Stereoselective synthesis of (3*R**,3a*S**,7a*S**)-3-aryloctahydroindol-2-ones using radical cyclisation: a formal synthesis of (±)-pancracine

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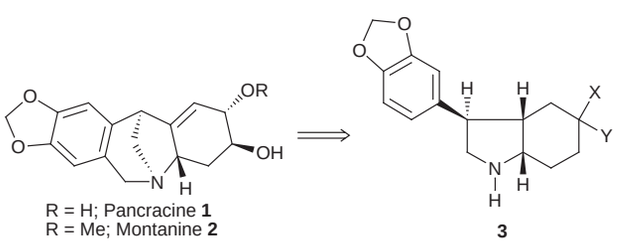
The Bu_3SnH- or $(TMS)_3SiH$-mediated 5-*endo-trig* radical cyclisation of the *N*-(cyclohex-1-enyl)acetamide **10** gives a mixture of the *cis*-fused (3*R**,3a*S**,7a*S**)- and *trans*-fused (3*R**,3a*S**,7a*R**)-3-aryloctahydroindol-2-ones **11a** and **11b**, whereas the 5-*exo-trig* radical cyclisation of the *N*-(cyclohex-2-enyl)acetamide **17** proceeds in a stereoselective manner to give only **11a**. The latter method has been applied to the synthesis of the 5,11-methanomorphanthridine derivative **30**, a key intermediate for the synthesis of (±)-pancracine **1**.

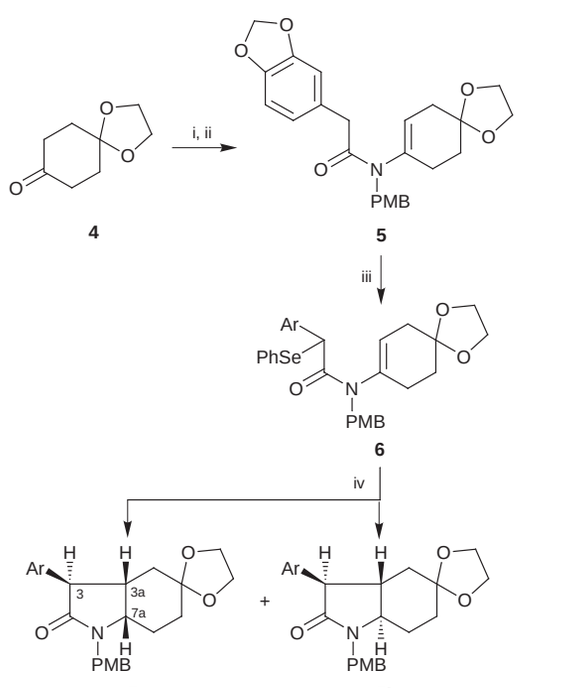
In recent years, radical cyclisation has emerged as a valuable tool for the construction of carbo- and heterocyclic compounds including natural products.[1] In continuation of our studies directed towards the synthesis of the nitrogen-containing natural products using radical cyclisations,[2,3] we turned our attention to the synthesis of (3*R**,3a*S**,7a*S**)-3-aryloctahydroindoles **3**, since the Pictet–Spengler cyclisation of compounds of type **3** is known[4] to provide the 5,11-methanomorphanthridine skeleton,[5] which is a basic structural element of montanine-type *Amaryllidaceae* alkaloids such as pancracine **1** and montanine **2**.[6] The present paper describes the results of our work in this area including a stereoselective formal synthesis of (±)-pancracine.[7]



Results and discussion

First, we examined the 5-*endo-trig* radical cyclisation[8] of the *N*-(cyclohex-1-enyl)acetamide **6**. The synthesis of **6** was begun by condensation of cyclohexane-1,4-dione monoethylene acetal **4** with 4-methoxybenzylamine. Acylation of the resulting imine with (3,4-methylenedioxyphenyl)acetic pivalic anhydride gave the enamide **5** (Scheme 1). Treatment of **5** with lithium diisopropylamide (LDA) and then with benzeneselenenyl chloride afforded **6**. Several attempts to introduce a phenylsulfanyl group into compound **5** failed, and attempted preparation of the haloacetyl halides as acylating agents was unsuccessful.

When the amide **6** was treated with Bu_3SnH (1.1 equiv.) and a small amount of azoisobutyronitrile (AIBN) in boiling benzene, an inseparable mixture of two cyclisation products **7a** and **7b** was obtained in a ratio of *ca.* 1:1 (by ^1H NMR spectroscopy) and in 82% combined yield. The following chemical operations allowed us to obtain pure samples of the compounds **7a** and **7b**. Hydrolysis of the mixture of the acetals **7a**,**b** gave the ketones **8a** and **8b** in 54 and 47% isolated yield, respectively, each of which was again protected with ethylene glycol to give the crystalline acetals **7a** and **7b**, respectively (Scheme 2).



Scheme 1 *Reagents and conditions* (*and yields*): i, 4-methoxybenzylamine, benzene, reflux; ii, (3,4-methylenedioxyphenyl)acetic pivalic anhydride, pyridine, benzene, 30–40 °C (77% from **4**); iii, LDA, HMPA, THF, −78 °C; then PhSeCl (65%); iv, Bu_3SnH or $(TMS)_3SiH$, AIBN, benzene, reflux.

The X-ray crystallographic analysis of compound **7b** (Fig. 1) shows, somewhat surprisingly, the stereochemistry of the ring juncture to be *trans* with a *trans*-stereochemistry between the protons at the 3- and 3a-position. The structure of the *cis*-fused compound **7a** was established by transforming it into the known compound **30** (*vide infra*).

In order to see the effect of the size of the hydride source on

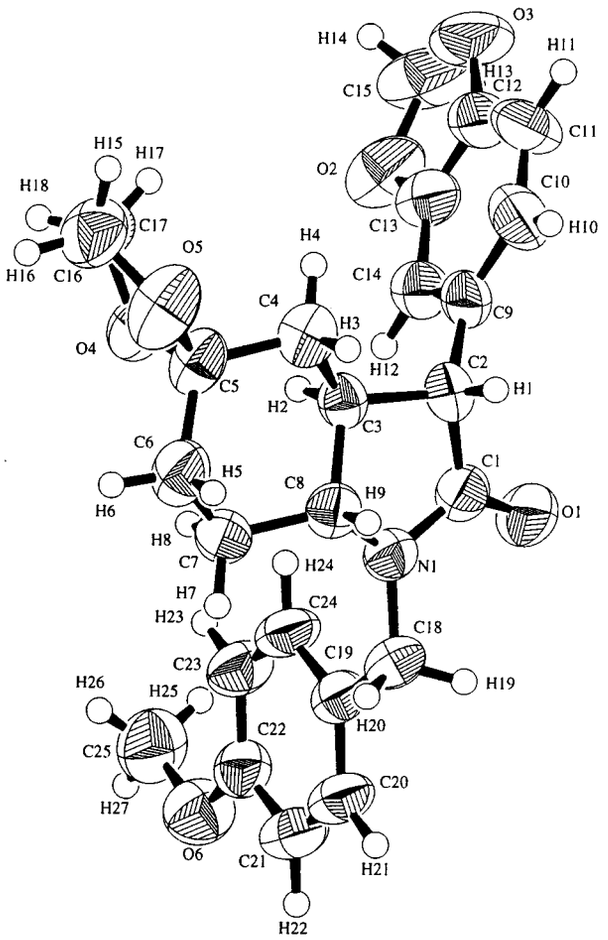
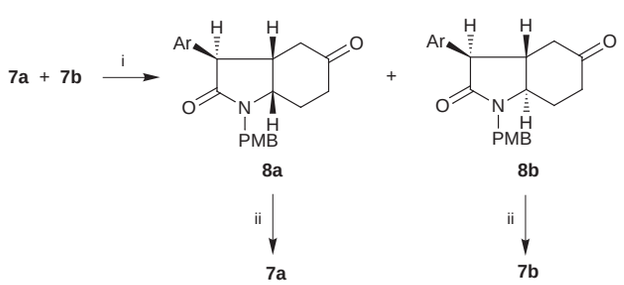


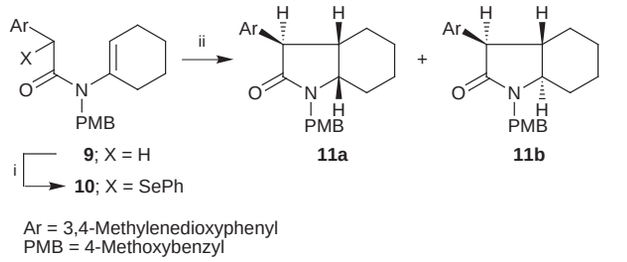
Fig. 1 Single-crystal X-ray structure of compound **7b** with crystallographic numbering scheme.



Scheme 2 *Reagents and conditions* (*and yields*): i, 5% HCl, acetone, reflux [54% (**8a**) + 47% (**8b**)]; ii, ethylene glycol, TsOH, benzene, reflux (95% for **7a**, 97% for **7b**).

the stereoselectivity of the cyclisation of **6**, compound **6** was treated with tris(trimethylsilyl)silane to give a mixture of **7a** and **7b** in a ratio of *ca.* 1:2 in 75% combined yield. This result suggests that a sterically more demanding hydride source such as $(TMS)_3SiH$ provides the *trans*-fused bicyclic compound **7b** as the major product, although the exact reason is obscure at the moment.

Next, to address an obvious question as to why the undesired *trans*-fused compound **7b** was formed from **6**, we next examined the behaviour of the cyclisation of compound **10** having no ethylene acetal group on the cyclohexene ring. Thus, compound **10** was treated with Bu_3SnH to give again a mixture of the *cis*- and *trans*-fused octahydroindol-2-one derivatives, **11a** and **11b**, in 17 and 21% yield, respectively (Scheme 3). With $(TMS)_3SiH$, the *trans*-fused compound **11b** was obtained as the major product in 39% yield along with the *cis* isomer **11a** (21% yield). The structures of **11a,b** were deduced from a comparison of their ^1H NMR spectra with those of **7a**,**b**. The chemical shift

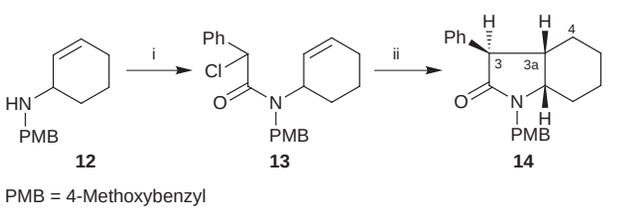


Scheme 3 *Reagents and conditions* (*and yields*): i, LDA, HMPA, THF, −78 °C; then PhSeCl (42%); ii, Bu_3SnH or $(TMS)_3SiH$, AIBN, benzene, reflux.

[δ 3.35 (1 H, dt, *J* 9.9 and 6.4)] due to the 7a-H of the *cis*-fused isomer **11a** closely resembled that for the *cis*-fused isomer **7a** [δ 3.40 (1 H, dt, *J* 9.3 and 6.5)] and the corresponding signals for the *trans*-fused isomers **11b** and **7b** appeared up field [δ 2.84–2.95 (1 H, m) and 2.88–2.97 (1 H, m), respectively]. The structure of **11a** was further confirmed by transforming it into the known compound **21** (*vide infra*).

Thus, the 5-*endo*-*trig* cyclisation of the *N*-(cyclohex-1-enyl) systems was found to be inadequate for our purposes. Therefore, our attention was next turned to the 5-*exo*-*trig* cyclisation[9] of the corresponding *N*-(cyclohex-2-enyl) systems.

First we examined the cyclisation of the simple *N*-(cyclohex-2-enyl) compound **13**, which was prepared by acylation of the amine **12** with 2-chloro-2-phenylacetyl chloride (Scheme 4).



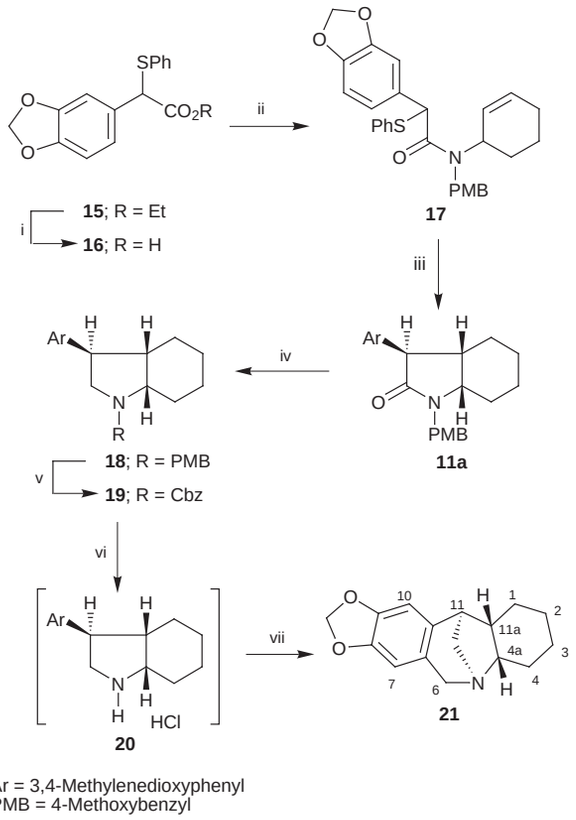
Scheme 4 *Reagents and conditions* (*and yields*): i, 2-chloro-2-phenylacetyl chloride, Et_3N, CH_2Cl_2, room temp. (65%); ii, Bu_3SnH or $(TMS)_3SiH$, AIBN, benzene, reflux.

Treatment of **13** with Bu_3SnH in the presence of AIBN in boiling benzene afforded the 3-phenyloctahydroindol-2-one **14** as a single stereoisomer in 81% yield. Similar treatment of **13** with $(TMS)_3SiH$ gave also **14** as the sole product in 85% yield. The structure of **14** was deduced from a striking resemblance of its ^1H NMR spectral data with those of **11a** (see Experimental section).

The observed high diastereoselectivity between C-3 and C-3a can be rationalised by assuming that the radical formed from **13** attacks the double bond of the cyclohexene ring *via* a transition state which minimises steric repulsion between the aryl group and the C3a–C4 bond of the newly forming octahydroindolone ring.

Thus, the 5-*exo*-*trig* radical cyclisation of the *N*-(cyclohex-2-enyl)acetamide **13** was found to take place in a completely stereoselective manner to give the desired (3*R**,3a*S**,7a*S**)-3-aryloctahydroindol-2-one skeleton. So we then undertook a model study of the synthesis of the 5,11-methanomorphanthridine skeleton using the 2-(3,4-methylenedioxyphenyl)-acetamide **17** as a radical precursor, which was prepared as follows. Treatment of 1,2-methylenedioxybenzene with ethyl 2-chloro-2-(phenylthio)acetate[10] in the presence of $TiCl_4$ gave the Friedel–Crafts reaction product **15** in 75% yield. Subsequent alkaline hydrolysis of the ester **15** afforded the carboxylic acid **16**, which was then treated with amine **12** in the presence of dicyclohexylcarbodiimide (DCC) to give **17** (Scheme 5).

When the amide **17** was treated with Bu_3SnH in the presence of AIBN in boiling benzene, the expected radical cyclisation product **11a** was obtained in 78% yield. Similar treatment with



Scheme 5 *Reagents and conditions* (*and yields*): i, 5% KOH, EtOH, reflux (quant.); ii, **12**, DCC, DMAP, CH_2Cl_2, room temp. (78%); iii, Bu_3SnH or $(TMS)_3SiH$, AIBN, benzene, reflux; iv, AlH_3, THF, room temp. (93%); v, Cbz-Cl, benzene, reflux (90%); vi, H_2, 10% Pd–C, conc. HCl, MeOH, room temp.; vii, (a) HCHO, Et_3N, MeOH, (b) 20% HCl, MeOH, 30–40 °C (47% from **19**).

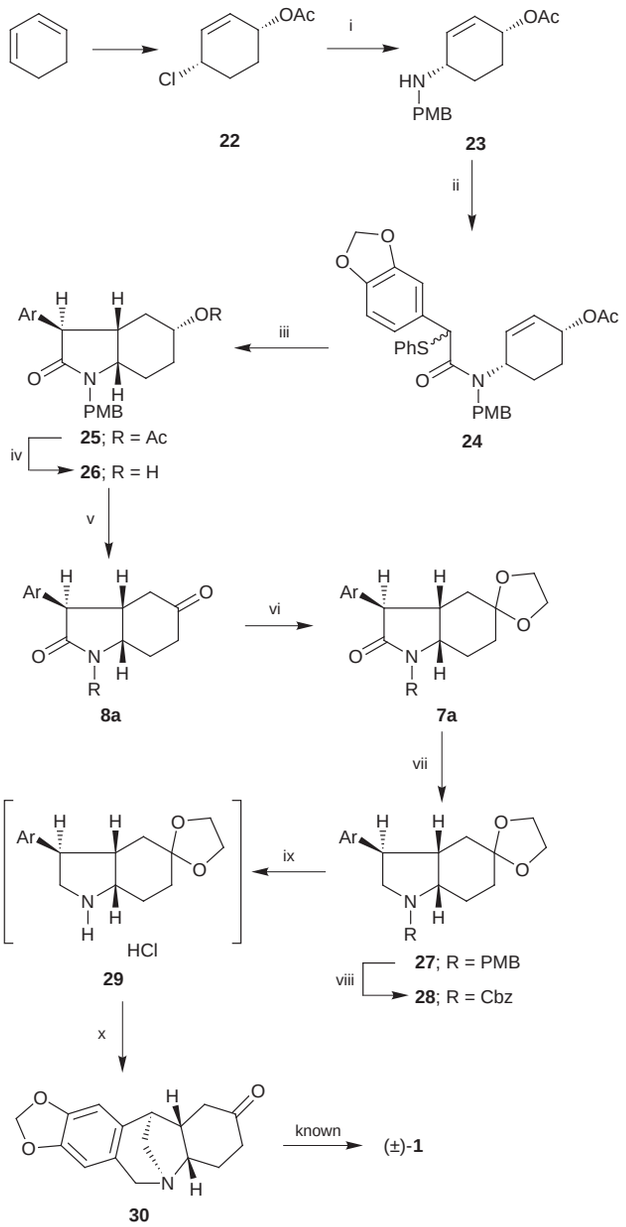
$(TMS)_3SiH$ gave **11a** in 85% yield. The spectral data of **11a** thus obtained were identical with those of an authentic sample prepared by cyclisation of **10** (see Scheme 3).

Reduction of the lactam **11a** with AlH_3 gave **18**, which was heated with benzyloxycarbonyl chloride (Cbz-Cl) in benzene[11] to give the carbamate **19** in 84% yield from **11a**. The Cbz group of **19** was then removed by catalytic hydrogenolysis over Pd–C in the presence of conc. HCl to give the amine hydrochloride **20**. An attempt to remove the *p*-methoxybenzyl (PMB) group of **18** with cerium(IV) ammonium nitrate (CAN) or with Na in liq. NH_3 resulted in recovery of the starting material. The Pictet–Spengler cyclisation of **20** was achieved by treatment with formalin in the presence of Et_3N and then with 20% HCl at 30–40 °C to give the desired 5,11-methanomorphanthridine derivative **21**, whose melting point (97–99 °C; lit.,[5a] 100 °C) and physical data were virtually identical with the literature values.[5a]

In planning the synthesis of (±)-pancrancine **1**, the amide **24** having an oxygen functionality at the 4-position of the cyclohex-2-enyl ring is needed as a radical precursor. This compound was prepared from the known (±)-*cis*-3-acetoxy-6-chlorocyclohexene **22**,[12] which in turn was prepared from cyclohexa-1,3-diene. Thus, according to the procedure reported by Bäckvall,[13] a mixture of **22** and 4-methoxybenzylamine was treated with bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] in the presence of Ph_3P to give the amine **23** in 72% yield. Compound **23** was then acylated with the carboxylic acid **16** in the presence of DCC to give the amide **24** in 79% yield (Scheme 6).

When the amide **24** was treated with $(TMS)_3SiH$ in the presence of AIBN in boiling benzene, (3*R**,3a*S**,7a*S**)-3-aryloctahydroindol-2-one **25** was obtained in 84% yield as a single stereoisomer.

With the requisite octahydroindol-2-one **25** so conveniently assembled, we then examined transformation of **25** into the key



Scheme 6 *Reagents and conditions* (*and yields*): i, $Pd(dba)_2$, Ph_3P, 4-methoxybenzylamine, Et_3N, THF, room temp. (72%); ii, **16**, DCC, DMAP, CH_2Cl_2, room temp. (79%); iii, $(TMS)_3SiH$, AIBN, benzene, reflux (84%); iv, LiOH, MeOH–H_2O, reflux (95%); v, DMSO, $(COCl)_2$, CH_2Cl_2; then Et_3N (99%); vi, ethylene glycol, TsOH, benzene, reflux (95%); vii, AlH_3, THF, room temp.; viii, Cbz-Cl, benzene, reflux (75% from **7a**); ix, H_2, 10% Pd–C, conc. HCl, MeOH, room temp.; x, (a) HCHO, Et_3N, MeOH, (b) 20% HCl, MeOH, 30–40 °C (64% from **28**).

intermediate **30** for the synthesis of (±)-pancracine **1**. Hydrolysis of the acetoxy group of **25** with LiOH followed by Swern oxidation of the resultant alcohol **26** gave the keto lactam **8a**. This compound was identical to that obtained by hydrolysis of the acetal **7a**, which was one of the radical-cyclisation products from **6** (see Schemes 1 and 2). Compound **8a** was then protected with ethylene glycol in a manner similar to that described above (see Scheme 2) to give the acetal **7a**. Reduction of **7a** with AlH_3 followed by treatment of the resultant amine **27** with Cbz-Cl gave the carbamate **28**. Catalytic hydrogenolysis in the presence of conc. HCl gave the amine hydrochloride **29**, which was subjected to Pictet–Spengler cyclisation in a manner similar to that described above for the preparation of **21**, to give, with concomitant deprotection of the ethylene acetal,

the 5,11-methanomorphanthridine **30** in 64% yield from **28**. The melting point (125–126 °C; lit.,[5d] 125 °C) and ^{1}H NMR spectral data of **30** herein obtained were identical with the literature values.[5d] Since compound **30** has already been converted into (±)-pancracine **1**,[5d] the present sequence of reactions herein described constitutes a formal total synthesis of (±)-pancracine.

Experimental

Mps were measured on a Yanaco MP-J3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^{1}H NMR (60 and 300 MHz) and ^{13}C NMR (75.4 MHz) spectra were measured on a JEOL-JNM-PMX 60 or a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ-Values quoted are relative to tetramethylsilane, and *J*-values are given in Hz. Exact mass determinations (EI and FAB mass spectra) were obtained on a JEOL-SX 102A instrument. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

2-(3,4-Methylenedioxyphenyl)acetic pivalic anhydride

To a stirred solution at −78 °C containing 2-(3,4-methylenedioxyphenyl)acetic acid (6 g, 33.3 mmol) in diethyl ether (360 cm^3) were added successively pivaloyl chloride (4.02 g, 33.3 mmol) and Et_3N (3.37 cm^3, 33.3 mmol). The mixture was stirred at the same temperature for 45 min and then at 0 °C for 15 min. The precipitated salts were filtered off and the filtrate was concentrated to give 2-(3,4-methylenedioxyphenyl)acetic pivalic anhydride (8.24 g, 94%) as an oil; δ_H(60 MHz) 1.17 (9 H, s), 3.65 (2 H, s), 5.92 (2 H, s) and 6.73 (3 H, s). This compound was used in the next step without further purification.

N-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)acetamide 5

A solution of cyclohexane-1,4-dione monoethylene acetal **4** (2.84 g, 18.2 mmol) and 4-methoxybenzylamine (2.09 g, 15.2 mmol) in benzene (140 cm^3) was heated at reflux with azeotropic removal of water for 2 h. To this mixture were added successively pyridine (2.4 g, 30.4 mmol) and a solution of 2-(3,4-methylenedioxyphenyl)acetic pivalic anhydride (8.02 g, 30.4 mmol) in benzene (50 cm^3) at room temperature. The mixture was stirred at 30–40 °C for 2 h. After this, the reaction mixture was washed successively with 5% HCl, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **5** (4.89 g, 77%) as an oil [Found: $(M + H)^+$, 438.1926. $C_{25}H_{28}NO_6$ requires MH^+, 438.1917]; $\nu_{max}(CCl_4)$/cm^{-1} 1640; δ_H(300 MHz) 1.78 (2 H, t, *J* 6.5), 2.16–1.25 (4 H, m), 3.57 (2 H, s), 3.78 (3 H, s), 3.98 (4 H, s), 4.54 (2 H, br s), 5.08–5.12 (1 H, m), 5.92 (2 H, s), 6.72–6.85 (5 H, m) and 7.18 (2 H, d, *J* 8.6).

N-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylseleno)acetamide 6

To a stirred solution at −78 °C containing LDA [prepared from diisopropylamine (429 mg, 4.24 mmol) and a 1.6 mol dm^{-3} solution of butyllithium in hexane (2.65 cm^3, 4.24 mmol)] was added a solution of **5** (1.24 g, 2.82 mmol) in THF (1 cm^3). The mixture was stirred at the same temperature for 30 min. HMPA (759 mg, 4.24 mmol) was added to the mixture, which was again stirred at the same temperature for 15 min. After this, benzeneselenenyl chloride (812 mg, 4.24 mmol) was added and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of saturated aq. NH_4Cl, and the mixture was extracted with diethyl ether. The extract was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (3:1)] to give **6** (1.08 g, 65%) as an oil; $\nu_{max}(CCl_4)$/cm^{-1} 1645; δ_H(60 MHz) 1.15–2.4 (6 H, m), 3.72 (3 H, s), 3.8–4.05 (4 H, m), 4.35–4.60 (2 H, br s), 4.7–5.0 (1 H, m), 5.13 (1 H, s), 5.86 (2 H, s) and 6.55–7.70 (12 H, m). This compound was used immediately in the next step.

Radical cyclisation of 6

With Bu_3SnH: general procedure. A solution of Bu_3SnH (320 mg, 1.1 mmol) and AIBN (17 mg, 0.1 mmol) in benzene (150 cm^3) was added dropwise to a solution of **6** (592 mg, 1 mmol) in boiling benzene (73 cm^3) *via* a syringe during 2 h, and the mixture was further refluxed for 2 h. After concentration of the reaction mixture by removal of the solvent, diethyl ether (50 cm^3) and 8% aq. KF (50 cm^3) were added to the residue, and the whole mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (2:1)] to give a *ca.* 1:1 mixture of (3*R**,3a*S**,7a*S**)- and (3*R**,3a*S**,7a*R**)-5,5-(ethylenedioxy)octahydro-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indol-2-one **7a** and **7b** (360 mg, 82%) as an oil. The physical data for the pure samples of compounds **7a** and **7b** are described later.

With $(TMS)_3SiH$. Following the general procedure, compound **6** (165 mg, 0.28 mmol) was treated with $(TMS)_3SiH$ (277 mg, 1.11 mmol) and AIBN (11 mg, 0.07 mmol) in boiling benzene. After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (2:1)] to give a *ca.* 1:2 mixture of **7a**,**b** (92 mg, 75%).

(3*R**,3a*S**,7a*S**)- and (3*R**,3a*S**,7a*R**)-Hexahydro-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indole-2,5(3*H*)-dione 8a and 8b

A solution of the mixture of **7a** and **7b** (353 mg, 0.81 mmol) in acetone (13 cm^3) and 5% HCl (9 cm^3) was heated at reflux for 1 h. After this, the reaction mixture was poured into brine (20 cm^3) and the mixture was extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel [hexane–AcOEt (2:1)]. The first eluent gave **8b** (148 mg, 47%) as an oil [Found: $(M + H)^+$, 394.1650. $C_{23}H_{24}NO_5$ requires MH^+, 394.1655]; $\nu_{max}(CHCl_3)$/cm^{-1} 1685; δ_H(300 MHz) 1.55–1.70 (1 H, m), 2.00–2.15 (1 H, m), 2.22–2.40 (3 H, m), 2.45–2.60 (2 H, m), 3.27 (1 H, d, *J* 11.8, 3-H), 3.32–3.36 (1 H, m, 7a-H), 3.80 (3 H, s), 4.20 (1 H, d, *J* 14.9), 4.87 (1 H, d, *J* 14.9), 5.94 (2 H, s), 6.61–6.68 (2 H, m), 6.78 (1 H, d, *J* 7.9), 6.87 (2 H, d, *J* 8.6) and 7.22 (2 H, d, *J* 8.6); δ_C 29.0, 39.0, 42.7, 44.2, 48.8, 54.4, 55.2, 58.4, 101.0, 108.4, 108.5, 114.1, 121.9, 128.6, 129.2, 129.7, 147.0, 148.0, 159.0, 175.3 and 206.8. The second eluent gave **8a** (170 mg, 54%), mp 103–104 °C (from hexane–AcOEt) (Found: C, 70.0; H, 5.9; N, 3.5. $C_{23}H_{23}NO_5$ requires C, 70.2; H, 5.9; N, 3.6%); $\nu_{max}(CHCl_3)$/cm^{-1} 1705 and 1675; δ_H(300 MHz) 1.90–2.18 (2 H, m, 7-H_2), 2.24–2.34 (2 H, m, 6-H_2), 2.47 (1 H, dd, *J* 15.9 and 5.6, one of 4-H_2), 2.55 (1 H, dd, *J* 15.9 and 6.3, one of 4-H_2), 2.67–2.79 (1 H, m, 3a-H), 3.29 (1 H, d, *J* 8.4, 3-H), 3.78–3.86 (1 H, m, 7a-H), 3.82 (3 H, s), 4.00 (1 H, d, *J* 14.8), 5.03 (1 H, d, *J* 14.8), 5.94 (2 H, s), 6.59–6.63 (2 H, m), 6.77 (1 H, d, *J* 8.4), 6.90 (2 H, d, *J* 8.6) and 7.24 (2 H, d, *J* 8.6); δ_C 24.4, 35.5, 40.1, 41.1, 44.2, 53.0, 54.2, 55.2, 101.1, 108.1, 108.5, 114.2, 121.6, 128.3, 129.4, 132.2, 147.0, 148.1, 159.2, 173.4 and 209.6.

(3*R**,3a*S**,7a*S**)-5,5-(Ethylenedioxy)octahydro-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indol-2-one 7a

A solution of **8a** (790 mg, 2.01 mmol), ethylene glycol (249 mg, 4.02 mmol) and toluene-4-sulfonic acid monohydrate (TsOH) (76 mg, 0.4 mmol) in benzene (50 cm^3) was heated at reflux for 2 h with azeotropic removal of water. Water was added to the reaction mixture and the whole was extracted with benzene.

The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **7a** (836 mg, 95%), mp 149–150 °C (from hexane–AcOEt) (Found: C, 68.6; H, 6.3; N, 3.4. $C_{25}H_{27}NO_6$ requires C, 68.6; H, 6.2; N, 3.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1670; δ_H(300 MHz) 1.43–1.84 (5 H, m), 1.95–2.05 (1 H, m), 2.35–2.48 (1 H, m), 3.40 (1 H, dt, *J* 9.3 and 6.5, 7a-H), 3.82 (3 H, s), 3.90–4.02 (6 H, m), 4.98 (1 H, d, *J* 15.0), 5.95 (2 H, s), 6.64–6.69 (2 H, m), 6.79 (1 H, d, *J* 7.7), 6.88 (2 H, d, *J* 8.6) and 7.22 (2 H, d, *J* 8.6); δ_C 24.9, 31.3, 32.8, 42.9, 44.0, 51.3, 53.5, 55.3, 64.0, 64.5, 100.9, 108.1, 108.4, 109.1, 114.1, 122.3, 129.0, 129.4, 132.0, 146.6, 147.9, 159.1 and 174.5.

(3*R**,3a*S**,7a*R**)-5,5-(Ethylenedioxy)octahydro-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indol-2-one 7b

Using a procedure similar to that described above for **7a**, compound **8b** (959 mg, 2.41 mmol) was treated with ethylene glycol (300 mg, 4.83 mmol) to give **7b** (1.03 g, 97%), mp 133–134 °C (from diethyl ether) (Found: C, 68.55; H, 6.3; N, 3.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1665; δ_H(300 MHz) 1.44–1.62 (3 H, m), 1.76–1.88 (2 H, m), 1.98–2.16 (2 H, m), 2.88–2.97 (1 H, m, 7a-H), 3.14 (1 H, d, *J* 12.3, 3-H), 3.80 (3 H, s), 3.84–3.93 (4 H, m), 4.24 (1 H, d, *J* 14.9), 4.72 (1 H, d, *J* 14.9), 5.95 (2 H, s), 6.66–6.72 (2 H, m), 6.79 (1 H, d, *J* 7.8), 6.86 (2 H, d, *J* 8.6) and 7.20 (2 H, d, *J* 8.6); δ_C 26.7, 33.7, 36.5, 44.2, 47.5, 54.1, 55.2, 60.0, 64.3, 64.5, 100.9, 108.3, 108.9, 114.0, 122.1, 129.2, 129.3, 130.6, 146.7, 147.9, 158.9 and 175.9.

N-(Cyclohex-1-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)acetamide 9

Using a procedure similar to that described above for the preparation of **5**, cyclohexanone (1.76 g, 18 mmol) was treated with 4-methoxybenzylamine (2.05 g, 15 mmol), and the resultant imine was then treated with 2-(3,4-methylenedioxyphenyl)acetic pivalic anhydride (7.9 g, 29.9 mmol) to give **9** (3.98 g, 59%) as an oil [Found: $(M + H)^+$, 380.1855. $C_{23}H_{26}NO_4$ requires MH^+, 380.1862]; $\nu_{max}(CCl_4)/cm^{-1}$ 1640; δ_H(300 MHz) 1.48–1.72 (4 H, m), 1.82–2.06 (4 H, m), 3.57 (2 H, s), 3.78 (3 H, s), 4.53 (2 H, br s), 5.27–5.31 (1 H, m), 5.92 (2 H, s), 6.65–6.82 (5 H, m) and 7.18 (2 H, d, *J* 8.6).

N-(Cyclohex-1-eny1)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylseleno)acetamide 10

Using a procedure similar to that described above for the preparation of **6**, compound **9** (3.98 g, 10.5 mmol) was treated successively with LDA (15.8 mmol) and benzeneselenenyl chloride (3.0 g, 15.8 mmol) to give **10** (2.31 g, 42%) as an oil; $\nu_{max}(CCl_4)/cm^{-1}$ 1650; δ_H(60 MHz) 1.3–2.0 (8 H, m), 3.73 (3 H, s), 4.3–4.6 (2 H, br), 4.7–5.0 (1 H, m), 5.06 (1 H, s), 5.87 (2 H, s) and 6.5–7.5 (12 H, m). This compound was used immediately in the next step.

Radical cyclisation of 10

With Bu_3SnH. Following the general procedure, compound **10** (534 mg, 1 mmol) was treated with Bu_3SnH (296 mg, 1.1 mmol) and AIBN (16 mg, 0.1 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)]. The first eluent gave (3*R**,3a*S**,7a*R**)-*octahydro*-1-(4-*methoxybenzyl*)-3-(3,4-*methylenedioxyphenyl*)*indol*-2-*one* **11b** (80 mg, 21%) as an oil [Found: $(M + H)^+$, 380.1854. $C_{23}H_{26}NO_4$ requires MH^+, 380.1862]; $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz) 1.15–1.35 (4 H, m), 1.60–1.90 (4 H, m), 2.04–2.12 (1 H, m), 2.84–2.95 (1 H, m, 7a-H), 3.12 (1 H, d, *J* 12.2, 3-H), 3.79 (3 H, s), 4.18 (1 H, d, *J* 14.8), 4.75 (1 H, d, *J* 14.8), 5.93 (2 H, s), 6.65–6.72 (2 H, m), 6.79 (1 H, d, *J* 7.8), 6.85 (2 H, d, *J* 8.7) and 7.20 (2 H, d, *J* 8.7); δ_C 21.1, 22.3, 24.8, 27.8, 42.0, 43.7, 50.5, 54.3, 55.2, 100.9, 108.2, 108.8, 113.9, 122.1, 129.0, 129.3, 132.0, 146.5, 147.8, 158.9 and 174.4. The second eluent gave (3*R**, 3a*S**,7a*S**)-*octahydro*-1-(4-*methoxybenzyl*)-3-(3,4-*methylenedioxyphenyl*)*indol*-2-*one* **11a** (64 mg, 17%), mp 148.5–150 °C (from hexane–AcOEt) (Found: C, 72.5; H, 7.0; N, 3.3. $C_{23}H_{25}NO_4$ requires C, 72.8; H, 6.6; N, 3.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz) 1.10–1.70 (7 H, m), 1.93–2.05 (1 H, m), 2.21–2.33 (1 H, m), 3.35 (1 H, dt, *J* 9.9 and 6.4), 3.47 (1 H, d, *J* 11.2), 3.80 (3 H, s), 3.95 (1 H, d, *J* 14.8), 4.98 (1 H, d, *J* 14.8), 5.92 (2 H, s), 6.63–6.70 (2 H, m), 6.78 (1 H, d, *J* 7.8), 6.88 (2 H, d, *J* 8.5) and 7.22 (2 H, d, *J* 8.5); δ_C 21.1, 22.3, 24.8, 27.8, 42.0, 43.7, 50.5, 54.3, 55.2, 100.9, 108.2, 108.8, 113.9, 122.1, 129.0, 129.3, 132.0, 146.5, 147.8, 158.9 and 174.4.

With $(TMS)_3SiH$. Following the general procedure, compound **10** (100 mg, 0.19 mmol) was treated with $(TMS)_3SiH$ (186 mg, 0.75 mmol) and AIBN (8 mg, 0.05 mmol) in boiling benzene. After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (3:1)]. The first eluent gave the reduction product **9** (10 mg, 14%). The second eluent gave **11b** (28 mg, 39%). The third eluent gave **11a** (15 mg, 21%).

2-Chloro-*N*-(cyclohex-2-enyl)-*N*-(4-methoxybenzyl)-2-phenylacetamide 13

To a stirred solution of 3-bromocyclohexene (1.13 g, 7 mmol) in CH_2Cl_2 (10 cm^3) was added 4-methoxybenzylamine (1.92 g, 14 mmol), and the mixture was stirred at room temperature for 5 h. The reaction mixture was washed successively with saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to give quantitatively *N*-(cyclohex-2-enyl)-4-methoxybenzylamine **12** as an oil [δ_H(60 MHz) 1.30–2.10 (6 H, m), 2.90–3.40 (1 H, m), 3.55–3.75 (1 H, m), 3.77 (3 H, s), 5.73 (2 H, s), 6.77 (2 H, d, *J* 8.5) and 7.20 (2 H, d, *J* 8.5)].

To a stirred solution at 0 °C containing **12** (969 mg, 4.56 mmol) and triethylamine (508 mg, 5.02 mmol) in CH_2Cl_2 (19 cm^3) was added dropwise a solution of 2-chloro-2-phenylacetyl chloride (949 mg, 5.02 mmol) in CH_2Cl_2 (6 cm^3). The mixture was stirred at room temperature overnight, then was washed with water, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (6:1)] to give a diastereoisomeric mixture of **13** (101 g, 65%) as an oil [Found: $(M + H)^+$, 369.1488. $C_{22}H_{24}ClNO_2$ requires MH^+, 369.1495]; $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(300 MHz) 1.30–2.10 (6 H, m), 3.78 (3 H × 1/5, s), 3.83 (3 H × 4/5, s), 4.24–4.68 (2.4 H, m), 5.31–5.40 (2.4 H, m), 5.81–5.93 (1.3 H, m) and 6.79–7.58 (9 H, m).

Radical cyclisation of 13

With Bu_3SnH. Following the general procedure, compound **13** (327 mg, 0.88 mmol) was treated with Bu_3SnH (386 mg, 1.33 mmol) and AIBN (22 mg, 0.13 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give (3*R**,3a*S**,7a*S**)-*octahydro*-1-(4-*methoxybenzyl*)-3-*phenylindol*-2-*one* **14** (238 mg, 81%) as an oil [Found: $(M + H)^+$, 335.1890. $C_{22}H_{25}NO_2$ requires MH^+, 335.1885]; $\nu_{max}(CCl_4)/cm^{-1}$ 1685; δ_H(300 MHz) 1.07–1.80 (7 H, m), 1.93–2.03 (1 H, m), 2.28–2.38 (1 H, m, 3a-H), 3.38 (1 H, dt, *J* 9.8 and 6.1, 7a-H), 3.54 (1 H, d, *J* 10.9, 3-H), 3.81 (3 H, s), 3.98 (1 H, d, *J* 14.9), 5.00 (1 H, d, *J* 14.9), 6.88 (1 H, d, *J* 8.7) and 7.18–7.38 (7 H, m); δ_C 21.1, 22.4, 25.0, 27.9, 42.1, 43.8, 51.0, 54.5, 55.2, 114.0, 126.9, 128.6, 128.7, 129.1, 129.4, 138.3, 159.0 and 174.5.

With $(TMS)_3SiH$. Following the general procedure, compound **13** (180 mg, 0.49 mmol) was treated with $(TMS)_3SiH$ (484 mg, 1.95 mmol) and AIBN (20 mg, 0.12 mmol) in boiling benzene. After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **14** (139 mg, 85%).

Ethyl 2-(3,4-methylenedioxyphenyl)-2-(phenylthio)acetate 15

To a stirred solution at 0 °C containing ethyl 2-chloro-2-

(phenylthio)acetate[10] (3.35 g, 16.7 mmol) and 1,2-methylenedioxybenzene (2.47 g, 20.2 mmol) in $CHCl_3$ was added $TiCl_4$ (3.17 g, 16.7 mmol). The mixture was stirred at room temperature for 30 min. Water was added and the mixture was extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (15:1)] to give **15** (3.59 g, 75%) as an oil (Found: C, 64.2; H, 5.0. $C_{17}H_{16}O_4S$ requires C, 64.5; H, 5.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1735; δ_H(300 MHz) 1.16 (3 H, t, *J* 7.1), 4.04–4.17 (2 H, m), 4.83 (1 H, s), 5.95 (2 H, s), 6.72 (1 H, d, *J* 8.0), 6.85 (1 H, dd, *J* 8.0 and 1.8), 7.05 (1 H, d, *J* 1.8) and 7.24–7.42 (5 H, m).

2-(3,4-Methylenedioxyphenyl)-2-(phenylthio)acetic acid 16

To a stirred solution at room temperature containing KOH (425 mg) in EtOH (10 cm^3) was added **15** (2 g, 6.32 mmol), and the mixture was heated at reflux for 5 h. After EtOH had been evaporated off, the residue was poured into water, and the mixture was acidified with 10% HCl. The mixture was extracted with AcOEt, and the extract was dried ($MgSO_4$) and concentrated to give **16** in almost quantitative yield, mp 118–119 °C (Found: C, 62.5; H, 4.2. $C_{15}H_{12}O_4S$ requires C, 62.5; H, 4.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710; δ_H(300 MHz) 4.89 (1 H, s), 5.96 (2 H, s), 6.72 (1 H, d, *J* 8.0), 6.84 (1 H, dd, *J* 8.1 and 1.7), 7.01 (1 H, d, *J* 1.7) and 7.25–7.47 (5 H, m) (the signal due to the carboxy group was not detected).

N-(Cyclohex-2-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylthio)acetamide 17

To a stirred solution at room temperature containing the acid **16** (182 mg, 0.6 mmol) and the amine **12** (130 mg, 0.6 mol) in CH_2Cl_2 (5 cm^3) were added successively 4-(dimethylamino)-pyridine (DMAP) (7 mg, 0.06 mmol) and DCC (124 mg, 0.6 mmol). The mixture was stirred at room temperature for 5 h. The precipitates were removed by filtration, and the filtrate was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (3:1)] to give **17** (235 mg, 78%) as an oil (Found: C, 70.9; H, 6.3; N, 2.6. $C_{29}H_{29}NO_4S$ requires C, 71.3; H, 6.2; N, 2.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 1635; δ_H(300 MHz) 1.19–2.05 (6 H, m), 3.78, 3.79, 3.83 (total 3 H, all s), 4.17–4.37 (2 H, m), 4.72, 5.18 (total 1 H, both d, *J* 1.6), 5.27–5.44 (1.7 H, m), 5.80–5.97 (2.7 H, m), 6.35–6.40 (0.6 H, m), 6.57–7.37 (12 H, m).

Radical cyclisation of 17

With Bu_3SnH. Following the general procedure, compound **17** (1.0 g, 2.05 mmol) was treated with Bu_3SnH (696 mg, 2.39 mmol) and AIBN (39 mg, 0.24 mmol) in boiling benzene. After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **11a** (603 mg, 78%), whose physical data were identical with those of an authentic sample prepared by radical cyclisation of **10**.

With $(TMS)_3SiH$. Following the general procedure, compound **17** (513 mg, 1.05 mmol) was treated with $(TMS)_3SiH$ (785 mg, 3.16 mmol) and AIBN (43 mg, 0.26 mmol) in boiling benzene. After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **11a** (338 mg, 85%).

(3*R**,3a*S**,7a*S**)-Octahydro-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indole 18

To a stirred suspension at −20 °C containing $LiAlH_4$ (480 mg, 12.65 mmol) in THF (30 cm^3) was added slowly $AlCl_3$ (1.69 g, 12.65 mmol). The mixture was stirred at room temperature for 30 min. To this mixture containing AlH_3 was added dropwise a solution of **17** (300 mg, 0.79 mmol), and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of 5% aq. NH_3, and the precipitates were removed by filtration. The filtrate was washed with brine, dried (Na_2SO_4) and concentrated to give **18** (270 mg, 93%) as an oil (Found: M^+, 365.2000. $C_{23}H_{27}NO_3$ requires *M*, 365.1991); δ_H(300 MHz) 1.18–1.70 (8 H, m), 2.08–2.18 (1 H, m, 3a-H), 2.45 (1 H, dd, *J* 10.0 and 7.8, one of 2-H_2), 2.83–2.98 (2 H, m, 3-, 7a-H), 3.19 (1 H, dd, *J* 10.0 and 8.6, one of 2-H_2), 3.43 (1 H, d, *J* 12.6, one of $ArCH_2$), 3.79 (3 H, s, OMe), 3.82 (1 H, d, *J* 12.6, one of $ArCH_2$), 5.90 (2 H, s, OCH_2O), 6.61–6.77 (3 H, ArH), 6.85 (2 H, d, *J* 8.7, ArH) and 7.27 (2 H, d, *J* 8.7, ArH). This compound was used immediately in the next step without further purification.

(3*R**,3a*S**,7a*S**)-1-Benzyloxycarbonyloctahydro-3-(3,4-methylenedioxyphenyl)indole 19

To a solution heated at reflux containing **18** (250 mg, 0.68 mmol) in benzene (8 cm^3) was added dropwise a solution of benzyloxycarbonyl chloride (Cbz-Cl) (175 mg, 1.03 mmol) in benzene (3 cm^3). The mixture was further heated at reflux for 2 h. After this, the reaction mixture was washed successively with dil. HCl and water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (8:1)] to give **19** (231 mg, 90%) as an oil (Found: M^+, 379.1778. $C_{23}H_{25}NO_4$ requires *M*, 379.1783); $\nu_{max}(CHCl_3)/cm^{-1}$ 1685; δ_H(300 MHz) 1.13–1.75 (7 H, m), 2.04–2.32 (2 H, m), 3.24–3.50 (2 H, m), 3.75–4.04 (2 H, m), 5.10–5.20 (2 H, m), 5.93 (2 H, s), 6.64–6.80 (3 H, m) and 7.25–7.45 (5 H, m).

(4a*S**,11*R**,11a*S**)-8,9-Methylenedioxy-5,11-methanomorphanthridine 21

To a solution of **19** (199 mg, 0.52 mmol) in MeOH (15 cm^3) containing conc. HCl (0.05 cm^3) was added 10% Pd on carbon (52 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 15 h. The inorganic materials were filtered off, and the filtrate was concentrated to give quantitatively the amine hydrochloride **20**, which was then dissolved in MeOH (1.6 cm^3). To this mixture were added 36% formalin (1.6 cm^3, 20.8 mmol) and Et_3N (84 mg, 0.83 mmol), and the mixture was stirred at room temperature for 15 min. The reaction mixture was extracted with $CHCl_3$, and the extract was dried (Na_2CO_3) and concentrated. After this, MeOH (2 cm^3) and 20% HCl (35 cm^3) were added to the residue, and the mixture was stirred at 30–40 °C overnight. The reaction mixture was made alkaline with 30% aq. NH_3, and the mixture was extracted with $CHCl_3$. The extract was dried (Na_2CO_3) and concentrated, and the residue was chromatographed on silica gel [$CHCl_3$–MeOH (20:1)] to give **21** (51 mg, 47% based on **19**), mp 97–99 °C (from hexane–AcOEt) (lit.,[5a] 100 °C); δ_H(300 MHz) 1.1–1.6 (7 H, m), 1.66–1.77 (1 H, m), 2.12–2.23 (1 H, m, 11a-H), 2.53 (1 H, d, *J* 2.7, 11-H), 2.87 (1 H, d, *J* 11.2, one of 12-H_2), 3.00 (1 H, dt, *J* 10.9 and 7.3, 4a-H), 3.12 (1 H, dd, *J* 11.2 and 2.7 one of 12-H_2), 3.71 (1 H, d, *J* 16.6, one of 6-H_2), 4.27 (1 H, d, *J* 16.6, one of 6-H_2), 5.81 (2 H, s, OCH_2O), 6.39 (1 H, s, ArH) and 6.44 (1 H, s, ArH); δ_C 18.2, 19.0, 23.8, 25.1, 45.7, 49.9, 52.5, 60.3, 65.4, 100.6, 106.4, 106.9, 124.6, 136.3, 145.7 and 146.2.

(±)-*cis*-3-Acetoxy-6-(4-methoxybenzylamino)cyclohexene 23

To a solution that had been stirred at room temperature for 20 min and which contained $Pd(dba)_2$ (172 mg, 0.29 mmol), Ph_3P (225 mg, 0.86 mmol), 4-methoxybenzylamine (942 mg, 6.87 mmol) and Et_3N (1.74 g, 17.18 mmol) in THF (30 cm^3) was added a solution of the *cis*-chloro acetate **22**[12] (1.00 g, 5.73 mmol) in THF (10 cm^3). The mixture was stirred at room temperature for 8 h and then concentrated. After the residue had been dissolved in diethyl ether (20 cm^3), the mixture was extracted with 5% HCl. The aqueous phase was made alkaline

(pH > 10) with 10% aq. KOH, and the mixture was extracted with diethyl ether. The extract was dried (K_2CO_3) and concentrated, and the residue was chromatographed on silica gel (AcOEt then pentane) which was first conditioned with 2% Et_3N in pentane, to give **23** (1.14 g, 72%) (Found: M^+, 275.1525. $C_{16}H_{21}NO_2$ requires *M*, 275.1521); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720; δ_H(300 MHz) 1.57–1.94 (5 H, m), 2.04 (3 H, s, COMe), 3.13–3.20 (1 H, m, 4-H), 3.78, 3.82 (1 H each, ABq, *J* 12.9, $ArCH_2$), 3.80 (3 H, s, OMe), 5.16–5.21 (1 H, m, 1-H), 5.78 (1 H, ddd, *J* 10.1, 3.9 and 1.9, olefinic), 5.99 (1 H, dd, *J* 10.1 and 2.6, olefinic), 6.86 (2 H, d, *J* 8.7, ArH) and 7.26 (2 H, d, *J* 8.7, ArH).

N-(4-Acetoxycyclohex-2-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylthio)acetamide 24

Using a procedure similar to that described above for the preparation of **17**, a mixture of the acid **16** (355 mg, 1.23 mmol) and the amine **23** (323 mg, 1.23 mmol) was treated with DCC (253 mg, 1.23 mmol) in the presence of DMAP (15 mg, 0.12 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **24** (530 mg, 79%) as an oil (Found: M^+, 545.1867. $C_{31}H_{31}NO_6S$ requires *M*, 545.1972); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1640; δ_H(300 MHz) 1.50–1.93 (4 H, m), 1.93, 1.98, 2.01 (total 3 H, all s), 3.79, 3.83 (total 3 H, all s), 4.15–4.40 (2 H, m), 4.73–5.35 (3 H, m), 5.61–6.03 (4 H, m) and 6.35–7.40 (12 H, m).

(3*R**,3a*S**,5*R**,7a*S**)-5-Acetoxyoctahydro-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indol-2-one 25

Following the general procedure, compound **24** (200 mg, 0.36 mmol) was treated with $(TMS)_3SiH$ (358 mg, 1.44 mmol) and AIBN (15 mg, 0.09 mmol). After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (4:1)] to give **25** (132 mg, 84%), mp 148–150 °C (from hexane–AcOEt) (Found: C, 69.0; H, 6.3; N, 3.4. $C_{25}H_{27}NO_6$ requires C, 68.6; H, 6.2; N, 3.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1680; δ_H(300 MHz) 1.42–1.89 (6 H, m), 2.12 (3 H, s, COMe), 2.25–2.35 (1 H, m, 3a-H), 3.40–3.48 (1 H, m, 7a-H), 3.74 (1 H, d, *J* 9.8, 3-H), 3.81 (3 H, s, OMe), 4.01 (1 H, d, *J* 14.7, one of $ArCH_2$), 4.97–5.03 (1 H, m, 5-H), 5.00 (1 H, d, *J* 14.7, one of $ArCH_2$), 5.94 (2 H, s, OCH_2O), 6.61 (1 H, dd, *J* 7.8 and 1.7, ArH), 6.64 (1 H, d, *J* 1.7, ArH), 6.77 (1 H, d, *J* 7.8, ArH), 6.87 (2 H, d, *J* 8.7, ArH) and 7.23 (2 H, d, *J* 8.7, ArH); δ_C 21.5, 22.3, 26.3, 29.2, 40.7, 43.9, 52.9, 53.6, 55.3, 69.0, 101.0, 108.4, 108.7, 114.1, 122.0, 128.9, 129.4, 131.7, 146.8, 148.0, 159.1, 174.6 and 184.3.

(3*R**,3a*S**,5*R**,7a*S**)-Octahydro-5-hydroxy-1-(4-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)indol-2-one 26

To a solution of **25** (295 mg, 0.67 mmol) in MeOH (6 cm^3) and water (5 cm^3) was added LiOH monohydrate (42 mg, 1.01 mmol), and the mixture was heated at reflux for 5 h. Water was added to the reaction mixture, which was then extracted with AcOEt. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **26** (252 mg, 95%) as an oil (Found: M^+, 395.1736. $C_{23}H_{25}NO_5$ requires *M*, 395.1732); $\nu_{max}(CHCl_3)/cm^{-1}$ 3650, 3470, 1670; δ_H(300 MHz) 1.46–1.95 (7 H, m), 2.20–2.29 (1 H, m, 3a-H), 3.39–3.45 (1 H, m, 7a-H), 3.81 (3 H, s, OMe), 3.86 (1 H, d, *J* 8.4, 3-H), 3.89–3.96 (1 H, m, 5-H), 4.00 (1 H, d, *J* 14.7, one of $ArCH_2$), 4.98 (1 H, d, *J* 14.7, one of $ArCH_2$), 5.92 (2 H, s, OCH_2O), 6.66–6.71 (2 H, m, ArH), 6.76 (1 H, d, *J* 8.8, ArH), 6.87 (2 H, d, *J* 8.7, ArH) and 7.22 (2 H, d, *J* 8.7, ArH); δ_C 22.1, 29.6, 32.7, 40.9, 43.7, 53.5, 53.8, 55.3, 66.4, 100.9, 108.3, 108.8, 114.0, 121.9, 129.0, 129, 4, 132.1, 146.5, 147.8, 159.0 and 175.3.

Swern oxidation of 26

A solution of dimethyl sulfoxide (DMSO) (695 mg, 8.90 mmol) in CH_2Cl_2 (6 cm^3) was added dropwise to a solution of oxalyl dichloride (565 mg, 4.45 mmol) in CH_2Cl_2 (4 cm^3) at −60 °C. After this, a solution of **26** (176 mg, 0.45 mmol) and DMSO (0.65 cm^3) in CH_2Cl_2 (6 cm^3), was added to the mixture, and the whole mixture was stirred at the same temperature for 40 min. After addition of Et_3N (2.25 g, 22.25 mmol) to the mixture, it was allowed to warm to room temperature. After 1 h, the mixture was diluted with water and extracted with diethyl ether. The extract was washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:1)] to give **8a** (174 mg, 99%) as an oil, whose physical data were identical with those of an authentic sample prepared by hydrolysis of the acetal **7a**.

(3*R**,3a*S**,7a*S**)-1-(Benzyloxycarbonyl)-5,5-(ethylenedioxy)-octahydro-3-(3,4-methylenedioxyphenyl)indole 28

Using a procedure similar to that described above for the preparation of **18**, compound **7a** (219 mg, 0.5 mmol) was treated with AlH_3 [prepared from $LiAlH_4$ (304 mg, 8 mmol) and $AlCl_3$ (1.07 g, 8 mmol)]. Work-up gave **27** (185 mg, 87%) as an oil, which was used immediately in the next step without further purification.

Compound **27** was treated with Cbz-Cl (112 mg, 0.66 mmol) as in a manner similar to that described above for the preparation of **19**. After work-up, the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)] to give **28** (165 mg, 75% based on **7a**) as an oil (Found: M^+, 437.1834. $C_{25}H_{27}NO_6$ requires *M*, 437.1838); $\nu_{max}(CHCl_3)/cm^{-1}$ 1685; δ_H(300 MHz) 1.49–1.78 (5 H, m), 2.06–2.40 (2 H, m), 3.30–3.45 (1 H, m), 3.60–3.74 (1 H, m), 3.78–4.07 (6 H, m), 5.10–5.20 (2 H, m), 5.93 (2 H, s), 6.67–6.78 (3 H, m) and 7.28–7.39 (5 H, m).

(4a*S**,11*R**,11a*S**)-8,9-Methylenedioxy-5,11-methanomorphanthridin-2-one 30

Using a procedure similar to that described above for the preparation of **20**, compound **28** (221 mg, 0.51 mmol) was subjected to catalytic hydrogenolysis. Work-up gave the amine hydrochloride **29** (178 mg), which was used immediately in the next step.

Compound **29** was treated in a manner similar to that described above for the preparation of **21**. After work-up, the crude material was chromatographed on silica gel [$CHCl_3$–MeOH (20:1)] to give **30** (89 mg, 64% based on **28**), mp 125–126 °C (from hexane–AcOEt) (lit.,[5d] 125 °C) (Found: M^+, 271.1211. $C_{16}H_{17}NO_3$ requires *M*, 271.1208); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710; δ_H(300 MHz) 1.72–1.88 (1 H, m), 1.97–2.12 (1 H, m), 2.18–2.28 (1 H, m), 2.36–2.67 (4 H, m), 2.68 (1 H, d, *J* 2.5, 11-H), 3.03 (1 H, d, *J* 12.1, one of 12-H_2), 3.21 (1 H, dd, *J* 11.7 and 2.7, one of 12-H_2), 3.71 (1 H, dt, *J* 11.8 and 6.8, 4a-H), 3.80 (1 H, d, *J* 17.1, one of 6-H_2), 4.33 (1 H, d, *J* 17.1, one of 6-H_2), 5.89 (2 H, s, OCH_2O), 6.46 (1 H, s, ArH) and 6.49 (1 H, s, ArH); δ_C 26.1, 36.7, 41.5, 46.0, 46.9, 51.9, 60.4, 64.3, 100.7, 106.4, 107.0, 125.0, 135.3, 145.9, 146.6 and 212.1.

X-Ray crystallographic analysis on compound 7b

X-Ray crystal data of compound **7b** were collected by a Rigaku AFC5R diffractometer. The structure was solved by the direct method using SIR 92[14] and refined with a full-matrix least-squares method.

Crystal data of compound 7b. $C_{25}H_{27}NO_6$, $M_r = 437.49$, orthorhombic, space group *Pna* 2_1(#33), $a = 12.749(2)$ Å, $b = 16.163(2)$ Å, $c = 10.624(2)$ Å, $V = 2189.2(4)$ Å^3, $Z = 4$, $D_x = 1.327$ Mg m^{-3}, $F(000) = 928.00$, $\lambda = 1.54178$ Å, μ(Cu-Ka) = 7.81 cm^{-1}.

CCDC reference number 207/335. See http://www.rsc.org/suppdata/p1/1999/1949 for crystallographic files in .cif format.

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