1670, 1590 and 1465; δ_H 1.18 (6 H, s, 2 × CH_3), 1.96–2.24 (2 H, m, $ArCOCH_2CH_2$), 2.44–2.68 (2 H, m, $ArCOCH_2$), 2.62 [2 H, s, *o*-$CH_3OArCH_2C(CH_3)_2$], 2.8–3.06 (2 H, m, $ArCH_2$), 3.18 [2 H, s, *m*-$CH_3OArCH_2C(CH_3)_2$], 3.9 (3 H, s, OCH_3) and 6.52 (1 H, s, ArH).

8-*Furfurylidene*-4-*methoxy*-2,2-*dimethyl*-2,3,6,7,8,9-*hexahydro*-1H-*benze*[e]*inden*-9-*one* **26**.—Condensation of the ketone **25** (1.8 g, 7.3 mmol) with 2-furaldehyde (0.6 cm^3, 7.3 mmol) as described above for **7** gave the furfurylidene derivative **26** (2.16 g, 91%) as a yellow solid which was recrystallised from hexane–ether, m.p. 126–129 °C (Found: M^+, 322.1569. $C_{21}H_{22}O_3$ requires *M*, 322.1569) (Found: C, 78.0; H, 7.0. $C_{21}H_{22}O_3$ requires C, 78.2; H, 6.9%); ν_{max}/cm^{-1} 1660 and 1590; δ_H 1.13 (6 H, s, 2 × CH_3), 2.6 [2 H, s, *o*-$CH_3OArCH_2C(CH_3)_2$], 2.87–3.34 (6 H, m, $ArCH_2$ and allylic), 3.87 (3 H, s, OCH_3) and 6.47–7.53 (5 H, m, C=CH ArH and furan–H).

5-(2-*Carboxyethyl*)-7-*methoxy*-2,2-*dimethylindan*-4-*carboxylic Acid* **27a**.—Ozonolysis of the furfurylidene derivative **26** (180 mg, 0.56 mmol) in dry ethyl acetate (20 cm^3) followed by work-up with the addition of glacial acetic acid (10 cm^3), 30% H_2O_2 (2 cm^3) and water (5 cm^3) gave the diacid **27a** (115 mg, 70%) which was recrystallised from ether–hexane, m.p. 130–32 °C; ν_{max}/cm^{-1} 1710, 1690, 1590 and 1450; δ_H 1.13 (6 H, s, 2 × CH_3), 2.3–3.4 (8 H, m, $ArCH_2$ and CH_2CO_2H), 3.77 (3 H, s, OCH_3), 6.66 (1 H, s, ArH) and 10.33 (1 H, br, CO_2H).

The above acid **27a** was esterified with ethereal diazomethane (200 mg) and worked up to yield the *diester* **27b** as a colourless liquid (Found: C, 67.8; H, 7.3. $C_{18}H_{24}O_5$ requires C, 67.5; H, 7.6%); ν_{max}/cm^{-1} 1735, 1715, 1590 and 1435; δ_H 1.06 (6 H, s, 2 × CH_3), 2.56 (2 H, s, *o*-CH_3OArCH_2), 2.44–2.72 (2 H, m, $CH_2CO_2CH_3$), 2.82 [2 H, s, *o*-$CH_3O_2CArCH_2C(CH_3)_2$], 2.92–3.2 (2 H, m, $ArCH_2CH_2$), 3.62 (3 H, s, CO_2CH_3), 3.78 (3 H, s, CO_2CH_3), 3.8 (3 H, s, OCH_3) and 6.52 (1 H, s, ArH).

Methyl 8-*Methoxy*-2,2-*dimethyl*-7-*oxo*-1,2,3,5,6,7-*hexahydro*-s-*indacene*-4-*carboxylate* **4**.—Cyclisation of the diacid **27a** (50 mg, 0.17 mmol) with polyphosphoric acid, prepared from phosphorus pentoxide (200 mg) and orthophosphoric acid (0.1 cm^3) as described for compound **19a** gave the keto acid which was esterified with ethereal diazomethane (100 mg) and worked up to yield the keto ester **4** (25 mg; 51%) which was recrystallised from hexane, m.p. 102 °C (lit.,[2] 100.5–102 °C) (Found: 288.1358. Calc. for $C_{17}H_{20}O_4$: 288.1362); ν_{max}/cm^{-1} 1710, 1593 and 1470; δ_H 1.16 (6 H, s, 2 × CH_3) 2.56–2.76 (2 H, m, $ArCOCH_2$), 2.8 [2 H, s, *o*-$CH_3OArCH_2C(CH_3)_2$], 3.1 [2 H, s, *o*-$CH_3O_2CArCH_2C(CH_3)_2$], 3.24–3.46 [2 H, m, $ArCOCH_2CH_2$), 3.92 (3 H, s, CO_2CH_3) and 4.04 (3 H, s, OCH_3); *m/z* 288 (M^+, 100%).

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