Use of the Electrophilic Arylation Reaction of Aryl-lead Triacetates in a Synthesis of (±)-Lycoramine

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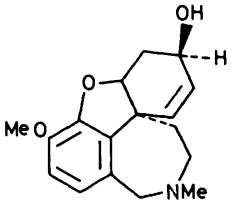
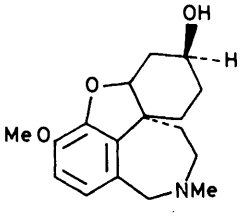
A formal total synthesis of (±)-lycoramine is reported. The quaternary carbon centre of the alkaloid was produced by a novel electrophilic arylation of the mixture of isomeric vinylogous keto esters (**4**) and (**5**) by 2,3-dimethoxyphenyl-lead triacetate. The resulting key intermediate (**7c**), which was formed in almost quantitative yield, was converted in a straightforward sequence into the formamide (**25**), from which the alkaloid has been produced previously by a Bischler-Napieralski cyclisation. Functional group protection was only required at one stage in the synthesis.

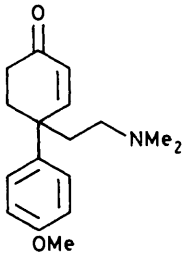
The synthesis of galanthamine (**1**) by Barton and Kirby,[1] by a sequence involving a phenol oxidative coupling as a key step, was the first successful route to a member of this group of Amaryllidaceae alkaloids. This also constituted a synthesis of lycoramine (**2**), as it is readily obtained by hydrogenation of (**1**).[2] Since that work there has been considerable activity by



(**1**)



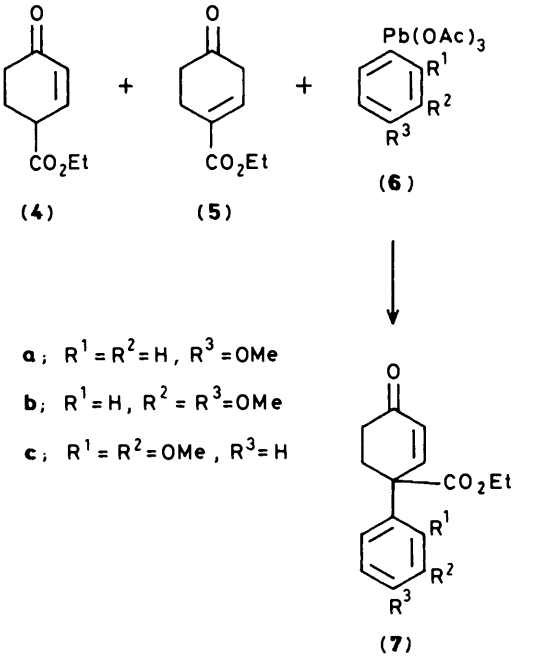
(**2**)



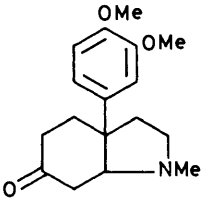
(**3**)

synthetic chemists in this area, due both to interest in the structural features of the alkaloids and to the biological activity displayed by certain members.[3] In a recent synthesis of *O*-methyljoubertiamine (**3**), a related but relatively simple *Sceletium* alkaloid, Pearson demonstrated[4] a new approach to the formation of the quaternary benzylic centre which is a feature of all these alkaloids. This involved the use of a cyclohexadienyl-$Fe(CO)_3$ cationic complex, an aryl cation equivalent, which was treated with a β-keto ester to generate the quaternary centre.

During the past 10 years we have shown that aryl-lead(IV) triacetates are useful aryl cation equivalents in the presence of certain soft carbon nucleophiles,[5] and in the preceding paper[6] we showed that they react with the mixture of isomeric keto esters (**4**) and (**5**) regiospecifically at C-1. By use of the aryl-lead triacetates (**6a**) and (**6b**) we were able to produce the arylated keto esters (**7a**) and (**7b**), potential intermediates for the synthesis of *O*-methyljoubertiamine (**3**) and mesembrine (**8**) respectively (see Scheme 1). We now report the use of this approach in the synthesis of ethyl 1-(2,3-dimethoxyphenyl)-4-



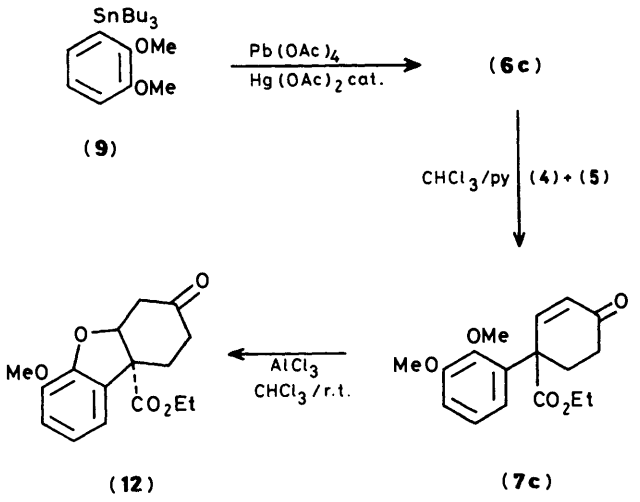
Scheme 1.



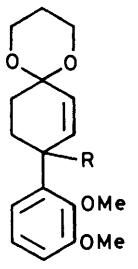
(**8**)

oxocyclohex-2-enecarboxylate (**7c**), and its efficient conversion into (±)-lycoramine (**2**).

2,3-Dimethoxyphenyl-lead triacetate (**6c**), which was required for the synthesis, was conveniently prepared by our tin-lead exchange procedure.[7] This involved the reaction of the readily available tributyl-(2,3-dimethoxyphenyl)stannane (**9**) with lead tetra-acetate in the presence of a catalytic amount of mercury(II) acetate (Scheme 2). The mixture of isomeric keto esters (**4**) and (**5**), for which we have reported an improved synthesis,[6] reacted smoothly with the aryl-lead compound (**6c**) in chloroform containing pyridine to produce the key intermediate (**7c**) in



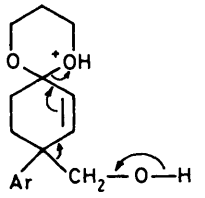
Scheme 2.



(10) R = CO_2Et

(11) R = CH_2OH

almost quantitative yield.* Initially, it was our intention to proceed by protecting the ketone as the propylene acetal (**10**), followed by lithium aluminium hydride reduction to the alcohol (**11**), which was to be the first step in a sequence aimed at converting the ethoxycarbonyl group into an aminoethyl group. The propylene acetal (**10**) was readily obtained; however, treatment with lithium aluminium hydride failed to yield the alcohol. As none of the ester (**10**) could be recovered, it would appear likely that the alcohol underwent an acid-catalysed fragmentation, as shown in (**I**), similar to that observed for an

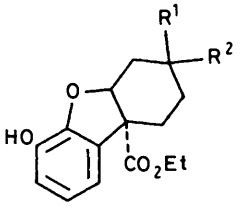


(**I**)

analogous compound by Pearson[4] in his O-methyljouberti-amine (**3**) synthesis.

Since the failure of the lithium aluminium hydride reduction step was probably due to the presence of the double bond, we elected to form the dihydrofuran ring at this stage. This was eventually achieved in good yield by reaction of the keto ester (**7c**) with aluminium chloride in chloroform at room temperature. Under these conditions demethylation of the second methoxy group did not occur and the only isolable product was the hexahydrodibenzofuran (**12**). Although a *cis* ring junction was expected for this compound on the basis of precedents in closely related systems,[3a,3b] the stereochemistry was confirmed by a study of the 400 MHz n.m.r. spectrum. The signal due to the proton α to the ether oxygen at δ 5.66 had a width at half height of 8 Hz showing that it was equatorial, and thus, indicating that the ring junction must be *cis*.

In our first attempt to achieve the above ring formation we examined the conditions employed by Sanchez and co-workers[3b] for a similar demethylation and ring closure, which generated the tetracyclic system in their lycoramine synthesis. This involved the treatment of keto ester (**7c**) with aluminium chloride and diethyl sulphide in methylene dichloride; however, this resulted in removal of both methyl groups and formation of the tricyclic phenol (**13**) in good yield. This compound proved to be of little use in the synthesis, since attempted re-methylation with dimethyl sulphate and sodium hydroxide produced the α,β-unsaturated ketone (**7c**), while methyl iodide and potassium carbonate in acetone failed to produce the methyl ether in acceptable yield. This problem



(**13**) $R^1, R^2 = O$

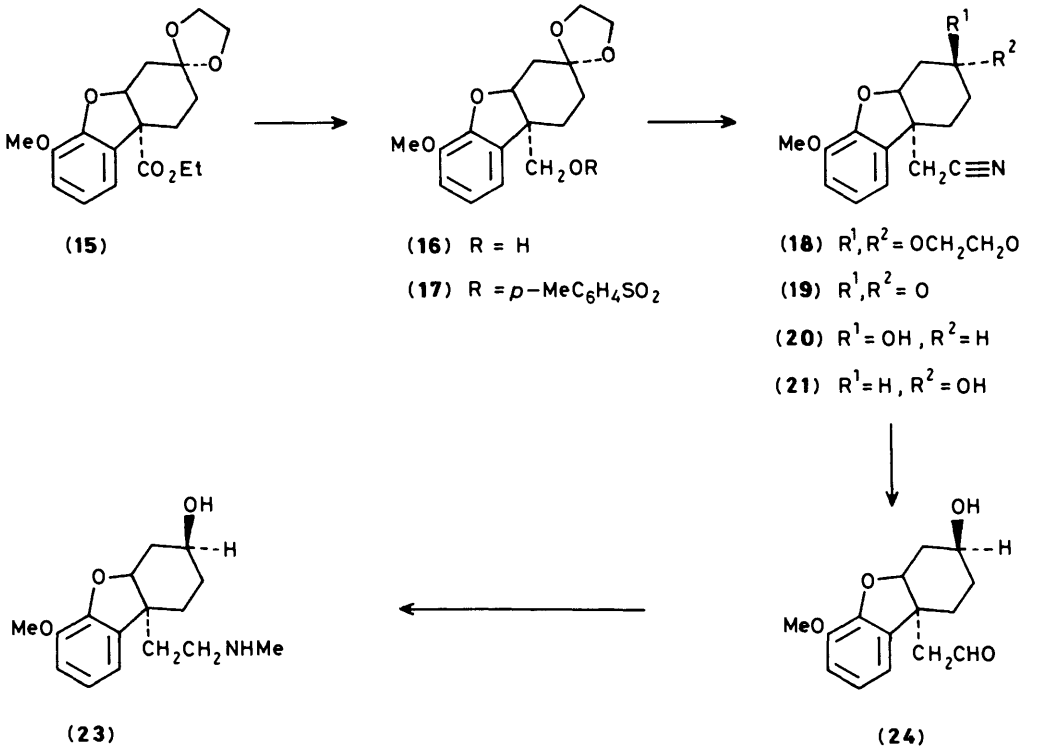
(**14**) $R^1, R^2 = OCH_2CH_2O$

could be overcome by conversion of (**13**) into the ethylene acetal derivative (**14**) which readily underwent methylation to give compound (**15**) in high yield. However, this approach was abandoned when the above conditions for the production of the tricyclic ether (**12**) from (**7c**) were found.

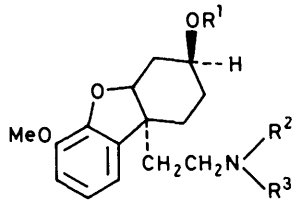
The required conversion of the ethoxycarbonyl group of (**12**) into an aminoethyl group was achieved by the steps outlined in Scheme 3. Its ethylene acetal derivative (**15**), which was identical with the material obtained from (**14**) above, was reduced with lithium aluminium hydride to give the alcohol (**16**), and this was readily converted into the toluene-*p*-sulphonate derivative (**17**) in >90% overall yield from (**12**). It had been expected that some difficulty might be experienced with the displacement by cyanide ion at the neopentyl type centre in (**17**); however, while potassium cyanide, in the presence of 18-crown-6, was ineffective, tetrabutylammonium cyanide in refluxing acetonitrile afforded the nitrile (**18**) in quantitative yield.

It was our original intention to proceed by reduction of the nitrile to the primary amine, followed by formation of the 7-membered ring by a Pictet-Spengler reaction.[9] This approach failed, as lithium aluminium hydride reduction of the nitrile (**18**) produced a complex mixture of products. We thus elected to remove the acetal protecting group and generate the hydroxy group at this stage. The ketone (**19**) was obtained in good yield and it was reduced with sodium borohydride in methanol to give a mixture of the isomeric alcohols (**20**) and (**21**), with the ratio of (**20**):(**21**) being 85:15 at room temperature and 95:5 at 0 °C. The required alcohol (**20**) was readily purified by flash chromatography in 90% yield. Although lithium aluminium hydride reduction of (**20**) did yield the required primary amine (**22**) in this case, it was not readily purified and complete

* The improvement in the yield, compared with that of our preliminary report[8] of this reaction, resulted from changes in the reaction conditions.



Scheme 3.



(22) $R^1 = R^2 = R^3 = H$

(25) $R^1 = R^2 = CHO$, $R^3 = Me$

characterisation was not carried out. In addition, it did not prove to be a useful intermediate due to the failure of various attempts to form the final ring by the Pictet-Spengler reaction. A similar failure of this type of ring formation was reported for the *N*-methyl derivative (**23**) by Martin and Garrison,[3a] while Sanchez and co-workers [3b] also attempted to use this reaction to produce the 7-membered ring in their lycoramine synthesis, without success.

The conversion of the amine (**23**) into (±)-lycoramine by application of the Bischler-Napieralski procedure has been reported,[3a] and thus, we were able to complete a formal synthesis of the alkaloid by converting the hydroxy nitrile (**20**) into the amine (**23**) by an efficient two-step procedure. This involved reduction of the nitrile (**20**) with di-isobutylaluminium hydride [10] to the aldehyde (**24**), which afforded the secondary amine (**23**) on treatment with methylamine hydrochloride and sodium cyanoborohydride.[11] The diformyl derivative (**25**), the compound used by Martin and Garrison [3a] in ring closure, was identical (by i.r. and n.m.r. spectroscopy) with their material.

Experimental

The instruments employed for spectroscopic determinations and general procedures have been noted previously,[12] except that flash chromatography was carried out on a column packed with Merck Kieselgel 60 (230—400 mesh), and n.m.r. spectra were recorded on either Varian XL 100 or Bruker MW 400 spectrometers.

2,3-*Dimethoxyphenyl-lead Triacetate* (**6c**).—Dry lead tetra-acetate (5.24 g, 11.8 mmol) was stirred with tributyl(2,3-dimethoxyphenyl)stannane [13] (5.0 g, 11.7 mmol) and mercury(II) acetate (188 mg, 0.59 mmol) in chloroform (20 ml) at 40 °C for 24 h. The mixture was cooled, filtered through Celite, evaporated, and diluted with light petroleum (25 ml). The precipitated material was collected and crystallised from chloroform–acetic acid (1:1) and light petroleum, to yield the *title compound* (**6c**) (3.24 g, 53%) as pale yellow crystals, m.p. 139—142 °C (Found: C, 32.5; H, 3.4. $C_{14}H_{18}O_8Pb$ requires C, 32.3; H, 3.5%); $\nu_{max.}$(CHCl$_3$) 1 560 cm^{-1}; $\lambda_{max.}$(EtOH) 221, 286, 299, and 351sh (ε 18 200, 6 460, and 2 090); δ_H(CDCl$_3$) 2.08 (9 H, s, 3 × OAc), 3.89 (3 H, s, OMe), 4.03 (3 H, s, OMe), and 7.00—7.49 (3 H, m, ArH); *m/z* 463 (522 — OAc, 8%).

Ethyl 1-(2,3-*Dimethoxyphenyl*)-4-*oxocyclohex*-2-*enecarboxylate* (**7c**).—2,3-Dimethoxyphenyl-lead triacetate (1.88 g, 3.6 mmol) was dissolved in a mixture of pyridine (0.71 g, 9.0 mmol) and chloroform (5 ml) at 0 °C and a mixture of keto esters (**4**) and (**5**) [6] (0.505 g, 3.0 mmol) was added with stirring. After 15 min, the reaction mixture was warmed to room temperature and stirred for a further 0.5 h. Finally, the mixture was stirred at 55 °C for 24 h, and then worked up by the procedure outlined in the preceding paper.[6] Purification of the product by flash chromatography using light petroleum–ethyl acetate as the eluting solvent afforded the *title compound* (**7c**) (877 mg, 96%) as an oil (Found; C, 67.2; H, 6.6. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); $\nu_{max.}$(film) 1 735, 1 680, and 1 480 cm^{-1}; $\lambda_{max.}$(EtOH) 220 and 281 nm (ε 18 100 and 2 500); δ_H(CDCl$_3$) 1.24 (3 H, t, *J* 7.0 Hz, Me), 2.20—2.35 (2 H, m, CH_2), 2.66—2.75 (1 H, m, 5 H), 2.81—2.90 (1 H, m, 5-H), 3.83 (3 H, s, OMe), 3.87 (3 H, s, OMe),

4.13—4.34 (2 H, m, OCH_2), 6.22 (1 H, d, *J* 10.0 Hz, 3-H), 6.75—7.05 (3 H, m, ArH), and 7.03 (1 H, d, *J* 10.0 Hz, 2-H); *m/z* 304 (*M*, 60%) and 231 (*M* − CO_2Et, 100).

Ethyl 1-(2,3-Dimethoxyphenyl)-4-oxocyclohex-2-enecarboxylate Propylene Acetal (**10**).—A mixture of α,β-unsaturated ketone (**7c**) (2.89 g, 9.5 mmol) and propane-1,3-diol (15 ml) was heated at reflux in benzene containing toluene-*p*-sulphonic acid (40 mg) for 20 h, with removal of water by means of a Dean and Stark apparatus. The reaction mixture was worked up and the product was purified by flash chromatography using light petroleum–ethyl acetate (1:1) as the eluting solvent. The solid obtained crystallised from ether–light petroleum to yield the *title compound* (**10**) (3.03 g, 88%), m.p. 115—117 °C (Found: C, 65.8; H, 6.6; M^+, 362.1723. $C_{20}H_{26}O_6$ requires C, 66.3; H, 7.2% M^+, 362.1729); $\nu_{max.}$($CHCl_3$) 1 720, 1 675, and 1 580 cm^{-1}; $\lambda_{max.}$(EtOH) 274 nm (ε 1 660); δ_H($CDCl_3$) 1.21 (3 H, t, *J* 7.0 Hz, Me), 1.60—2.28 (5 H, m), 2.52—2.82 (1 H, m), 3.80 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.85—4.35 (6 H, m, 3 × OCH_2), 6.00 (1 H, d, *J* 10.0 Hz, 2-H or 3-H), 6.39 (1 H, d, *J* 10.0 Hz, 2-H or 3-H), and 6.78—7.10 (3 H, m, ArH); *m/z* 362 (*M*, 62%), 289 (*M* − CO_2Et, 48), and 126 (100).

(4aS*,9bR*)-*Ethyl 6-Methoxy-3-oxo-1,2,3,4,4a,9b-hexahydrodibenzofuran-9b-carboxylate* (**12**).—Aluminium chloride (13.14 g, 98.5 mmol) was dissolved in dry chloroform (120 ml) at 0 °C, and the mixture was stirred at room temperature for 24 h. A solution of the keto ester (**7c**) (3.0 g, 9.85 mmol) in dry chloroform (40 ml) was then added dropwise with stirring to the aluminium chloride solution. After 24 h the reaction mixture was diluted with ethyl acetate (500 ml) and washed with cold dilute hydrochloric acid (1M, 200 ml). The mixture was then washed in turn with water (400 ml) and brine (400 ml), dried (Na_2SO_4), and the solvent removed. The crude product was purified by flash chromatography using light petroleum–ethyl acetate (60:40) to yield the *title compound* (**12**) (1.89 g, 66%), m.p. 79—80 °C (from ethyl acetate–light petroleum) (Found: C, 66.1; H, 6.3. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.3%); $\nu_{max.}$($CHCl_3$) 1 725 and 1 615 cm^{-1}; $\lambda_{max.}$(EtOH) 280 nm (ε 3 310); δ_H($CDCl_3$) 1.32 (3 H, t, *J* 7.0 Hz, Me), 1.96—2.06 (1 H, m, 1-H_{ax}), 2.27—2.39 (3 H, m, 1-H_{eq}, 2-H_2), 2.79 (1 H, dd, J_{gem} 17.5 Hz, $J_{4.4a}$ 3.5 Hz, 4-H), 3.04 (1 H, dd, J_{gem} 17.5 Hz, $J_{4.4a}$ 3.5 Hz, 4-H), 3.87 (3 H, s, OMe), 4.24—4.32 (2 H, m, OCH_2), 5.66 (1 H, t, *J* 3.5 Hz, 4a-H), 6.83 (1 H, dd, $J_{7.8}$ 8.0 Hz, $J_{7.9}$ 1.0 Hz, 7-H), 6.92 (1 H, t, *J* 8.0 Hz, 8-H), and 7.03 (1 H, dd, $J_{8.9}$ 8.0 Hz, $J_{7.9}$ 1.0 Hz, 9-H); δ_C($CDCl_3$) 14.09 (q, Me), 30.91 (t, CH_2), 35.26 (t, CH_2), 41.49 (t, CH_2), 54.93 (s, C-9b), 55.97 (q, OMe), 61.81 (t, OCH_2), 83.24 (d, C-4a), 113.24 (d, C-7), 116.75 (d, C-9), 122.07 (d, C-8), 128.82 (s, C-9a), 144.60 (s, C-6), 147.98 (s, C-5a), 172.40 (s, CO_2), and 207.06 (s, C-3); *m/z* 290 (*M*, 53%) and 217 (*M* − CO_2Et, 100).

(4aS*,9bR*)-*Ethyl 6-Hydroxy-3-oxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-9b-carboxylate* (**13**).—Aluminium chloride (1.50 g, 11.25 mmol) and diethyl sulphide (1.05 g, 11.63 mmol) were dissolved in dry dichloromethane (10 ml) at 0 °C. The resulting solution was allowed to warm to room temperature, and the keto ester (**7c**) (300 mg, 0.986 mmol) in dry dichloromethane (6 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 24 h, treated with dilute sulphuric acid (10%, 20 ml), and extracted with chloroform (3 × 40 ml). The chloroform extract was washed and dried as for the preparation of (**12**) above, and the crude product was fractionated by flash chromatography using ether, to afford the *title compound* (**13**) (210 mg, 77%) as an oil (Found: C, 65.4; H, 5.7. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%); $\nu_{max.}$(film) 3 400 and 1 725 cm^{-1}; $\lambda_{max.}$(EtOH) 282 nm (ε 2 400); δ_H($CDCl_3$) 1.32 (3 H, t, *J* 7.0 Hz, Me), 1.7—2.5 (4 H, m, 1-H_2 and 2-H_2), 2.77 (1 H, dd, J_{gem} 17.3 Hz, $J_{4.4a}$ 3.5 Hz, 4-H_{ax}), 3.01 (1 H, dd, J_{gem} 17.3 Hz, $J_{4.4a}$ 3.5 Hz, 4-H_{eq}), 4.29 (2 H, q, *J* 7.0 Hz, OCH_2), 5.38 (1 H, b, exchangeable, OH), 5.66 (1 H, t, *J* 3.5 Hz, 4a-H), 6.75—7.02 (3 H, m, ArH); δ_C($CDCl_3$) 14.15 (q, Me), 30.84 (t, CH_2), 35.13 (t, CH_2), 41.62 (t, CH_2), 55.66 (s, C-9b), 62.07 (t, OCH_2), 83.37 (d, C-4a), 116.35 (d, C-7), 116.68 (d, C-9), 122.39 (d, C-8), 128.20 (s, C-9a), 140.20 (s, C-6), 146.17 (s, C-5a), 172.32 (s, CO_2), and 208.60 (s, C-3); *m/z* 276 (*M*, 38%) and 203 (*M* − CO_2Et, 53).

Ethylene Acetal Derivative (**14**).—The phenol (**13**) (290 mg, 1.05 mmol) in benzene (30 ml) was heated at reflux for 20 h with ethane-1,2-diol (10 ml) and toluene-*p*-sulphonic acid (40 mg), with removal of water by means of a Dean and Stark apparatus. The mixture was cooled, washed in turn with saturated aqueous sodium hydrogen carbonate and brine, dried, and evaporated. The crude product was purified by flash chromatography using light petroleum–ethyl acetate (1:1) to give the *ethylene acetal derivative* (**14**) (310 mg, 92%) as an oil (Found: M^+, 320.1247. $C_{17}H_{20}O_6$ requires M^+, 320.1260); $\nu_{max.}$(film) 3 400 and 1 730 cm^{-1}; $\lambda_{max.}$(EtOH) 283 nm (ε 2 290); δ_H($CDCl_3$) 1.28 (3 H, t, *J* 7.0 Hz, Me), 1.62 (2 H, m), 1.85—2.45 (4 H, m), 3.95 (4 H, m), 4.23 (2 H, q, *J* 7.0 Hz, OCH_2), 5.30 (1 H, t, 4a-H), 5.50 (1 H, b, exchangeable, OH), and 6.73—6.96 (3 H, m, ArH); δ_C($CDCl_3$) 14.15 (q, Me), 30.00 (t, CH_2), 30.84 (t, CH_2), 35.71 (t, CH_2), 54.67 (s, C-9b), 61.55 (t, OCH_2), 63.89 (t, OCH_2), 64.54 (t, OCH_2), 84.27 (d, C-4a), 107.52 (s, C-3), 115.57 (d, C-7), 116.35 (d, C-9), 121.81 (d, C-8), 127.90 (s, C-9a), 140.9 (s, C-6), 145.57 (s, C-5a), and 172.32 (s, CO_2); *m/z* 320 (*M*, 48%) 276 (*M* − OCH_2CH_2, 40), 247 (*M* − CO_2Et, 30), and 203 (276 − CO_2Et, 77).

(4aS*,9bR*)-*Ethyl 6-Methoxy-3-oxo-1,2,3,4,4a,9b-hexahydrodibenzofuran-9b-carboxylate Ethylene Acetal* (**15**).—(*a*) The ethylene acetal derivative (**14**) (190 mg, 0.59 mmol) was heated at reflux in anhydrous acetone (8 ml) with methyl iodide (2 ml) and powdered anhydrous potassium carbonate (500 mg). After 24 h the mixture was cooled, diluted with water (50 ml), and extracted with ethyl acetate (3 × 50 ml). The organic phase was washed with water, dried (Na_2SO_4), and the solvent removed to yield the *title compound* (**15**) as an oil (198 mg, 100%) (Found: C, 64.7; H, 6.6. $C_{18}H_{22}O_6$ requires C, 64.7; H, 6.6%); $\nu_{max.}$(film) 1 725 cm^{-1}; $\lambda_{max.}$(EtOH) 282 nm (ε 2 400); δ_H($CDCl_3$) 1.28 (3 H, t, *J* 7.0 Hz, Me), 1.89 (2 H, m), 2.02—2.10 (1 H, m), 2.18—2.35 (3 H, m), 3.86 (3 H, s, OMe), 3.85—4.01 (4 H, m, OCH_2CH_2O), 4.22 (2 H, m, OCH_2), 5.32 (1 H, t, 4a-H), and 6.78—6.98 (3 H, m, ArH); δ_C($CDCl_3$) 14.09 (q, Me), 29.87 (t, CH_2), 30.91 (t, CH_2), 35.64 (t, CH_2), 54.35 (s, C-9b), 55.84 (q, OMe), 61.42 (t, OCH_2), 64.02 (t, OCH_2), 64.49 (t, OCH_2), 84.15 (d, C-4a), 107.33 (s, C-3), 112.07 (d, C-7), 115.83 (d, C-9), 121.35 (d, C-8), 131.09 (s, C-9a), 144.93 (s, C-6), 146.87 (s, C-5a), and 172.40 (s, CO_2); *m/z* 334 (*M*, 32%).

(*b*) The keto ester (**12**) (2.0 g, 6.89 mmol) was dissolved in benzene (60 ml) containing ethane-1,2-diol (10 ml) and toluene-*p*-sulphonic acid (50 mg), and the solution was heated at reflux for 20 h with water removal by means of a Dean and Stark apparatus. The mixture was worked up as for the preparation of (**14**) above, to afford the ethylene acetal derivative (**15**) (2.19 g, 94%), identical (i.r. and ^1H n.m.r. spectra) with the material obtained in (*a*) above.

Lithium Aluminium Hydride Reduction of the Ester (**15**).—The ester (**15**) (170 mg, 0.508 mmol) was heated at reflux for 24 h in dry ether (12 ml) containing lithium aluminium hydride (150 mg, 3.75 mmol). Methanol (0.5 ml) and water 0.2 ml) were added and the mixture was stirred at room temperature for 0.5 h. The precipitate was filtered off, washed with ether, and the filtrate was dried (Na_2SO_4), and evaporated. The residue crystallised from ethyl acetate–light petroleum to

give, (4aS*,9bS*)-9b-*hydroxymethyl*-6-*methoxy*-1,4,4a,9b-*tetrahydrodibenzofuran*-3(2H)-*one ethylene acetal* (**16**) (148 mg, 100%) as colourless crystals, m.p. 101—102 °C (Found: C, 65.6; H, 6.6. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%); $\nu_{max.}$(CHCl$_3$) 3 400 cm^{-1}; $\lambda_{max.}$ 278 nm (ε 2 570); δ_H(CDCl$_3$) 1.52—1.61 (1 H, m, 1-H$_{ax}$), 1.64—1.73 (1 H, m, 2-H$_{eq}$), 1.67 (1 H, b, exchangeable, OH), 1.90 (1 H, dd, J_{gem} 13.8 Hz, $J_{4.4a}$, 7.8 Hz, 4-H$_{ax}$), 1.95—2.10 (2 H, m, 1-H$_{eq}$ and 2-H$_{ax}$), 2.18 (1 H, ddd, J_{gem} 13.8 Hz, $J_{4.4a}$ 6.0 Hz, $J_{2eq.4}$, 1.8 Hz, 4-H$_{eq}$), 3.51—3.65 (2 H, m, OCH$_2$), 3.86 (3 H, s, OMe), 3.84—3.97 (4 H, m, OCH$_2$CH$_2$O), 4.84 (1 H, dd, $J_{4ax.4a}$ 7.8 Hz, $J_{4eq.4a}$ 6.0 Hz, 4a-H), 6.73—6.92 (3 H, m, ArH); δ_C(CDCl$_3$) 25.97 (t, CH$_2$), 30.58 (t, CH$_2$), 36.82 (t, CH$_2$), 50.06 (s, C-9b), 55.91 (q, OCH$_2$), 64.22 (t, OCH$_2$), 64.67 (t, OCH$_2$), 68.24 (t, OCH$_2$), 84.22 (d, C-4a), 107.91 (s, C-3), 112.26 (d, C-7), 115.25 (d, C-9), 121.42 (d, C-8), 131.81 (s, C-9a), 145.38 (s, C-6), and 147.07 (s, C-5a); *m/z* 292 (*M*, 17%) and 99 (100).

Preparation of the Toluene-p-*sulphonate Derivative* (**17**).—The primary alcohol (**16**) (130 mg, 0.445 mmol) and toluene-*p*-sulphonyl chloride (500 mg, 2.62 mmol) were dissolved in pyridine (4 ml) and the mixture was kept at room temperature for 48 h. It was then diluted with water (0.5 ml) and stirred for 30 min after which the product was isolated in the usual way be means of ether. The crude product was purified by flash chromatography using light petroleum–ethyl acetate (3:7), to give (4aS*,9bR*)-6-*methoxy*-9b-(p-*tolylsulphonyloxymethyl*)-1,4,4a,9b-*tetrahydrodibenzofuran*-3(2H)-*one ethylene acetal* (**17**) (195 mg, 98%), m.p. 117—118° (from ethyl acetate) (Found: C, 62.0; H, 5.9. $C_{23}H_{26}O_7S$ requires C, 61.9; H, 5.9%); δ_H(CDCl$_3$) 1.47—1.56 (1 H, m, 1-H$_{ax}$), 1.62—1.69 (1 H, m, 2-H$_{eq}$), 1.81 (1 H, dd, J_{gem} 13.9 Hz, $J_{4.4a}$ 8.0 Hz, 4-H$_{ax}$), 2.00—2.16 (3 H, m, 1-H$_{eq}$, 2-H$_{ax}$, 4-H$_{eq}$), 2.43 (3 H, s, ArMe), 3.83 (3 H, s, OMe), 3.83—3.97 (6 H, m, 3 × OCH$_2$), 4.69 (1 H, dd, $J_{4ax.4a}$ 8.0 Hz, $J_{4eq.4a}$ 6.3 Hz, 4a-H), 6.69—6.87 (3 H, m, ArH), and 7.27 and 7.66 (4 H, AA′BB′); δ_C(CDCl$_3$) 21.56 (q, Me), 25.58 (t, CH$_2$) 30.26 (t, CH$_2$), 36.69 (t, CH$_2$), 48.18 (s, C-9b), 55.91 (q, OMe), 64.22 (t, 2 × OCH$_2$), 73.57 (t, CH$_2$OSO$_2$), 83.77 (d, C-4a), 107.39 (s, C-3), 112.59 (d, C-7), 115.83 (d, C-9), 121.68 (d, C-8), 127.22 (d, 2 × ArC), 129.74 (d and s, 2 × ArC), 132.59 (s, C-9a), 144.67 (s, ArC), 145.45 (s, C-6), and 146.94 (s, C-5a); *m/z* 446 (*M*, 1%) and 274 (*M* − $C_7H_8SO_3$, 68).

(4aS*,9bR*)-9b-*Cyanomethyl*-6-*methoxy*-1,4,4a,9b-*tetrahydrodibenzofuran*-3(2H)-*one Ethylene Acetal* (**18**).—A solution of the toluene-*p*-sulphonate derivative (**17**) (1.00 g, 2.24 mmol) and tetrabutylammonium cyanide (2.40 g, 8.96 mmol) in acetonitrile (3 ml) was heated at 80 °C for 24 h. After cooling to room temperature, ethyl acetate (250 ml) was added, and the solution was washed in turn with water (2 × 250 ml) and brine (250 ml). The crude product, which was isolated in the usual way, was purified by flash chromatography using light petroleum–ethyl acetate (60:40) to yield the *title compound* (**18**) (674 mg, 100%), m.p. 119—122 °C (from ethyl acetate–light petroleum) (Found: C, 67.7; H, 6.5; N, 5.1. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%); $\nu_{max.}$(CDCl$_3$) 2 250 cm^{-1}; $\lambda_{max.}$(EtOH) 280 nm (ε 2 190); δ_H(CDCl$_3$) 1.51—1.61 (1 H, m, 1-H$_{ax}$), 1.66—1.73 (1 H, m, 2-H$_{eq}$), 1.75 (1 H, dd, $J_{4.4a}$ 8.8 Hz, J_{gem} 14.0 Hz, 4-H$_{ax}$), 2.00—2.14 (1 H, m, 1-H$_{eq}$), 2.21 (1 H, ddd, J_{gem} 14.0 Hz, $J_{4.4a}$ 6.4 Hz, $J_{2eq.4}$ 2.4 Hz, 4-H$_{eq}$), 2.38 (1 H, m, 2-H$_{ax}$), 2.55 (1 H, d, *J* 16.4 Hz, CH$_2$CN), 2.60 (1 H, d, *J* 16.4 Hz, CH$_2$CN), 3.88 (3 H, s, OMe), 3.90—4.00 (4 H, m, OCH$_2$CH$_2$O), 4.67 (1 H, dd, $J_{4ax.4a}$ 8.8 Hz, $J_{4eq.4a}$ 6.4 Hz, 4a-H), and 6.85—6.97 (3 H, m, ArH); δ_C(CDCl$_3$) 27.98 (t, CH$_2$), 29.28 (t, CH$_2$), 30.58 (t, CH$_2$), 36.94 (t, CH$_2$), 46.29 (s, C-9b), 56.23 (q, OMe), 64.41 (t, OCH$_2$CH$_2$O), 86.55 (d, C-4a), 107.46 (s, C-3), 113.63 (d, C-7), 115.12 (d, C-9), 116.81 (s, CN), 122.20 (d, C-8), 131.55 (s, C-9a), 145.90 (s, C-6), and 146.66 (s, C-5a); *m/z* 301 (*M*, 76%), 261 (*M* − CH$_2$CN, 27), and 99 (100).

Hydrolysis of the Nitrile Acetal (**18**).—The nitrile acetal (200 mg, 0.664 mmol) was added to a mixture of dioxane (22 ml), methanol (14 ml), water (4 ml), and concentrated hydrochloric acid (0.4 ml), and the solution was stirred at 40 °C for 18 h. The product was isolated by means of ether (400 ml), and purified by flash chromatography using light petroleum–ethyl acetate (1:1) to afford (4aS*,9bR*)-9b-*cyanomethyl*-6-*methoxy*-1,4,4a,9b-*tetrahydrodibenzofuran*-3(2H)*one* (**19**) (123 mg, 72%), m.p. 125—127 °C (from ethyl acetate–light petroleum) (Found: C, 69.8; H, 5.8; N, 5.2. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%); $\nu_{max.}$(CDCl$_3$) 2 260 and 1 720 cm^{-1}; $\lambda_{max.}$(EtOH) 284 nm (ε 2 510); δ_H(CDCl$_3$) 1.94—2.05 (1 H, m, 1-H$_{ax}$), 2.14—2.20 (1 H, m, 2-H$_{eq}$), 2.26—2.40 (2 H, m, 1-H$_{eq}$ and 2-H$_{ax}$), 2.81 (1 H, d, J_{gem} 16.8 Hz, CH$_2$CN), 2.83 (1 H, dd, J_{gem} 17.4 Hz, $J_{4.4a}$ 3.6 Hz, 4-H), 2.89 (1 H, d, J_{gem} 16.8 Hz, CH$_2$CN), 3.05 (1 H, dd, J_{gem} 17.4 Hz, $J_{4.4a}$ 3.6 Hz, 4-H), 3.87 (3 H, s, OMe), 5.00 (1 H, t, *J* 3.6 Hz, 4a-H), 6.82—6.98 (3 H, m, ArH); δ_C(CDCl$_3$) 29.14 (t, CH$_2$), 31.33 (t, CH$_2$), 35.27 (t, CH$_2$), 41.68 (t, CH$_2$), 46.26 (s, C-9b), 55.96 (q, OMe), 85.75 (d, C-4a), 112.81 (d, C-7), 114.64 (d, C-9), 116.46 (s, CN) 122.81 (d, C-8), 130.02 (s, C-9a), 144.68 (s, C-6), 147.45 (s, C-5a), and 191.91 (s, C-3); *m/z* 257 (*M*, 95%) and 217 (*M* − CH$_2$CN, 94).

(3S*,4aS*,9bR*)-9b-*Cyanomethyl*-6-*methoxy*-1,2,3,4,4a,9b-*hexahydrodibenzofuran*-3-*ol* (**20**).—Sodium borohydride (0.86 g, 22.68 mmol) was added slowly (15 min) to a solution of the keto nitrile (**19**) (1.16 g, 4.53 mmol) in methanol at 0 °C and the mixture was stirred at 0 °C for 3 h. Ethyl acetate (200 ml) was added, and the excess of borohydride was decomposed with dilute hydrochloric acid (2 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml) and brine (200 ml), dried (Na$_2$SO$_4$), and evaporated. The crude product was purified by flash chromatography using light petroleum–ethyl acetate (3:7) to give the *title compound* (**20**) (1.06 g, 90%) as an oil (Found: C, 69.7; H, 6.9; N. 5.5. $C_{15}H_{17}NO_3$ requires C, 69.5, H, 6.6; N, 5.4%); $\nu_{max.}$(CHCl$_3$) 3 470 and 2 240 cm^{-1}; $\lambda_{max.}$(EtOH) 280 nm (ε 2 140); δ_H(CDCl$_3$) 1.28—1.38 (1 H, m, 2-H$_{ax}$), 1.64—1.94 (3 H, m, 1-H$_{ax}$, 1-H$_{eq}$, and 2-H$_{eq}$), 2.07—2.17 (1 H, b, exchangeable, OH), 2.26—2.35 (2 H, m, 2 × 4-H), 2.55 (2 H, s, CH$_2$CN), 3.75—3.83 (1 H, m, 3-H), 3.88 (3 H, s, OMe), 4.64 (1 H, dd, *J* 5.8 Hz, *J* 7.8 Hz, 4a-H), and 6.81—7.00 (3 H, m, ArH); δ_C(CDCl$_3$) 27.81 (t, CH$_2$), 28.55 (t, CH$_2$), 30.03 (t, CH$_2$), 36.39 (t, CH$_2$), 46.28 (s, C-9b), 56.04 (q, OMe), 65.86 (d, C-3), 86.24 (d, C-4a), 112.86 (d, C-7), 114.72 (d, C-9), 117.13 (s, CN), 122.43 (d, C-8), 131.83 (s, C-9a), 145.73 (s, C-6), and 146.04 (s, C-5a); *m/z* 259 (*M*, 55%), 219 (*M* − CH$_2$CN, 42), 201 (219 − H$_2$O, 60), and 175 (201 − C_2H_2, 100).

(3S*,4aS*,9bR*)-9b-*Formylmethyl*-6-*methoxy*-1,2,3,4,4a,9b-*hexahydrodibenzofuran*-3-*ol* (**24**).—Di-isobutylaluminium hydride (25% w/v in toluene; 441 mg, 3.10 mmol) was added dropwise over 15 min to a solution of the hydroxy nitrile (**20**) (201 mg, 0.78 mmol) in 1,2-dimethoxyethane (2 ml) at −78 °C. The solution was stirred at −78 °C for 2 h, and then for 2 h at room temperature. Methanol (1 ml) in benzene (1 ml) was added dropwise with stirring followed by the addition of hydrochloric acid (5%, 10 ml) and extraction with ethyl acetate (3 × 50 ml). The organic extract was washed in turn with hydrochloric acid (5%), water, and brine, dried (Na$_2$SO$_4$), and evaporated. The crude product was purified by flash chromatography using ethyl acetate to yield the *title compound* (**24**) (151 mg, 74%) as an oil (Found: M^+, 262.1204. $C_{15}H_{18}O_4$ requires M^+, 262.1205); $\nu_{max.}$(film) 3 400, 1 720, 1 610, and 1 585 cm^{-1}; δ_H(CDCl$_3$) 1.32—1.43 (1 H, m, 1-H$_{ax}$), 1.67—1.88 (3 H, m, 2 × 1-H and 2-H$_{eq}$), 2.15—2.30 (2 H, m, 2 × 4-H), 2.62 (1 H, dd, J_{gem} 16.0 Hz, *J* 2.4 Hz, C*H*$_2$CHO), 2.71 (1 H, dd, J_{gem}, *J* 2.4 Hz, C*H*$_2$CHO), 3.82 (1 H, m, 3-H), 3.88 (3 H, s,

OMe), 4.69 (1 H, dd, *J* 5.6 Hz, *J* 7.2 Hz, 4a-H), 6.80—6.95 (3 H, m, ArH), and 9.7 (1 H, t, *J* 2.4 Hz, CHO); $\delta_C(CDCl_3)$ 29.09, 29.97, 35.67, 46.23, 51.95, 56.01, 66.00, 76.69, 77.01, 77.32, 86.76, 112.21, 114.99, 122.19, and 200.79 (d, CHO); *m/z* 262 (*M*, 68%), 219 (*M* − CH_2CHO, 28), 201 (219 − H_2O, 46), and 175 (201 − C_2H_2, 100).

(3S*,4aS*,9bR*)-9b-[2-(N-*Formyl*-N-*methylamino*)*ethyl*]-3-*formyloxy*-6-*methoxy*-1,2,3,4,4a,9b-*hexahydrodibenzofuran* (**25**).—The aldehyde (**24**) (121 mg, 0.461 mmol) was dissolved in anhydrous methanol (2 ml), and methylamine hydrochloride (187 mg, 2.77 mmol) and sodium cyanoborohydride (125 mg, 2.0 mmol) were added with stirring. The mixture was stirred at 25 °C for 72 h, concentrated hydrochloric acid was then added until the pH was less than 2, and the methanol was removed under reduced pressure. Water (10 ml) was added and the mixture was extracted with ether (3 × 20 ml). The aqueous solution was made alkaline (pH > 10) by the addition of solid potassium hydroxide, saturated with sodium chloride, and extracted with ether (5 × 20 ml). The combined ether extracts were dried (Na_2SO_4) and evaporated.

The oily residue was dissolved in pyridine (10 ml) containing formic acetic anhydride (1.0 ml), and the solution was heated at 80 °C under nitrogen for 6 h. The pyridine was then evaporated under reduced pressure, ethyl acetate (10 ml) was added, and the solution was washed in turn with hydrochloric acid (1M; 2 ml), saturated aqueous sodium hydrogen carbonate (2 ml), and brine (2 ml). The solution was dried (Na_2SO_4), evaporated, and the residue purified by flash chromatography using ethyl acetate to afford the amide (**25**) (121 mg, 79%) as a colourless oil with i.r., ^1H n.m.r., and mass spectral data corresponding closely with those reported previously,[3a] $\nu_{max.}(CHCl_3)$ 1 720 and 1 660 cm^{-1}; $\delta_H(CDCl_3)$ 1.43 (1 H, m, 1-H_{ax}), 1.60—2.04 (5 H, m), 2.22 (1 H, m, CH_2N), 2.32 (1 H, m, CH_2N), 2.74 (1.5 H, s, 0.5 × NMe), 2.81 (1.5 H, s, 0.5 × NMe), 2.95—3.32 (1 H, m), 3.88 (1.5 H, s, 0.5 × OMe), 3.89 (1.5 H, s, 0.5 × OMe), 4.66 (1 H, m, 4a-H), 4.94 (1 H, m, 3-H), 6.70—6.98 (3 H, m, ArH), 7.88 (0.5 H, s), 7.94 (0.5 H, s), 7.97 (0.5 H, s), and 7.98 (0.5 H, s); *m/z* 333 (*M*, 71%), 247 (*M* − C_3H_7NCHO, 10), 228 (10), 201 (247 − HCO_2H, 100), and 175 (201 − C_2H_2, 10).

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