Use of the Electrophilic Arylation Reaction of Aryllead Triacetates in Syntheses of (±)-*O*-Methyljoubertiamine and (±)-Mesembrine

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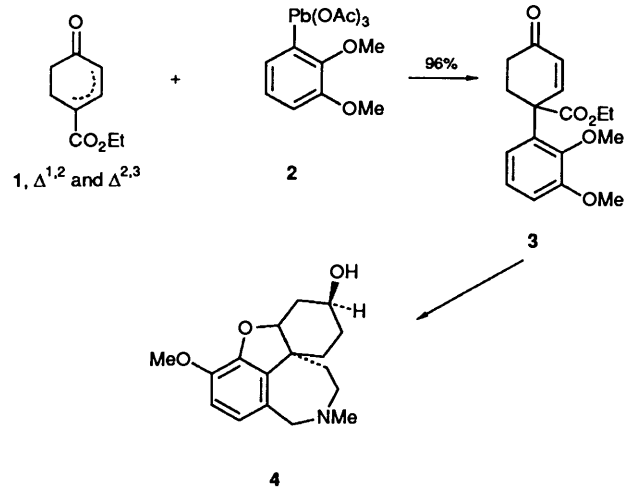
p-Methoxyphenyllead triacetate and 3,4-dimethoxyphenyllead triacetate are used as electrophilic arylating agents to generate the quaternary benzylic centres in formal syntheses of (±)-*O*-methyljoubertiamine and (±)-mesembrine respectively.

Electrophilic arylation of soft carbon nucleophiles by aryllead triacetates has been shown by us to be an efficient method for the generation of a quaternary benzylic centre.[1] The usefulness of the method has been illustrated in a synthesis of the *Amaryllidaceae* alkaloid, (±)-lycoramine **4**,[2] where the regiospecific arylation of the isomeric mixture of keto esters **1** by 2,3-dimethoxyphenyllead triacetate **2** produced the key intermediate **3** (Scheme 1). Clearly, this approach was potentially useful for the synthesis of a wide range of related *Amaryllidaceae* and *Aizoaceae* alkaloids.



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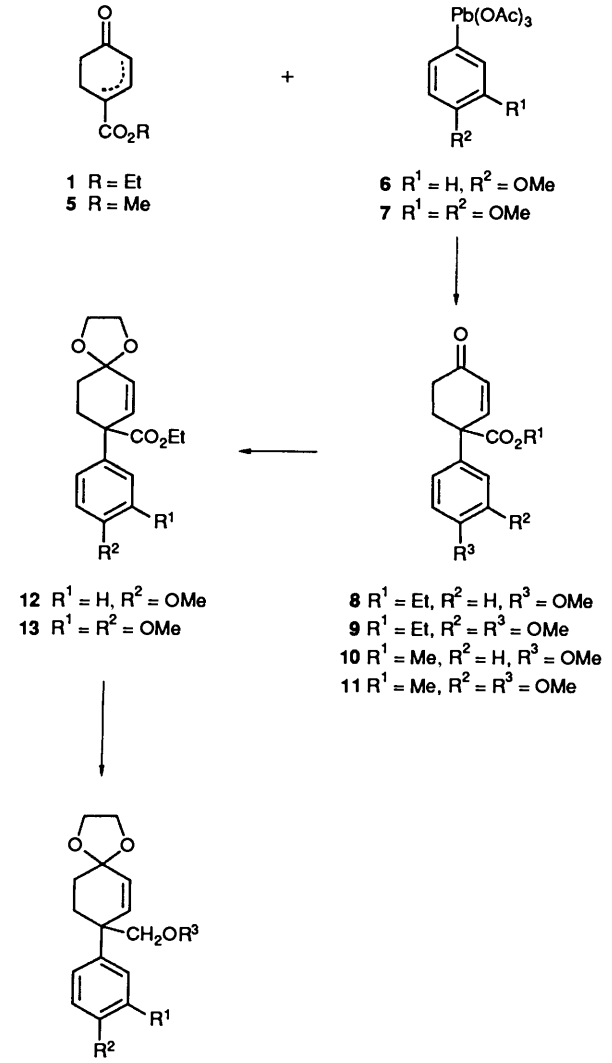
Scheme 1

In our preliminary report of the above route to the (±)-lycoramine synthon **3**,[3] we also outlined syntheses of the keto esters **8** and **9** (see Scheme 2), potentially useful intermediates for the synthesis of (±)-*O*-methyljoubertiamine **23** and (±)-mesembrine **25** respectively. We subsequently presented the details of some of that work,[4] and we now report on improvements in the arylation steps, and completion of formal syntheses of the alkaloids **23** and **25**.

Although lycoramine **4** might appear to be a more challenging synthetic target than compounds **23** and **25**, the need to retain the double bond of the enone system in these cases did present a potential difficulty, which will be outlined below. Conjugate addition of oxygen to the double bond, to produce the dihydrofuran ring in the lycoramine synthesis, led to intermediates which were more stable in the chain extension of the ethoxycarbonyl group.

Yields for the arylation of the mixture of vinylogous β-keto esters **1** proved to be dependent on the nature of substitution in the aromatic ring. Whereas 2,3-dimethoxyphenyllead triacetate **2** reacted with esters **1** to give the intermediate **3** in almost quantitative yield when 20% excess of the reagents was employed, reactions of *p*-methoxyphenyllead triacetate **6** and



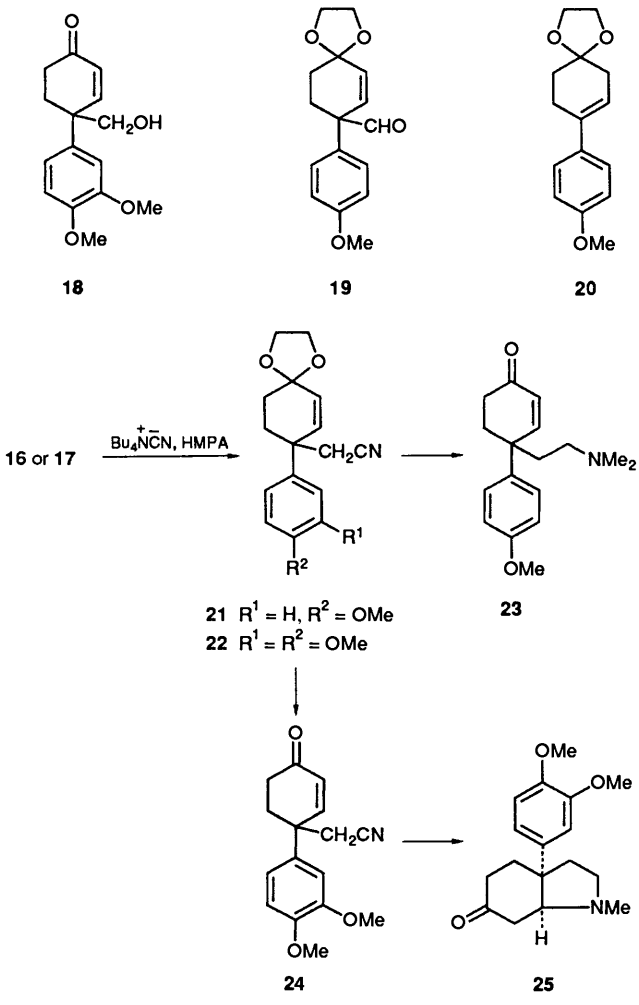
Scheme 2

3,4-dimethoxyphenyllead triacetate **7** gave considerably lower yields (53–69%) of the corresponding arylated keto esters, **8** and **9** respectively, even with a 50% excess of aryllead reagent. Similar yields were obtained in dimethyl sulphoxide, or in chloroform containing pyridine or 1,10-phenanthroline. The syntheses of **23** and **25** were completed by using the intermediates **8** and **9** respectively; however, since their

completion, we have found that by use of the mixture of isomeric methyl esters **5**, rather than the ethyl esters, in the arylation step, the arylated keto esters **10** and **11** may be obtained in *ca.* 90% yield under our usual arylation conditions (chloroform, pyridine, 55 °C). Thus, overall yields of compounds **23** and **25** by our new approach are comparatively good.

For both syntheses protection of the keto group was required at this stage, and this was readily achieved by formation of the corresponding ethylene ketals **12** and **13** in high yield in the usual way. Completion of both syntheses then required the conversion of the ethoxycarbonyl groups of the compounds **12** and **13** into aminoethyl groups by the route we had successfully used in our lycoramine **4** synthesis.[2] Lithium aluminium hydride reduction of esters **12** and **13** yielded the acid sensitive alcohols **14** and **15** respectively; the latter compound slowly produced the corresponding ketone **18** on being kept at room temperature. Both alcohols were readily converted in high overall yield into the corresponding toluene-*p*-sulphonates **16** and **17** in the usual way. Pearson[5] had obtained the ester **16** in a related synthesis of *O*-methyljoubertiamine **23**, but had found that the displacement of the toluene-*p*-sulphonate group by cyanide ion was 'capricious'. He reported a 60% yield on a small scale (50 mg) by the use of sodium cyanide in HMPA (hexamethylphosphoramide), but found that the reaction could not be scaled up due to a competing ring expansion. Our initial attempts to repeat this displacement by cyanide proved to be even less successful, and we turned our attention to employing the aldehyde **19** in a chain extension. Oxidation of the alcohol **14** to the aldehyde **19** was readily achieved with CrO_3–3,5-dimethylpyrazole; however, attempted condensation of **14** with nitromethane led to loss of the formyl group with formation of the compound **20** in almost quantitative yield. Wittig reagents also produced a similar result.

A re-examination of the conditions for the reaction of the toluene-*p*-sulphonate **16** with cyanide ion eventually led to a reliable method for its conversion into the nitrile **21**. This involved reaction with a high concentration of tetrabutylammonium cyanide in HMPA at 80 °C (see Scheme 3). Yields were reproducible and the reaction could be carried out on a large scale. This constitutes a formal synthesis of (±)-*O*-methyljoubertiamine **23**, since the nitrile **21** has been hydrolysed to the ketone,[5] which was converted in four steps into the racemic alkaloid by Sanchez and Tallabs.[6] The same reaction conditions resulted in the formation of the nitrile **22** from the toluene-*p*-sulphonate **17** in good yield, and since the ketone **24** has been converted into (±)-mesembrine **25**,[6] we were able to complete its formal synthesis by the hydrolysis of the ketal **22** to ketone **24**.



Scheme 3

Experimental

M.p.s are uncorrected. IR spectra were recorded on a Digilab FTS-80 spectrometer, and UV spectra were obtained on a Hitachi Model 150-20 apparatus. NMR spectra were determined with $SiMe_4$ as internal standard on Bruker WM-400 and AC-200F, and Varian XL-400, XL-100 and EM-390 spectrometers. *J* Values are given in Hz. Column chromatography was carried out with Merck Kieselgel 60 (230–240 mesh), and radial chromatography was performed with a Chromatotron Model 7924 instrument on Merck Kieselgel 60 (PF_{254} gipshaltig) using UV (254 nm) detection. HPLC was conducted on a Waters 6000 instrument equipped with a Whatman Partisil 10 M20 column (22 mm i.d. × 50 cm). Light petroleum refers to the fractions of b.p. 60–80 °C. Ether refers to diethyl ether. Microanalyses were performed by Chemical and Micro Analytical Services Pty Ltd., North Essendon. *p*-Methoxyphenyllead triacetate,[7] 3,4-dimethoxyphenyllead triacetate,[8] and the isomeric mixtures of vinylogous β-keto esters **1**[4] and **5**[9] were obtained by previously reported methods.

Ethyl 1-(4-*Methoxyphenyl*)-4-*oxocyclohex*-2-*enecarboxylate* **8**.—The mixture of keto esters **1** (0.336 g, 2.00 mmol) in chloroform (2 cm^3) was added to a solution of 4-methoxyphenyllead triacetate (1.33 g, 3.00 mmol) in chloroform (10 cm^3) and pyridine (0.474 g, 6.00 mmol) at 0 °C. The solution was stirred at 0 °C for 15 min and then at 55 °C for 24 h. The resulting mixture was cooled, filtered, and the residue was washed with chloroform (2 × 40 cm^3). The chloroform washes were added to the filtrate and washed in turn with dilute sulphuric acid (1.5 mol dm^{-3}; 3 × 100 cm^3), aqueous sodium hydrogen carbonate (5%; 2 × 100 cm^3), water (100 cm^3) and brine (50 cm^3), dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by flash chromatography using ethyl acetate–light petroleum (1:3), to yield the title compound **8** (0.378 g, 69%) as a pale yellow oil. IR and ^1H NMR spectroscopic data were in accord with those reported.[4]

Methyl 1-(4-*Methoxyphenyl*)-4-*oxocyclohex*-2-*enecarboxylate* **10**.—The mixture of keto esters **5** (0.154 g, 1.00 mmol) in chloroform (1 cm^3) was added to a solution of 4-methoxyphenyllead triacetate (0.665 g, 1.50 mmol) in chloroform (5 cm^3) and pyridine (0.237 g, 3.00 mmol) at room temperature, and the solution was stirred at 55 °C for 24 h. The reaction mixture was then worked up as in the preparation of compound **8** above. The crude product was purified by flash chromatography using ethyl

acetate–light petroleum (1:4), to yield the title compound **10** (0.242 g, 93%) as an oil. IR and ^{1}H NMR spectroscopic data were in accord with those reported.[5]

Ethyl 1-(3,4-*Dimethoxyphenyl*)-4-*oxocyclohex*-2-*enecarboxylate* **9**.—The mixture of keto esters **1** (0.168 g, 1.00 mmol) in chloroform (1 cm^3) was added to a solution of 3,4-dimethoxyphenyllead triacetate (0.665 g, 1.50 mmol) and anhydrous 1,10-phenanthroline (0.54 g, 3.00 mmol) in chloroform (5 cm^3) at room temperature. The solution was stirred at 55 °C for 48 h and then worked up as in the preparation of compound **8** above. The crude product was purified by flash chromatography using ethyl acetate–light petroleum (1:3) to yield the title compound **9** (0.173 g, 57%) as an oil. IR and ^{1}H NMR spectroscopic data were in accord with those reported.[4]

Methyl 1-(3,4-*Dimethoxyphenyl*)-4-*oxocyclohex*-2-*enecarboxylate* **11**.—The mixture of keto esters **5** (0.154 g, 1.00 mmol) in chloroform (1 cm^3) was added to a solution of 3,4-dimethoxyphenyllead triacetate (0.665 g, 1.50 mmol) in pyridine (0.237 g, 3.00 mmol) and chloroform (5 cm^3) at room temperature. This was stirred at 55 °C for 48 h and then worked up as in the preparation of compound **8** above. The crude product was purified by flash chromatography using ethyl acetate–light petroleum (1:3) to yield the *title compound* **11** (0.258 g, 89%) as a pale yellow oil (Found: C, 66.2; H, 6.4. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.2%); $\delta_H(CDCl_3)$ 2.23–2.60 (3 H, m, 6-H and 5-H_2), 2.65–2.80 (1 H, m, 6-H), 3.76 (3 H, s, CO_2Me), 3.87 (3 H, s, OMe), 3.88 (3 H, s, OMe), 6.23 (1 H, d, *J* 10, 3-H), 6.78–6.87 (3 H, m, ArH) and 7.35 (1 H, d, *J* 10, 2-H); $\delta_C(CDCl_3)$ 34.0 (C-5 or C-6), 34.6 (C-5 or C-6), 52.0 (C-1), 52.9 (CO_2CH_3), 55.9 (OCH_3), 56.0 (OCH_3), 109.4 (C-Ar), 111.2 (C-Ar), 118.7 (C-2), 130.4 (C-Ar), 132.6 (C-1′), 148.7 (C-3′ or C-4′), 149.3 (C-3′ or C-4′), 149.7 (C-3), 172.8 (CO_2Me) and 198.4 (C-4); ν_{max}(film)/cm^{-1} 1733, 1687 and 1590; λ_{max}(EtOH)/nm 278 and 228 (ε 2850 and 16 476); *m/z* 290 (*M*, 73%), 232 (*M* − CO_2CH_2, 67) and 231 (*M* − CO_2Me, 100).

Ethyl 8-(4-*Methoxyphenyl*)-1,4-*dioxaspiro*[4.5]*dec*-6-*ene*-8-*carboxylate* **12**.—Ethyl 1-(4-methoxyphenyl)-4-oxocyclohex-2-enecarboxylate **8** (1.64 g, 6.00 mmol) in toluene (60 cm^3) was heated at reflux with ethylene glycol (1.86 g, 30.0 mmol) and toluene-*p*-sulphonic acid (0.1 g) for 18 h with removal of water. The mixture was allowed to cool and was poured into cold aqueous sodium hydroxide (1.5 mol dm^{-3}; 60 cm^3). The organic layer was separated and the aqueous phase was washed with toluene (2 × 20 cm^3). The toluene extracts were combined, washed with water and evaporated. The residue was fractionated by flash chromatography using ethyl acetate–light petroleum (2:3) to yield the *title compound* **12** (1.75 g, 92%) as an oil which decomposed slowly by loss of the ketal group at room temperature (Found: M^+, 318.1460. $C_{18}H_{22}O_5$ requires *M*, 318.1467); $\delta_H(CDCl_3)$ 1.19 (3 H, t, *J* 7.1, Me) 1.67–1.86 (2 H, m, 9-H_2), 2.04 (1 H, m, 10-H), 2.56 (1 H, m, 10-H), 3.79 (3 H, s, OMe), 3.88–4.06 (4 H, m, 2-H_2 and 3-H_2), 4.19 (2 H, q, *J* 7.1, CH_2), 5.86 (1 H, d, *J* 10.0, 7-H), 6.33 (1 H, d, *J* 10.0, 6-H) and 6.85 and 7.19 (4 H, AA′BB′, 3-H, 5-H and 2-H, 6-H respectively); ν_{max}(film)/cm^{-1} 1731 and 1609; λ_{max}(EtOH)/nm 226 and 274 (ε 17 280 and 2870); *m/z* 318 (*M*, 2%), 274 (*M* − C_2H_4O, 14) and 201 (274 − CO_2Et, 100).

Ethyl 8-(3,4-*Dimethoxyphenyl*)-1,4-*dioxaspiro*[4.5]*dec*-6-*ene*-8-*carboxylate* **13**.—Ethyl 1-(3,4-dimethoxyphenyl)-4-oxocyclohex-2-enecarboxylate **9** (1.52 g, 5.00 mmol) was treated with ethylene glycol (1.55 g, 25.0 mmol) as for the preparation of compound **12** above. The work-up and fractionation of the product was carried out in the same way to give the *title compound* **13** (1.53 g, 88%) as an unstable oil (Found: M^+, 348.1577. $C_{19}H_{24}O_6$ requires *M*, 348.1573); $\delta_H(CDCl_3)$ 1.21 (3 H, t, *J* 7.1, Me), 1.70–1.85 (2 H, m, 9-H_2), 2.06 (1 H, m, 10-H), 2.56 (1 H, m, 10-H), 3.86 (6 H, br s, 2 × OMe), 3.91–4.04 (4 H, m, 2-H_2 and 3-H_2), 4.16 (2 H, q, *J* 7.1, CH_2), 5.88 (1 H, d, *J* 10.0, 7-H), 6.35 (1 H, d, *J* 10.0, 6-H) and 6.79–6.85 (3 H, m, ArH); $\delta_C(CDCl_3)$ 14.0 (Me), 30.6 (C-9 or C-10), 32.5 (C-9 or C-10), 51.6 (C-8), 55.8 (2 × OMe), 61.2 (CO_2CH_2), 64.6 (C-2 and C-3), 104.8 (C-5), 109.8 (C-Aryl), 111.0 (C-Aryl), 118.9 (C-6), 129.7 (C-Aryl), 130.1 (C-1′), 134.7 (C-7), 148.1 (C-3′ or C-4′), 148.9 (C-3′ or C-4′) and 173.3 (C=O); ν_{max}(film)/cm^{-1} 1727 and 1609; λ_{max}(EtOH)/nm 228 and 275 (ε 10 750 and 1273); *m/z* 348 (*M*, 4%), 304 (*M* − C_2H_4O, 26) and 231 (304 − CO_2Et, 100).

8-*Hydroxymethyl*-8-(4-*methoxyphenyl*)-1,4-*dioxaspiro*[4.5]*dec*-6-*ene* **14**.—Lithium aluminium hydride (0.15 g, 4.00 mmol) was added to a solution of the ethyl ester **12** (1.27 g, 4.00 mmol) in dry ether (40 cm^3) and the mixture was stirred for 3 h at room temperature. Saturated aqueous sodium sulphate (40 cm^3) was added dropwise with cooling, and the mixture was extracted with ether (3 × 50 cm^3). The ether extracts were washed with water (50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and evaporated. The crude oil was purified by flash chromatography using ethyl acetate–light petroleum (2:3) to yield the title compound **14** (0.96 g, 87%) as an oil with IR and ^{1}H NMR spectroscopic data in accord with reported values.[5]

8-(3,4-*Dimethoxyphenyl*)-8-*hydroxymethyl*-1,4-*dioxaspiro*[4.5]*dec*-6-*ene* **15**.—Lithium aluminium hydride (0.12 g, 3.0 mmol) was added to a solution of the ethyl ester **13** (1.04 g, 3.00 mmol) in dry ether (30 cm^3) and the mixture was stirred for 3 h at room temperature. The crude product, obtained by work-up as for the preparation of compound **14** above, was purified by radial chromatography using ether–light petroleum (1:1) to yield the *title compound* **15** (0.77 g, 84%) as an oil (Found: M^+, 306.1471. $C_{17}H_{22}O_5$ requires *M*, 306.1467); $\delta_H(CDCl_3)$ 1.57–2.08 (4 H, m, 9-H_2 and 10-H_2), 2.60 (1 H, br, exch., OH), 3.69 (1 H, d, *J* 7.1, CH_2OH), 3.82 (1 H, d, *J* 7.1, CH_2OH), 3.87 (6 H, br s, 2 × OMe), 3.86–4.01 (4 H, m, 2-H_2 and 3-H_2), 5.88 (1 H, d, *J* 10.0, 7-H), 6.19 (1 H, d, *J* 10.0, 6-H) and 6.88 (3 H, m, ArH); $\delta_C(CDCl_3)$ 29.7 (C-9 or C-10), 30.8 (C-9 or C-10), 45.5 (C-8), 55.8 (OMe), 56.3 (OMe), 64.3 (C-2 or C-3), 64.6 (C-2 or C-3), 70.0 (CH_2OH), 105.3 (C-5), 110.6 (C-Ar), 111.2 (C-Ar), 119.5 (C-7), 129.2 (C-Ar), 135.0 (C-1′), 135.4 (C-6), 148.8 (C-3′ or C-4′) and 151.2 (C-3′ or C-4′); ν_{max}(film)/cm^{-1} 3475; λ_{max}(EtOH)/nm 229 and 279 (ε 8710 and 2570); *m/z* 306 (*M*, 4%), 276 (*M* − CH_2O, 85), 275 (*M* − CH_2OH, 60), 231 (275 − C_2H_4O, 80) and 203 (231 − CO, 100).

The alcohol **15** slowly deposited a crystalline material at room temperature, and this was crystallised from ethyl acetate to give 4-(3,4-*dimethoxyphenyl*)-4-*hydroxymethylcyclohex*-2-*enone* **18**, m.p. 123–124 °C (Found: C, 68.4; H, 6.9. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); $\delta_H(CDCl_3)$ 1.49 (1 H, dd, *J* 8.0, 4.0, exch., OH), 2.21 (2 H, m, 5-H_2), 2.28 (1 H, m, 6-H), 2.40 (1 H, m, 6-H), 3.73 (1 H, dd, *J* 11.0, 8.0, CH_2OH), 3.88 (6 H, br s, 2 × OMe), 3.93 (1 H, dd, *J* 11.0, 4.0, CH_2OH), 6.25 (1 H, *J* 10.0, 2-H), 6.79–6.92 (3 H, m, ArH) and 7.25 (1 H, d, *J* 10.0, 3-H); $\delta_C(CDCl_3)$ 32.2 (C-5 or C-6), 34.1 (C-5 or C-6), 46.3 (C-4), 55.9 (OMe), 56.0 (OMe), 70.0 (CH_2OH), 110.4 (C-Ar), 111.5 (C-Ar), 119.8 (C-2), 130.3 (C-Ar), 132.1 (C-1′), 148.0 (C-3′ or 3-4′), 149.1 (C-3′ or C-4′), 153.0 (C-3), 199.1 (C-1); $\nu_{max}(CHCl_3)$/cm^{-1} 3471, 1684 and 1519; *m/z* 262 (*M*, 35%), 232 (*M* − CH_2O, 21), 231 (*M* − CH_2OH, 100) and 203 (231 − CO, 55).

8-*Formyl*-8-(4-*methoxyphenyl*)-1,4-*dioxaspiro*[4.5]*dec*-6-*ene* **19**.—Chromium trioxide (1.00 g, 10.0 mmol) and 3,5-dimethylpyrazole (0.96 g, 10.0 mmol) were mixed in dichloromethane (40 cm^3) at −30 °C for 15 min. The alcohol **14** (0.552 g, 2.00 mmol)

in dichloromethane (2 cm^3) was added, and the solution was stirred at −30 °C for 75 min. The mixture was allowed to warm to −10 °C, the supernatant liquid was decanted, and the residue was washed with ether (5 × 30 cm^3). The combined organic phases were washed with water (3 × 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4), and evaporated. The crude product was filtered through a short column of silica gel in ethyl acetate, the solvent was evaporated, and the residue was crystallised from ethyl acetate–light petroleum to yield the *title compound* **19** (0.406 g, 74%), m.p. 99–99.5 °C (Found: C, 69.9; H, 6.7. $C_{16}H_{18}O_4$ requires C, 70.1; H, 6.6%); $\delta_H(CDCl_3)$ 1.77 (2 H, m, 9-H_2), 1.97 (1 H, m, 10-H), 2.47 (1 H, m, 10-H), 3.79 (3 H, s, OMe), 3.95–4.03 (4 H, m, 2-H_2 and 3-H_2), 6.03 (1 H, d, *J* 11.0, 7-H), 6.17 (1 H, d, *J* 11.0, 6-H), 6.91 and 7.14 (4 H, AA'BB', 3'-H, 5'-H and 2'-H, 6'-H respectively) and 9.47 (1 H, s, CHO); $\delta_C(CDCl_3)$ 29.0 (C-9 or C-10), 30.0 (C-9 or C-10), 55.4 (OMe), 63.7 (C-2 or C-3), 64.7 (C-2 or C-3), 104.8 (C-5), 114.6 (C-7), 128.9 (C-6), 129.5 (2 × C-Ar), 132.0 (C-1'), 132.5 (2 × C-Ar), 146.3 (C-4') and 197.7 (CHO); $\nu_{max}(CHCl_3)/cm^{-1}$ 1723, 1605 and 1586; λ_{max}(EtOH)/nm 277 (ε 2188); *m/z* 274 (*M*, 4%), 246 (*M* − CO, 50), 245 (*M* − CHO, 90), 201 (245 − C_2H_4O, 21) and 173 (201 − CO, 100).

8-(4-*Methoxyphenyl*)-1,4-*dioxaspiro*[4.5]*dec*-7-*ene* **20**.—The aldehyde **19** (471 mg, 1.72 mmol) was added to nitromethane (18 cm^3) and ethylenediamine (10.3 mg, 0.172 mmol), and the mixture was heated at reflux under nitrogen for 4 h. The excess of reagent was evaporated under reduced pressure, and the residue was fractionated by flash chromatography using ethyl acetate–light petroleum (1:9) to yield the title compound **20** (376 mg, 88%), m.p. 88–89 °C (from hexane) (lit.,[5] 87–89 °C).

8-(4-*Methoxyphenyl*)-8-[(p-*tolylsulphonyloxy*)*methyl*]-1,4-*dioxaspiro*[4.5]*dec*-6-*ene* **16**.—Toluene-*p*-sulphonyl chloride (0.61 g, 3.2 mmol) was added to a solution of the alcohol **14** (0.22 g, 0.80 mmol) in pyridine (5 cm^3) at room temperature. The mixture was stirred at room temperature for 48 h, diluted with water (1 cm^3), and the mixture was stirred for a further 30 min and then shaken with ether (100 cm^3). The ether fraction was washed with water (2 × 100 cm^3), aqueous copper sulphate (5%; 3 × 50 cm^3), water (2 × 50 cm^3) and saturated brine (50 cm^3), dried (Na_2SO_4) and evaporated. The crude product was purified by radial chromatography using ether–light petroleum (1:1) to yield the title compound **16** (0.31 g, 91%) as a colourless oil. IR and ^1H NMR spectroscopic data were in accord with reported values.[5]

8-(3,4-*Dimethoxyphenyl*)-8-[(p-*tolylsulphonyloxy*)*methyl*]-1,4-*dioxaspiro*[4.5]*dec*-6-*ene* **17**.—Toluene-*p*-sulphonyl chloride (1.43 g, 7.50 mmol) was added to a solution of the alcohol **15** (0.459 g, 1.50 mmol) in pyridine (10 cm^3) at room temperature. The mixture was stirred at room temperature for 48 h, and then worked up as for the preparation of compound **16** above. The crude product was fractionated by radial chromatography using ether–light petroleum (1:1) to afford the *title compound* **17** as a very unstable oil (0.545 g, 79%); $\delta_H(CDCl_3)$ 1.52–2.11 (4 H, m, 9-H_2 and 10-H_2), 2.44 (3 H, s, Me), 3.74 (6 H, br s, 2 × OMe), 3.89–3.95 (4 H, m, 2-H_2 and 3-H_2), 3.99 (1 H, d, *J* 9.2, CH_2OTs), 4.19 (1 H, d, *J* 9.2, CH_2OTs), 5.83 (1 H, d, *J* 10.0, 7-H), 6.00 (1 H, d, *J* 10.0, 6-H), 6.65–6.75 (3 H, m, ArH) and 7.31 and 7.67 (4 H, AA'BB', ArH).

8-*Cyanomethyl*-8-(4-*methoxyphenyl*)-1,4-*dioxaspiro*[4.5]*dec*-6-*ene* **21**.—The toluene-*p*-sulphonate **16** (0.782 g, 1.70 mmol) in HMPA (1 cm^3) was added to a solution of tetrabutylammonium cyanide (4.56 g, 17.0 mmol) in HMPA (5 cm^3) at 80 °C under nitrogen, and the solution was stirred at 80 °C for 30 h. Ether (200 cm^3) was added, and the solution was washed with water (5 × 100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and evaporated. The crude product was fractionated by HPLC using ethyl acetate–light petroleum (3:17) to yield the title compound **21** (0.38 g, 76%) as an oil. IR and ^1H NMR spectroscopic data were in accord with reported values.[5]

8-*Cyanomethyl*-8-(3,4-*dimethoxyphenyl*)-1,4-*dioxaspiro*-[4.5]*dec*-6-*ene* **22**.—The toluene-*p*-sulphonate **17** (0.782 g, 1.70 mmol) in HMPA (1 cm^3) was added to a solution of tetrabutylammonium cyanide (4.56 g, 17.0 mmol) in HMPA (5 cm^3) at 80 °C under nitrogen, and the solution was stirred at 80 °C for 30 h. The reaction was worked up as for the preparation of compound **20** above, and the crude product was purified by flash chromatography using ethyl acetate–light petroleum (1:4) to yield the *title compound* **22** (0.391 g, 73%), m.p. 121–122 °C (from ethyl acetate–light petroleum) (Found: C, 68.5; H, 6.8, N, 4.2. $C_{18}H_{21}NO_4$ requires C, 68.6; H, 6.7; N, 4.4%); $\delta_H(CDCl_3)$ 1.64–1.80 (2 H, m, 9-H_2), 2.05–2.16 (2 H, m, 10-H_2), 2.69 (1 H, d, *J* 17.0, CH_2CN), 2.80 (1 H, d, *J* 17.0, CH_2CN), 3.86 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.90–4.06 (4 H, m, 2-H_2 and 3-H_2), 5.91 (1 H, d, *J* 9.6, 6-H), 6.09 (1 H, d, *J* 9.6, 7-H) and 6.82–6.91 (3 H, m, ArH); $\delta_C(CDCl_3)$ 30.0 (C-9 or C-10), 30.6 (C-9 or C-10), 34.6 (CH_2CN), 41.5 (C-8), 55.8 (OMe), 56.0 (OMe), 64.5 (C-2 or C-3), 64.7 (C-2 or C-3), 104.6 (C-5), 110.0 (C-Ar), 111.2 (C-Ar), 117.4 (CN), 118.9 (C-7), 130.1 (C-Ar), 132.1 (C-1'), 134.7 (C-6), 148.3 (C-3' or C-4') and 149.0 (C-3' or C-4'); $\nu_{max}(CHCl_3)/cm^{-1}$ 2253, 1606 and 1592; λ_{max}(EtOH)/nm 229 and 278 (ε 8122 and 2008); *m/z* 315 (*M*, 20%), 288 (10), 276 (15), 275 (*M* − C_2H_2N, 95) and 203 (100).

4-*Cyanomethyl*-4-(3,4-*dimethoxyphenyl*)*cyclohex*-2-*enone* **24**.—Hydrochloric acid (10 mol dm^{-3}; 3 cm^3) and water (10 cm^3) were added to a solution of the nitrile **22** (0.105 g, 0.333 mmol) in tetrahydrofuran (15 cm^3) at room temperature, and stirred for 30 min. The mixture was poured into ether (150 cm^3), washed with water (3 × 70 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and evaporated. The crude product was filtered through silica gel in ethyl acetate and the solvent was evaporated to give material which crystallised from ethyl acetate–light petroleum, to afford the title compound (0.086 g, 94%), m.p. 130–131 °C (lit.,[6] 131–132 °C) (Found: C, 70.7; H, 6.3; N, 5.0. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%); $\delta_H(CDCl_3)$ 2.15–2.49 (4 H, m, 9-H_2 and 10-H_2), 2.86 (2 H, AB, *J* 17.0, CH_2CN), 3.88 (3 H, s, OMe), 3.89 (3 H, s, OMe), 6.28 (1 H, d, *J* 10.0 6-H), 6.81–6.89 (3 H, m, ArH) and 7.08 (1 H, d, *J* 10.0, 7-H); δ_C 30.9 (CH_2), 34.0 (CH_2), 35.4 (CH_2), 42.3 (C-4), 55.9 (OMe), 56.0 (OMe), 109.5 (C-Ar), 111.3 (C-Ar), 116.8 (CN), 118.9 (C-2), 130.9 (C-Ar), 132.3 (C-1'), 148.8 (C-3' or C-4'), 149.3 (C-3' of C-4'), 151.2 (C-3) and 197.6 (C-1); $\nu_{max}(CHCl_3)/cm^{-1}$ 2256, 1686 and 1519; λ_{max}(EtOH)/nm 278 (ε 3075); *m/z* 271 (*M*, 46%) and 231 (*M* − C_2H_2N, 100).

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