PERKIN 1

New asymmetric route to bridged indole alkaloids: formal enantiospecific syntheses of (−)-suaveoline, (−)-raumacline and (−)-N^b-methylraumacline

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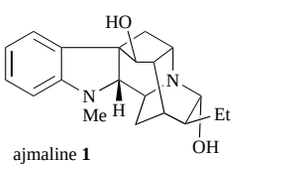
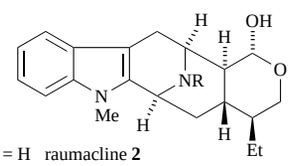
The homologous nitrile 13 derived from L-tryptophan undergoes a modified Pictet–Spengler reaction with methyl propynoate, under conditions of kinetic control, to afford the *cis*-tetrahydro-β-carboline 15a (*cis*:*trans* = 77:23). After protection, Dieckmann–Thorpe cyclisation to the bridged keto nitrile 20 proceeds in 90% yield. Simple functional group modifications *via* the alcohol 21a and nitrile 22 (structures confirmed by X-ray crystallography) allow convergence with the tetracyclic α,β-unsaturated aldehyde 10, which is an advanced intermediate for the synthesis of a range of bridged indole alkaloids.

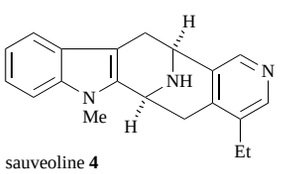
Originally obtained from many species of *Rauwolfia*, the indole alkaloids of the ajmaline–sarpagine family (*e.g.* **1**–**5**) have been



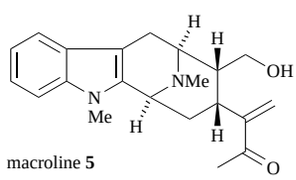
ajmaline **1**



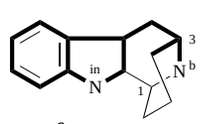
R = H raumacline **2**
R = Me N^b-methylraumacline **3**



sauveoline **4**

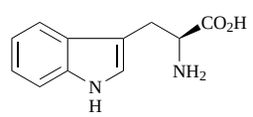


macroline **5**



6

cf.

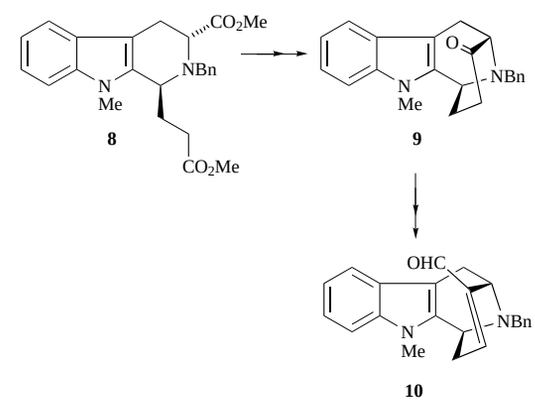


L-trytophan **7**

widely studied, both because of their diverse biological properties, and because of their structural complexity.[1] The tetracyclic subunit **6**† occurs in all these alkaloids and recent asymmetric syntheses have been centred around the construction of related key intermediates such as **9** and **10** *via* the methodology outlined in Scheme 1.

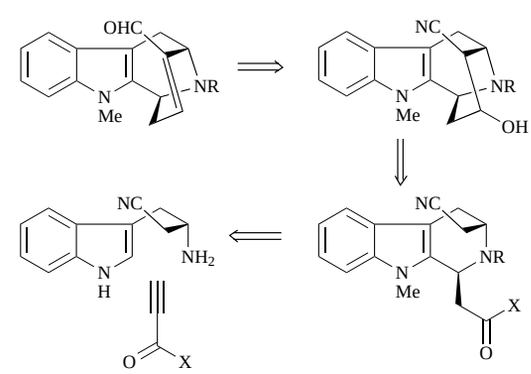
Starting from D-tryptophan, Cook has achieved the synthesis of a range of these alkaloids, for which the α,β-unsaturated aldehyde **10** is a common advanced intermediate.[2] Key steps involve the stereospecific formation of the *trans*-tetrahydro-β-carboline **8**, followed by epimerisation of the C(3) chiral centre during Dieckmann cyclisation to give (after hydrolysis and decarboxylation) the tetracyclic ketone **9**. A similar initial strategy has been employed by Magnus in his elegant synthesis of the kopsinine alkaloids.[3]

† Numbering and *N*-notation for tetrahydro-β-carbolines are indicated on structure **6**.



Scheme 1

Our own development of the *cis*-selective Pictet–Spengler reaction has allowed us to achieve asymmetric syntheses of bridged indole alkaloids using cheaper proteinogenic L-tryptophan **7**, again *via* the bridged ketone **9**.[4] However, conversion of this to the α,β-unsaturated aldehyde **10** is not trivial, and a more direct route would be a great advantage. We therefore studied the feasibility of introducing the additional carbon at the first step in the synthesis, leading to the route implied by the retrosynthetic analysis outlined in Scheme 2.

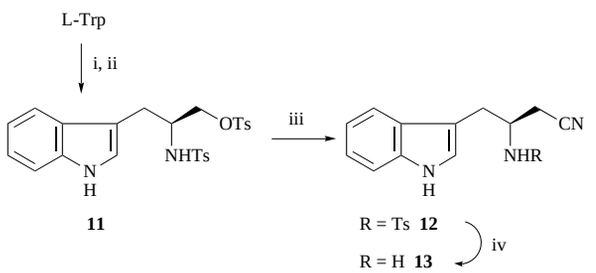


Scheme 2 Retrosynthetic analysis of route to bridged indole alkaloids

Modified Pictet–Spengler reactions between activated alkynes and tryptamine derivatives were first reported by Massiot *et al.*[5] We later extended this methodology to include a range of tryptophan derivatives, and demonstrated that substituents on N^{in} and/or N^{b} greatly reduced the *cis*-selectivity.[6] Thus, we planned to protect both nitrogens after the Pictet–Spengler reaction but prior to the next key step, Dieckmann–Thorpe cyclisation. Simple functional group interconversions should then lead to the required α,β-unsaturated aldehyde.[7]

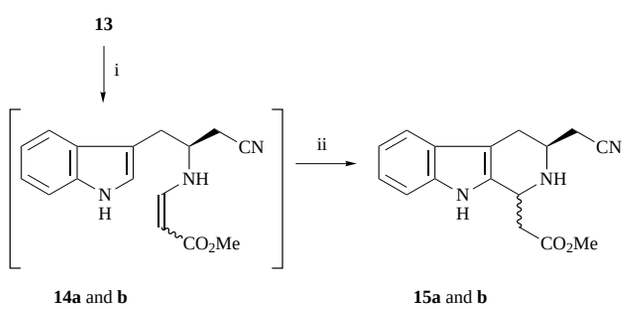
Results and discussion

The homologated nitrile **13** has been prepared by Kutney *et al.*,[8] but in order for us easily to process a large quantity of L-tryptophan (1 mol), several modifications were required. For the initial reduction, commercially available solutions of $LiAlH_4$ in THF were employed, with increased reaction times ensuring complete conversion. A modified work-up procedure then generated granular precipitates of lithium and aluminium salts, which were easily removed by filtration. Slow addition of toluene-*p*-sulfonyl chloride to a solution of crude amino alcohol in pyridine at 0 °C afforded the bis(toluene-*p*-sulfonate) **11** which was refluxed with potassium cyanide in methanol to afford the nitrile **12** as an amorphous solid. By performing a single recrystallisation at this point we avoided column chromatography in the whole of this sequence, since subsequent detosylation with sodium in liquid ammonia proceeded very cleanly. Thus, the homologated nitrile **13** was readily obtained from L-tryptophan in 50% overall yield (Scheme 3).



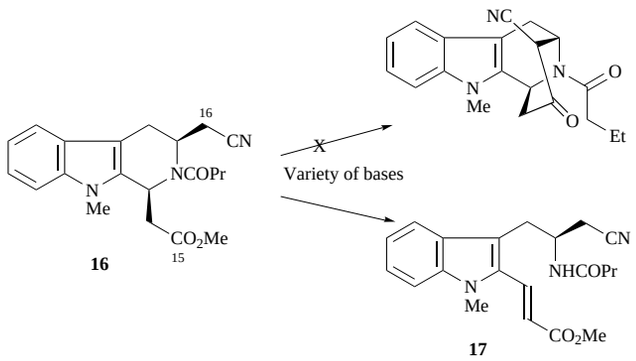
Scheme 3 *Reagents and conditions:* i, LAH, THF; ii, TsCl, pyridine; iii, KCN, MeOH; iv, Na, NH_3 (liq.)

The homologated nitrile **13** was treated with methyl propynoate to afford the enamines **14a** and **b**. Acidification with excess trifluoroacetic acid (TFA) promoted a rapid, kinetically controlled ring closure and afforded a 77 : 23 mixture (inseparable at this stage) of *cis* : *trans* diastereoisomers **15a** and **b** in 60% overall yield (Scheme 4).



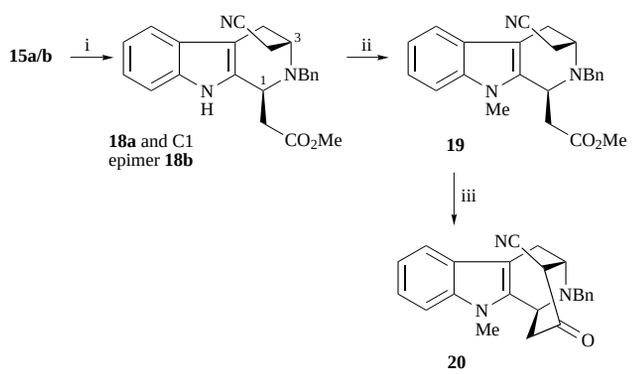
Scheme 4 *Reagents and conditions:* i, methyl propynoate, $CHCl_3$, reflux, 100 h; ii, cool to 0 °C, and add TFA (2 equiv.), 30 min

Protection of both nitrogens was required firstly to facilitate separation of the *cis*-tetrahydro-β-carboline **15a** from the *trans*-isomer **15b**, and secondly to prevent unwanted cyclisations in later steps. However, as our target alkaloids all possessed the N^{in}-methyl sub-structure, we chose to 'protect' the indole nitrogen by methylation, once the N^{b}-protection was in place. The choice of applicable N^{b}-protecting groups was limited, since any electron withdrawing character caused problems later on in the synthesis, due to opening of the tetrahydro-β-carboline ring being promoted in preference to the desired C(15)–C(16) ring closure (Scheme 5).[9]



Scheme 5

We performed a wide range of trial reactions in seeking a suitable protecting group for the N^{b} nitrogen. Steric hindrance proved to be a major problem and TLC indicated that protection of the *cis*-tetrahydro-β-carboline **15a** was slower than of the *trans*-isomer **15b**. Eventually we benzylated this nitrogen in reasonable yield (44% yield of **18a** from **15a**, Scheme 6) by



Scheme 6 *Reagents and conditions:* i, BnBr, $NaHCO_3$, CH_2Cl_2, reflux, 96 h; ii, MeI, NaH, DMF, room temp., 30 min; iii, $LiNEt_2$, THF, −78 °C, 1 h

treating **15a** and **b** with benzyl bromide in refluxing dichloromethane over $NaHCO_3$ for several days, and recycling unreacted starting material **15a**. The N^{in}-methyl moiety is present in many indole alkaloids, such as ajmaline **1**, and methylation with sodium hydride and methyl iodide in dimethylformamide (DMF) proceeded smoothly to afford the fully protected tetrahydro-β-carboline **19** in 92% yield (Scheme 6).

The critical C(15)–C(16) ring closure to the tetracyclic ketone **20**, mediated by the action of lithium diethylamide on **19** in tetrahydrofuran at −78 °C, proceeded exceptionally cleanly on a large scale; aqueous work-up and flash chromatography afforded the ketone **20** in 90% overall yield. All resonances in the NMR spectra of **20** were unusually broad, presumably since this material existed as a mixture of C(16)-epimers and the conjugated enol (Scheme 7).

The oxygen functionality at C(15) was removed *via* a two-step process, the first part of which was hydride reduction of the ketone **20** to the alcohol **21a**. The reduction displayed remarkably high diastereoselectivity (>90%). The relative stereochemistry was originally assigned on the basis of NOE experiments (Fig. 1) and later confirmed by an X-ray structure of the OTMS derivative **21b**[10] (Fig. 2).

From molecular models, it would appear that the *re* face of the ketone (*i.e.* away from the indole system) is the less hindered, and we infer that reduction from this side occurred more

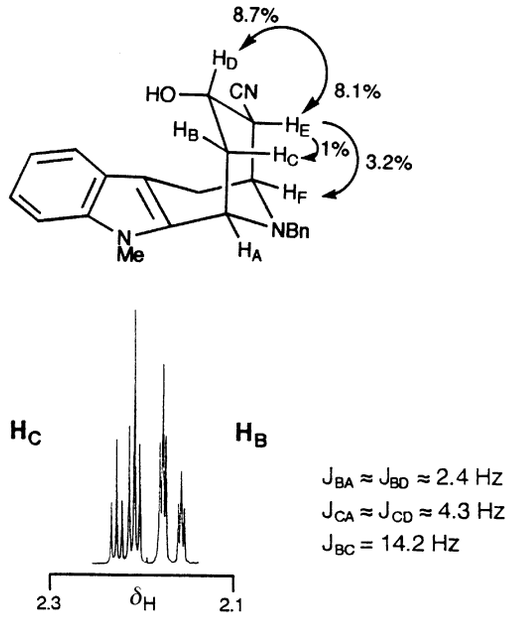
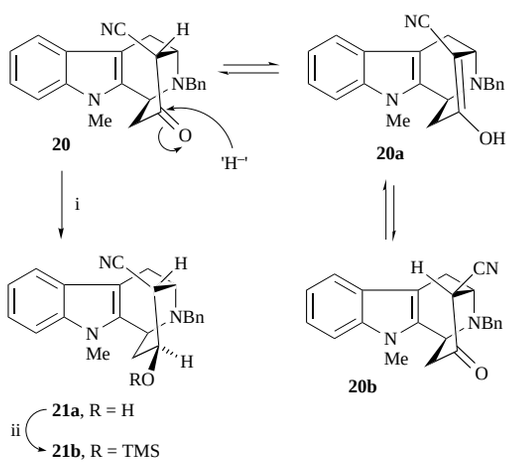


Fig. 1 Selected NMR data for **21a** (NOEs and ^{1}H NMR) indicating the relative stereochemistry



Scheme 7 *Reagents and conditions:* i, $NaBH_4$, MeOH, room temp., 2 h; ii, Me_3SiCl, CH_2Cl_2, imidazole, −10 °C to room temp., 1 h

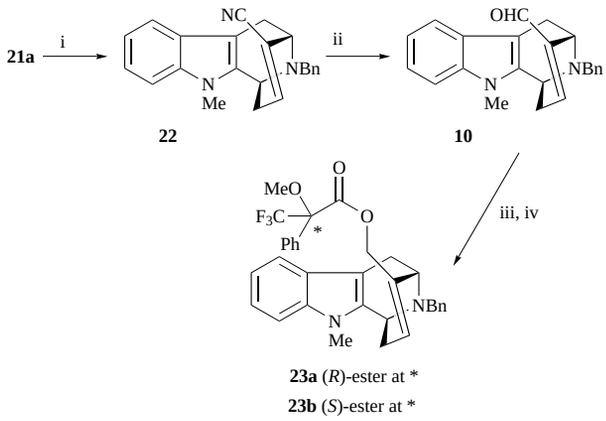
rapidly when the nitrile was *anti* (rather than *syn*). Thus, a single keto nitrile diastereoisomer was continuously removed from the enol–keto equilibrium mixture, allowing the single diastereoisomer **21a** to be obtained in excellent yield (Scheme 7).

Dehydration of **21a** with phosphoryl chloride and pyridine in dry refluxing benzene afforded the α,β-unsaturated nitrile **22**, in 87% yield (X-ray structure shown in Fig. 2). Finally, diisobutylaluminium hydride (DIBAL) reduction of the nitrile **22** in CH_2Cl_2 at −78 °C afforded the corresponding aldimine, which was easily hydrolysed by aqueous acid on warming to room temperature to afford the aldehyde (−)-**10** isolated in 99% yield (Scheme 8).

The enantiomeric purity of the aldehyde (−)-**10** was determined by $NaBH_4$ reduction to the alcohol, followed by analysis of the ^{19}F NMR spectra of the (*R*)- and (*S*)-Mosher's esters **23a** and **b** (Fig. 3).[11] By forming both the (*R*)- and (*S*)-esters, we were able to locate the diastereoisomeric ^{19}F signals definitively, and show that **23a** and **23b** [and hence (−)-**10**] were optically pure within our detection limits (ee >97%).

Conclusions

The modified homologation procedure enabled 1 mol of L-tryptophan to be processed through to the nitrile **13**. Using this material, large quantities of the tetracyclic ketone **20**, alcohol



Scheme 8 *Reagents and conditions:* i, $POCl_3$, pyridine, benzene, reflux, 48 h; ii, DIBAL, CH_2Cl_2, −78 °C (30 min) to room temp. (5 h); iii, $NaBH_4$, MeOH, room temp., 2 h; iv, (*R*)- or (*S*)-PhC(OMe)(CF_3)COCl, pyridine, CH_2Cl_2, room temp.

21a, αβ-unsaturated nitrile **22** and aldehyde (−)-**10** were prepared. The overall yield for the seven-step synthesis of the α,β-unsaturated aldehyde (−)-**10** from the homologated nitrile **22** was 15%. The tetracyclic aldehyde (−)-**10** is an intermediate in Cook's recent synthesis of suaveoline and the related indole alkaloids raumacline and *N*^{b}-methylraumacline.[2] Our work constitutes a formal synthesis of these natural products, and represents a particularly efficient approach for accessing alkaloids of the ajmaline–sarpagine family.

Experimental

Melting points were determined on a Reichert hot-stage microscope apparatus and are uncorrected. IR Spectra were recorded on a Pye-Unicam SP3-200 or a Perkin-Elmer 1420 spectrophotometer. NMR Spectra were recorded on a JEOL FX90Q spectrometer at 90 MHz (^{1}H) or 22.5 MHz (^{13}C), unless otherwise stated; chemical shifts are quoted in ppm downfield from Me_4Si as internal standard and coupling constants *J* are given in Hz. For ^{1}H NMR spectra, signals showing strong second order effects (*e.g.* AB quartets) have been quoted with the positions of the outer peaks stated, and the apparent coupling constant(s); for ^{13}C NMR spectra, off-resonance multiplicities are given in parentheses, although the number of attached hydrogens was usually determined using DEPT. Mass spectra were obtained by electron impact on an AEI MS-3074 or a VG Autospec spectrometer. The specific rotations of oils/foams of basic compounds were found to be unreliable (possibly due to traces of water or acid); consequently only $[\alpha]_D$ values (in 10^{-1} deg cm^2 g^{-1}) for crystalline intermediates are quoted. Solvents were dried by standard methods or obtained anhydrous from Rathburn Chemicals or Aldrich; ether refers to diethyl ether. Flash chromatography was performed using silica gel 60 (230–400 mesh) as the stationary phase.

Preparation of (2*S*)-2-amino-3-(2-indolyl)propan-1-ol

Lithium aluminium hydride (2.4 l of 1 M solution in THF, 2.4 mol, 9.6 equiv.) was transferred by cannula into a dry 5 l reaction vessel, stirred with an efficient pneumatic stirrer and cooled to 0 °C. L-Tryptophan (160 g, 0.78 mol) was added in small batches, then the solution was stirred for a further 30 min at ambient temperature before being gently heated to reflux. After 48 h the reaction mixture was cooled to 0 °C and cautiously treated with water (90 ml), aqueous NaOH (90 ml of 15% solution) and water (270 ml). Vigorous stirring was maintained for 30 min and the granular inorganic precipitate was removed by filtration and washed with THF. Evaporation of the combined filtrates under reduced pressure afforded a colourless oil which was redissolved in EtOAc, washed three times with saturated brine, dried over $MgSO_4$, filtered and evaporated to afford the

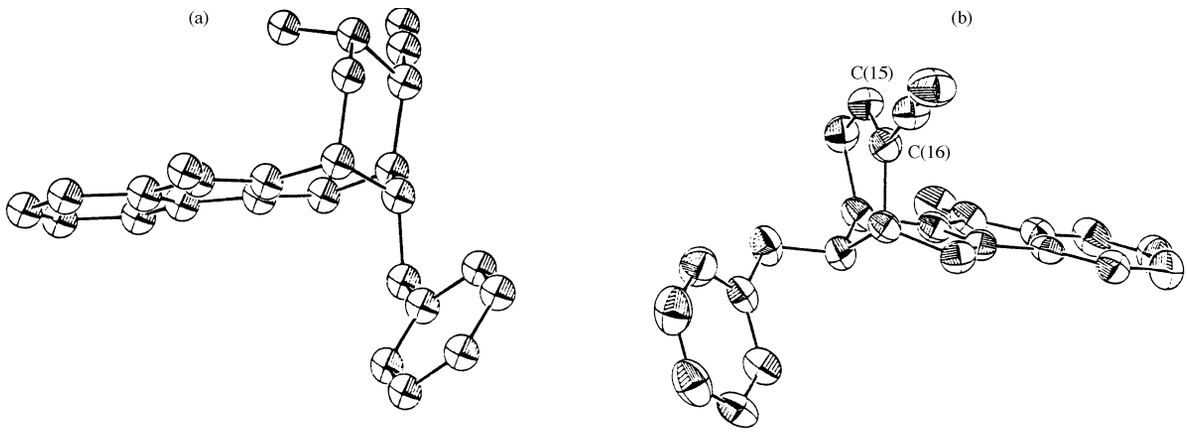


Fig. 2 (a) X-Ray crystal structure of the TMS-protected alcohol **21b**,‡ with the TMS group removed for clarity. (b) X-Ray crystal structure of the α,β-unsaturated nitrile **22**,§ where the position of the double bond was confirmed by the C(15)–C(16) bond length of 1.332(8) Å.

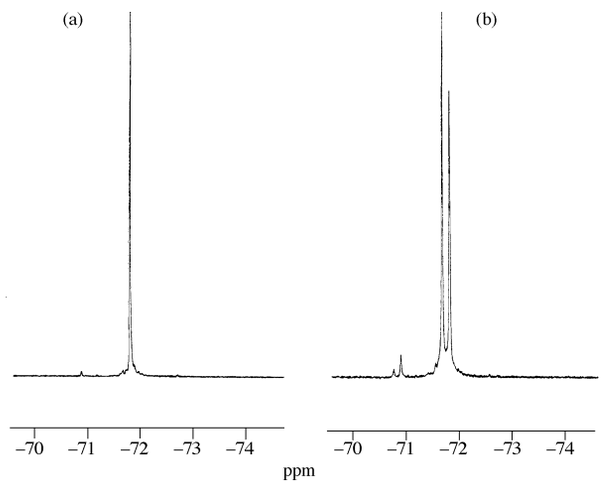


Fig. 3 (a) ^{19}F NMR of (*R*)-Mosher's ester **23a** (crude product). (b) ^{19}F NMR of (*R*)- plus (*S*)-Mosher's esters **23a** and **23b**, for assignment of peaks. Spiking experiments allowed quantification of the diastereoisomeric peaks and confirmed the ee of (−)-**10** to be >97%.

amino alcohol as a colourless oil (143 g, 97%). All data were identical to those reported previously.[8]

Preparation of (2*S*)-3-(2-indolyl)-2-(tosylamino)propyl toluene-*p*-sulfonate 11

The amino alcohol (142 g, 0.75 mol) was stirred in anhydrous pyridine (800 ml) at 0 °C, and toluene-*p*-sulfonyl chloride (500 g, 2.6 mol, 3.5 equiv.) was added in small portions over 5 h. The reaction mixture was maintained at 0 °C for 20 h then poured into saturated brine (1 l). The inorganic precipitate formed was removed by filtration and washed with CH_2Cl_2. The combined filtrates were shaken together, the organic layer separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were washed four times with 2 M hydrochloric acid and twice with saturated brine, dried over $MgSO_4$, filtered and evaporated to afford the bis(toluene-*p*-sulfonate) **11** as a yellow oil (330 g, 89%). All data were identical to those reported previously.[8]

Preparation of (3*S*)-3-(tosylamino)-4-(2-indolyl)butanenitrile 12

Potassium cyanide (25 g, 380 mmol, 2 equiv.) and the bis-(toluene-*p*-sulfonate) **11** (100 g, 200 mmol) were refluxed together in anhydrous MeOH (1500 ml) for 2 h. After cooling, the solvent was removed under reduced pressure and the solid residue partitioned between EtOAc and saturated brine. The organic layer was washed six times with saturated brine, dried over $MgSO_4$, filtered and evaporated to afford the nitrile **12** as an amorphous brown solid (64 g, 98%). This material was redissolved in hot MeOH, treated with decolorising charcoal, filtered and allowed to cool, to afford pale yellow cubic crystals of **12** (43 g, 70%). All data were identical to those reported previously.[8]

Preparation of (3*S*)-3-amino-4-(2-indolyl)butanenitrile 13

Sodium (36 g, 1.56 mol, 5 equiv.) was added in small portions to a stirred solution of the tosylamino nitrile **12** (110 g, 311 mmol) in liquid ammonia (2 l) at −78 °C. The reaction was stirred for 2 h then quenched with excess NH_4Cl. The solvent was allowed to evaporate at atmospheric pressure overnight and the white residue was partitioned between 2 M aqueous hydrochloric acid and EtOAc. The aqueous layer was washed with EtOAc, basified with conc. aqueous ammonia and extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and evaporated to afford the amino nitrile **13** as an amorphous solid (47 g, 75%). All data were identical to those reported previously.[8]

Preparation of (1*S*,3*S*)- and (1*R*,3*S*)-3-(cyanomethyl)-1-[(methoxycarbonyl)methyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles 15a and b

The cyano amine **13** (35 g, 176 mmol) and methyl propynoate (30 g, 357 mmol) were stirred together in $CHCl_3$ (1 l), under reflux for 100 h. The solution was then cooled to 0 °C, TFA (37.3 g, 25 ml, 352 mmol, 2 equiv.) added and stirring maintained for 30 min. Water (500 ml) was added, followed by aqueous 2 M NaOH dropwise to basify the aqueous layer (to pH 8). The organic layer was separated from the basic aqueous layer which was extracted a further five times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to afford the amines **15a** and **b** as an amorphous

‡ Crystal data for compound **21b**: $C_{26}H_{31}N_3OSi$, $M_r = 429.64$, crystal dimensions 0.30 × 0.50 × 0.50 mm. Orthorhombic space group $P2_12_12_1$, $a = 9.987(2)$, $b = 30.88(6)$, $c = 8.095(2)$ Å, $V = 2496(4)$ Å^3, $Z = 4$, $D_c = 1.143$ g cm^{-3}, Mo-Kα radiation (graphite monochromator), $\lambda = 0.710\ 69$ Å, $\mu = 1.15$ cm^{-1}, $F(000) = 720$. Total of 2574 reflections collected at 296 K in an ω scan. An empirical absorption correction was applied. The structure was solved by direct methods (SHELXS86) and refinement converged with $R_w = 0.052$. All hydrogen atoms were placed at calculated positions.

§ Crystal data for compound **22**: $C_{23}H_{21}N_3$, $M_r = 339.44$, crystal dimensions 0.30 × 0.40 × 0.60 mm. Orthorhombic, space group $P2_12_12_1$, $a = 10.777(4)$, $b = 18.682(3)$, $c = 8.927(6)$ Å, $V = 1997(1)$ Å^3, $Z = 4$, $D_c = 1.254$ g cm^{-3}, Mo-Kα radiation (graphite monochromator), $\lambda = 0.710\ 69$ Å, $\mu = 0.75$ cm^{-1}, $F(000) = 720$. Total of 4616 reflections collected at 296 K in an ω scan of which 1854 were unique. A polynomial absorption correction was applied. The structure was solved by direct methods (SHELXS86) and refinement converged with $R_w = 0.048$. All hydrogen atoms were placed at calculated positions. For both compounds **21b** and **22**, atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See refs. 10 and 7.

yellow solid (55 g). Flash chromatography on silica eluted with a solvent gradient (1:9 ether–CH_2Cl_2 to 2:10:88 MeOH–Et_2O–CH_2Cl_2) afforded the carbolines **15a** and **b** as a pale yellow foam (30 g, 60%), mp 186–188 °C; δ_H 1.82 (1 H, br s, N^bH), 2.40–3.21 (6 H, m, ArCH_2CHCH_2CN and CH_2CO_2Me), 3.50 (1 H, m), 3.70 (3 H, s, CO_2CH_3), 4.38 (1 H, m), 6.95–7.48 (4 H, m, ArH), 8.50–8.71 (1 H, br s, N^{in}H); δ_C 24.1 (t), 24.8 (t), 27.8 (t), 28.3 (t), 40.3 (t), 40.8 (t), 47.0 (d), 47.4 (d), 50.0 (d), 50.9 (d), 52.2 (q), 107.2 (s), 108.2 (s), 111.2 (d), 117.8 (s), 118.1 (d), 119.6 (d), 122.1 (d), 126.8 (s), 134.3 (s), 136.1 (s), 173.2 (s), 173.4 (s); ν_{max}/cm^{-1} 3455, 2240, 1734; *m*/*z* 283 (M^+), 210 (Found: M^+, 283.1327. $C_{16}H_{17}N_3O_2$ requires *M*, 283.1321).

Preparation of (1*S*,3*S*)- and (1*R*,3*S*)-2-benzyl-3-(cyanomethyl)-1-[(methoxycarbonyl)methyl]-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indoles 18a and b

The amines **15a** and **b** (40 g, 141 mmol) and benzyl bromide (26.6 g, 155 mmol, 18.4 ml, 1.1 equiv.) were stirred over $NaHCO_3$ (110 g, *ca.* 10 equiv.) in refluxing CH_2Cl_2 (450 ml) for 96 h, then the mixture was cooled, filtered and evaporated. Flash chromatography of the residue on silica eluted with a gradual solvent gradient (1:9 ether–CH_2Cl_2 to 5:10:85 MeOH–ether–CH_2Cl_2) afforded three main components: the (1*S*,3*S*) *cis* isomer **18a** (9.5 g, 24%); the (1*R*,3*S*) *trans* isomer **18b** (8.8 g, 72%) and starting material **15a** and **b** (13.8 g, 40%). Recycling the 13.8 g of starting material under identical conditions afforded two main components: the (1*S*,3*S*) *cis* isomer **18a** (3.3 g, 18%) and starting material **15a** and **b** (10.0 g, 72%). Subsequent recycling afforded the (1*S*,3*S*) *cis* isomer **18a** (total of 17.5 g, 44%).

Data for *cis* isomer **18a**: R_f 0.42 ($CHCl_3$); δ_H 2.25–3.28 (6 H, m, ArCH_2CHCH_2CN and CH_2CO_2Me), 3.58–3.68 (1 H, m, ArCH_2C*H*), 3.73 (3 H, s, CO_2CH_3), 3.95 (2 H, s, CH_2Ph), 4.24–4.45 (1 H, m, C*H*CH_2CO_2Me), 7.03–7.55 (9 H, m, ArH), 8.75 (1 H, br s, N^{in}H); δ_C 21.8 (t), 23.5 (t), 41.3 (t), 52.0 (q), 52.1 (d), 53.1 (d), 59.6 (t), 104.3 (s), 111.1 (d), 118.1 (d), 118.5 (s), 119.5 (d), 122.2 (d), 126.9 (s), 127.5 (d), 128.3 (d), 128.6 (d), 132.2 (s), 136.0 (s), 138.7 (s), 174.0 (s); ν_{max}/cm^{-1} 3435, 2245, 1728, 1654; *m*/*z* 373 (M^+), 333, 300, 282, 91 (Found: M^+, 373.1789. $C_{23}H_{23}N_3O_2$ requires *M*, 373.1790).

Data for *trans* isomer **18b**: R_f 0.33 ($CHCl_3$); mp 143.5–145 °C [ether–light petroleum (bp 40–60 °C)]; $[a]_D$ +97.4 (*c* = 1, MeOH); δ_H 2.59–2.88 (6 H, m, ArCH_2CHCH_2CN and CH_2CO_2Me), 3.24–3.83 (2 H, ABq, *J* 14.1, CH_2Ph), 3.45–3.60 (1 H, m, ArCH_2C*H*), 3.62 (3 H, s, CO_2CH_3), 4.15 (1 H, dd, *J* 8.3, 6.1, C*H*CH_2CO_2Me), 7.02–7.55 (9 H, m, ArH), 8.53 (1 H, br s, N^{in}H); δ_C 21.7 (t), 23.1 (t), 40.2 (t), 49.8 (t), 51.5 (d), 51.9 (q), 52.8 (d), 107.1 (s), 111.2 (d), 118.0 (s), 118.1 (d), 119.6 (d), 122.l (d), 126.6 (s), 127.3 (d), 128.5 (d), 133.3 (s), 136.1 (s), 138.6 (s), 173.2 (s); ν_{max}/cm^{-1} 3470, 2250, 1740; *m*/*z* 373 (M^+), 333, 300, 282, 91 (Found: M^+, 373.1789. $C_{23}H_{23}N_3O_2$ requires *M*, 373.1790).

Preparation of (1*S*,3*S*)-2-benzyl-3-(cyanomethyl)-1-[(methoxycarbonyl)methyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole 19

Sodium hydride (684 mg of 80% dispersion in oil, 22.8 mmol, 1.05 equiv.) was added to a stirred solution of the *N*-benzyl amine **18a** (8.1 g, 21.7 mmol) and methyl iodide (3.24 g, 1.42 ml, 22.8 mmol, 1.05 equiv.) in DMF (150 ml) at 0 °C. After 1 h the reaction mixture was allowed to warm to ambient temperature and stirred for a further 30 min. The DMF was removed under reduced pressure, and the residue dissolved in EtOAc, washed sequentially with water and brine, dried over $MgSO_4$, filtered and evaporated to afford a brown amorphous solid. Flash chromatography through a short silica column eluted with CH_2Cl_2 afforded the cyano ester **19** as a pale yellow foam (7.7 g, 92%); δ_H 2.45–3.05 (6 H, m, ArCH_2CHCH_2CN and CH_2CO_2Me), 3.38–3.55 (1 H, m, ArCH_2C*H*), 3.63 (3 H, s), 3.71 (3 H, s), 3.86 (2 H, s, CH_2Ph), 4.52 (1 H, dd, *J* 8.4, 6.2, C*H*CH_2CO_2Me), 7.02–7.56 (9 H, m, ArH); δ_C 20.6 (t), 24.2 (t), 30.5 (q), 41.5 (t), 51.3 (d), 51.9 (q), 53.3 (d), 61.1 (t), 104.4 (s), 109.0 (d), 118.3 (d), 118.7 (s), 119.5 (d), 122.1 (d), 127.5 (d), 128.5 (d), 128.6 (d), 133.0 (s), 137.8 (s), 138.6 (s), 171.4 (s); ν_{max}/cm^{-1} 2240, 1742; *m*/*z* 387 (M^+), 347, 314, 91 (Found: M^+, 318.1943. $C_{24}H_{25}N_3O_2$ requires *M*, 318.1947).

Ring closure of the *cis* cyano ester 19

A solution of the cyano ester **19** (11.24 g, 29.0 mmol) in 20 ml of THF was added dropwise to a stirred solution of lithium diethylamide (7.5 equiv.) at −78 °C. This base was prepared by the slow addition of BuLi (21.7 ml of 10 M solution in hexanes, 217 mmol) to a stirred solution of freshly distilled diethylamine (16 g, 22.3 ml, 217 mmol) in 200 ml of THF at 0 °C. The reaction mixture was stirred at −78 °C for 1 h, quenched with brine and then allowed to warm to ambient temperature and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and evaporated. Flash chromatography of the residue on silica eluted with 1:19 MeOH–CH_2Cl_2 afforded the tetracyclic ketone **20** as a pale yellow foam (9.25 g, 90%). This gave broad NMR spectra that indicated a mixture of compounds, and this crude material was used in the next step.

Preparation of (6*S*,8*S*,9*S*,10*S*)-12-benzyl-9-cyano-8-hydroxy-5-methyl-6,7,8,9,10,11-hexahydro-6,10-epimino-5*H*-cyclooct[*b*]-indole 21a

Sodium borohydride (8.8 g, 233 mmol, 40 equiv.) was added in portions to a stirred solution of the tetracyclic ketone **20** (8.27 g, 23.3 mmol) in anhydrous MeOH (250 ml). After 2 h the solvent was evaporated and the residue partitioned between CH_2Cl_2 and water. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, filtered and evaporated to afford a pale yellow foam. Flash chromatography of this material on silica eluted with a solvent gradient (1:9 ether–CH_2Cl_2 to 2:10:88 MeOH–ether–CH_2Cl_2) afforded the tetracyclic alcohol **21a** as a white foam (4.0 g, 47%) and starting material as a pale yellow foam (4.1 g, 50%). Recycling starting material afforded a total of 7.5 g of the alcohol **21a** (90%), $[a]_D$ −46.5 after recrystallisation (MeOH); mp 159–160.5 °C (MeOH) (Found: C, 77.0; H, 6.4; N, 11.7. Calc. for $C_{23}H_{23}N_3O$: C, 77.3; H, 6.5; N, 11.8%); δ_H(360 MHz) (see Fig. 1) 2.03 (1 H, d, *J* 12.0, OH), 2.12 (1 H, dt, *J* 14.2, 2.4, H_B), 2.22 (1 H, dt, *J* 14.2, 4.3, H_C), 3.21 (1 H, dd, *J* 17.3, 1.2, 11-H), 3.29 (1 H, dd, *J* 17.3, 6.5, 11-H), 3.43 (1 H, dd, *J* 5.2, 4.2, H_E), 3.58–3.71 (2 H, ABq, *J* 13.2, CH_2Ph), 3.61 (3 H, s, $N^{in}CH_3$), 3.67 (1 H, br t, *J* 5.6, H_F), 3.93 (1 H, dd, *J* 4.3, 2.7, H_A), 4.20 (1 H, dtd, *J* 12.0, 4.2, 2.2, H_D), 7.15–7.58 (9 H, m, ArH); δ_C 17.8 (t), 28.2 (q), 35.2 (t), 39.2 (d), 45.9 (d), 50.4 (d), 56.5 (t), 63.8 (d), 102.2 (s), 108.2 (d), 117.7 (d), 118.1 (s), 118.8 (d), 121.1 (d), 125.3 (s), 126.5 (d), 2 × 127.5 (d), 134.7 (s), 136.5 (s), 136.8 (s); ν_{max}/cm^{-1} 3505, 2225; *m*/*z* 357 (M^+), 91 (Found: M^+, 357.1841. $C_{23}H_{23}N_3O$ requires *M*, 357.1841).

Preparation of (6*S*,8*S*,9*S*,10*S*)-12-benzyl-9-cyano-8-trimethylsilyloxy-5-methyl-6,7,8,9,10,11-hexahydro-6,10-epimino-5*H*-cyclooct[*b*]indole 21b

The alcohol **21a** (50 mg, 0.14 mmol) and imidazole (10.5 mg, 0.15 mmol) were stirred in dry CH_2Cl_2 (10 ml) at −10 °C. Trimethylsilyl chloride (TMSCl) (18.2 mg, 21 ml, 0.17 mmol) was added slowly and then the reaction was allowed to warm to room temp. and stirred for 1 h. The organic solution was then washed with brine, dried over $MgSO_4$, filtered and evaporated to afford a pale yellow foam (71 mg). Flash chromatography on silica gel eluted with CH_2Cl_2 afforded the silyl protected alcohol (57 mg, 95%). Slow crystallisation of this material from MeOH afforded large colourless needles suitable for X-ray diffraction studies.‡[10]

Mp 186–188 °C; R_f 0.84 (1:9 ether–$CHCl_3$); δ_H(80 MHz) −0.43 [9 H, s, SiC$(CH_3)_3$], 1.85–2.10 (2 H, m, 7-H_2), 3.03–3.39 (4 H, m, 6-H, 7-H_2 and CHCN), 3.54 (3 H, s, $N^{in}CH_3$), 3.68–3.91 (3 H, m, CH_2Ph and ArC*H*), 4.05–4.26 (1 H, m, C*H*OTMS),

6.92–7.61 (9 H, m, ArH); *m*/*z* 429 (M^+), 414, 273, 91 (Found: M^+, 429.2235. $C_{26}H_{31}N_3OSi$ requires *M*, 429.2236).

Preparation of (6*S*,10*S*,8*E*)-12-benzyl-9-cyano-5-methyl-6,7,10,11-tetrahydro-6,10-epimino-5*H*-cyclooct[*b*]indole 22

The cyano alcohol **21a** (2.31 g, 6.5 mmol), phosphoryl chloride (4 g, 2.4 ml, 26 mmol, 4 equiv.) and anhydrous pyridine (10.3 g, 10.5 ml, 130 mmol, 20 equiv.) were refluxed in dry benzene (100 ml) for 48 h. The solution was then cooled, treated with water and stirred for 30 min. The organic layer was separated, twice washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. Flash chromatography of the residue on silica eluted with CH_2Cl_2 afforded the α,β-unsaturated nitrile **22** as a white foam (1.89 g, 87%). A small sample (*ca.* 10 mg) of the nitrile **22** was placed in a small vial and dissolved in $CHCl_3$ (*ca.* 1 ml). The open vial was then placed within a larger vial containing hexane (10 ml). After 2 weeks, vapour diffusion produced large, pale yellow crystals of the nitrile **22** in the smaller vial. These crystals were amenable to X-ray diffraction studies.§,[7]

Mp 190–191 °C (MeOH); $[\alpha]_D$ −102 (*c* 1.0, CH_2Cl_2) (Found: C, 81.1; H, 6.1; N, 12.3. Calc. for $C_{23}H_{21}N_3$: C, 81.4; H, 6.2; N, 12.4%); δ_H 1.98–3.20 (4 H, m), 3.45 (3 H, s, $N^{in}CH_3$), 3.57 (2 H, s, CH_2Ph), 3.72–4.14 (2 H, m), 6.50–6.62 (1 H, m, CH=CCN), 7.02–7.58 (9 H, m, ArH); δ_C 22.6 (t), 29.3 (q), 30.1 (t), 47.5 (d), 53.4 (d), 56.4 (t), 104.2 (s), 109.0 (d), 115.8 (s), 118.2 (s), 118.3 (d), 119.4 (d), 121.6 (d), 126.6 (s), 127.5 (d), 128.6 (d), 128.7 (d), 134.0 (s), 137.1 (s), 137.6 (s), 141.5 (d); ν_{max}/cm^{-1} 2200, 1635; *m*/*z* 339 (M^+), 248, 91 (Found: M^+, 339.1738. $C_{23}H_{21}N_3$ requires *M*, 339.1735).

Preparation of (6*S*,10*S*,8*E*)-12-benzyl-5-methyl-6,7,10,11-tetrahydro-6,10-epimino-5*H*-cyclooct[*b*]indole-9-carbaldehyde 10

DIBAL (1.2 ml of 1 M solution in CH_2Cl_2, 1.2 mmol) was added dropwise to a stirred solution of the nitrile **22** (340 mg, 1 mmol) in anhydrous CH_2Cl_2 (20 ml) at −78 °C. After 30 min the reaction mixture was allowed to warm to ambient temperature and stirring maintained for a further 5 h. The solution was then cooled to −78 °C and treated sequentially with MeOH, saturated aqueous NH_4Cl and 0.1 M aqueous H_2SO_4. Upon warming to ambient temperature the reaction mixture was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and evaporated. Flash chromatography of the residue on silica eluted with CH_2Cl_2 afforded the α,β-unsaturated aldehyde (−)-**10** as a colourless foam (339 mg, 99%), $[\alpha]_D^{20}$ −220 (*c* 2.0, $CHCl_3$) {lit.,[2] $[\alpha]_D^{24}$ −310.5 (*c* 0.55, $CHCl_3$)} (see Results and discussion). Importantly, ^{19}F NMR analysis of Mosher's esters **23a** and **b** confirmed the high optical purity of our compounds (ee >97%). δ_H 2.19–3.30 (5 H, m), 3.58 (3 H, s, $N^{in}CH_3$), 3.59–3.93 (2 H, ABq, *J* 13.0, CH_2Ph), 4.14 (1 H, dd, *J* 9.5, 6.6), 6.71 (1 H, br s, CH=CCHO), 7.05–7.52 (9 H, m, ArH), 9.33 (1 H, s, CHO); δ_C 21.9 (t), 29.3 (q), 32.4 (t), 48.1 (d), 50.1 (d), 56.3 (t), 105.3 (s), 108.8 (d), 118.3 (d), 119.2 (s), 121.4 (d), 126.9 (s), 127.2 (d), 128.4 (d), 128.7 (d), 134.1 (s), 137.0 (s), 138.5 (s), 143.8 (d), 147.6 (d), 192.5 (d); ν_{max}/cm^{-1} 1680, 1642; *m*/*z* 342 (M^+), 313, 273, 251, 91 (Found: M^+, 342.1720. $C_{23}H_{22}N_2O$ requires *M*, 342.1732).

Determination of the optical purity of the α,β-unsaturated aldehyde (−)-10

Sodium borohydride (13.2 mg, 0.34 mmol) was added to the aldehyde (−)-**10** stirred in dry MeOH (5 ml) at room temperature. After 2 h the solvent was evaporated and the residue partitioned between CH_2Cl_2 and 0.1 M aqueous HCl. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated to afford the alcohol as a colourless oil (58 mg, 95%) which was used directly for the formation of both (*R*)- and (*S*)-Mosher's esters **23a** and **b** according to established procedures.[11]

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