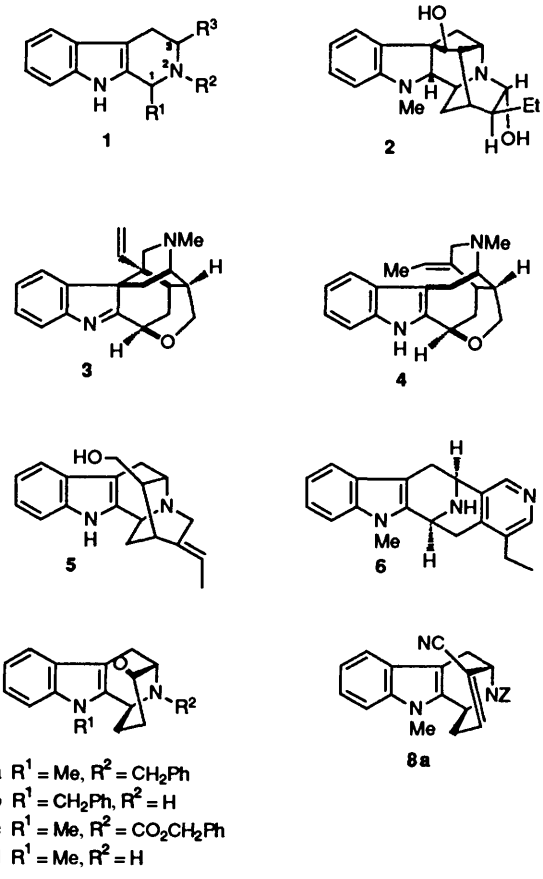
Use of the Kinetically Controlled Pictet–Spengler Reaction in the Asymmetric Synthesis of Indole Alkaloids: Formal Syntheses of (−)-Ajmaline, (−)-Koumine, (−)-Taberpsychine, (−)-Koumidine and (−)-Suavoline

Patrick D. Bailey[†,*] **and Neil R. McLay**
Department of Chemistry, University of York, Heslington, York YO1 5DD, UK

By employing the kinetically controlled Pictet–Spengler reaction L-tryptophan was used as the chiral starting material for the synthesis of the *cis*-1,3-disubstituted tetrahydro-β-carboline **14a**. Protection of the two nitrogens and subsequent cyclisation/decarboxylation led to generation of the bridged ketone (−)-(**7c**), which was shown to be optically pure within our detection limits (ee > 95%). Simple protecting group modifications gave access to (−)-**7a** and (−)-**7b**, and constituted formal synthesis of (−)-ajmaline, (−)-koumine, (−)-taberpsychine, (−)-koumidine and (−)-suavoline. These results demonstrate that such alkaloids with the correct absolute configuration are accessible in a stereocontrolled manner from L-tryptophan.

The indole alkaloids constitute an enormous class of natural products with a wide range of structural types, and correspondingly diverse biological properties. One of the most important sub-groups are the tetrahydro-β-carbolines **1**, many of which possess intriguing three-dimensional cage structures (*e.g.* ajmaline **2** and koumine **3**). These latter compounds possess an unusual structural feature amongst indole alkaloids – that the skeleton of L-tryptophan can be discerned within the C/N framework (although this is not the biosynthetic source of the chirality[1]), and this allows the proposal of asymmetric syntheses of these compounds using L-trypophan as an optically pure starting material. This approach has been largely ignored, primarily because the necessary sterochemical control was hard to achieve. However, using methodology developed by us, and reported in the preceding paper, we are able to demonstrate herein that L-tryptophan can be readily transformed into advanced intermediates for the synthesis of many indole alkaloids.

In this work, we had three main targets molecule.[2] The first was the bridged ketone **7a**, the racemic form of which had been converted into (±)-ajmaline (±)-**2** by Mashimo and Sato,[3] and into (±)-suavoline (±)-**6** by Cook *et al.*[4] Secondly, we wanted to transform **7a** into the α,β-unsaturated nitrile **8**, for use as a new advanced intermediate for entry into the sarpagine family of alkaloids. Finally, we targetted the bridged ketone **7c**, the antipode of which was the common intermediate used by Magnus and co-workers in their elegant syntheses of the unnatural (+)-isomers of **3**, **4** and **5**;[5] retro-synthetic analysis of **7a/b** and **8** guided us back to L-tryptophan as shown in Scheme 1 and this was the route that we explored.

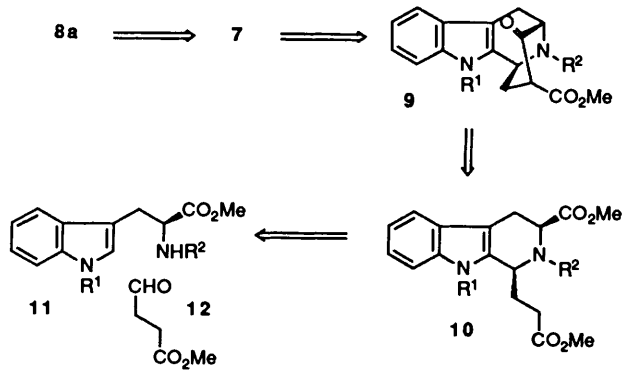


Results and Discussion

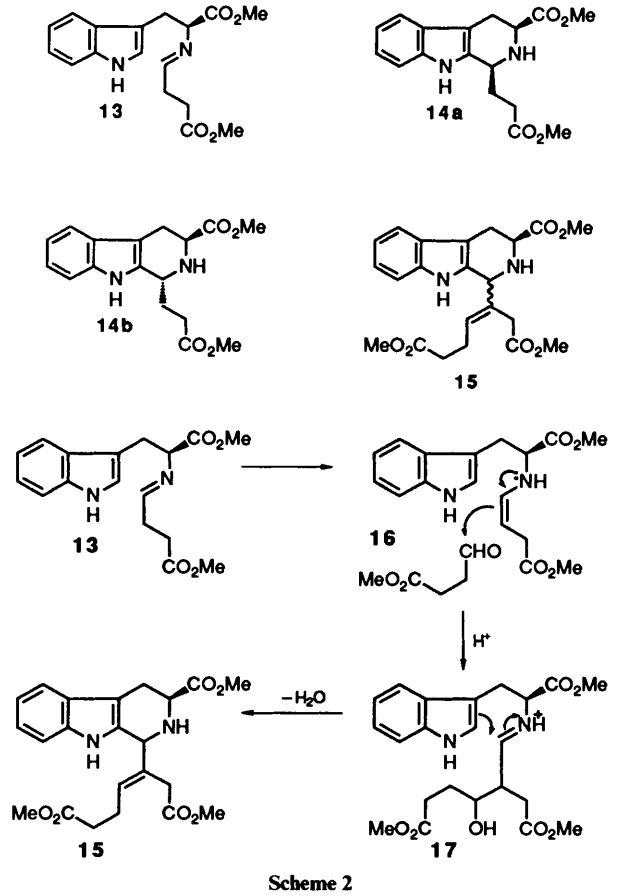
The first and most demanding step in the sequence was the stereo-controlled formation of the *cis*-1,3-disubstituted tetrahydro-β-carboline **10**. In previous model studies, we had demonstrated that such compounds could be accessed *via* the Pictet–Spengler reaction under conditions of kinetic control.[6,7] Accordingly, methyl 4-oxobutanoate was condensed with L-tryptophan methyl ester under acid catalysis to generate the imine intermediate **13**, which was treated at 0 °C with an excess of TFA to induce cyclisation. Although the desired tetrahydro-β-carbolines **14a/b** were isolated, the yield was disappointingly low, owing to the formation of substantial amounts of the triester **15**.

We suspected that this by-product was generated during the acid-catalysed formationof the imine [0 °C/CH_2Cl_2/TFA(cat.)/molecular sieves (4 Å)], by trapping of an intermediate enamine **16** with unchanged aldehyde as depicted in Scheme 2. We therefore used modified conditions in which imine formation was rapidly accomplished under non-acidic conditions (Dean–Stark apparatus, benzene reflux, 15 min), in order to remove all aldehyde before imine–enamine tautomerism could occur. Subsequent cyclisation was triggered by the addition of an excess of TFA to the imine in dichloromethane at 0 °C, giving a

† *Present address*: Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, EH14 4AS, UK.



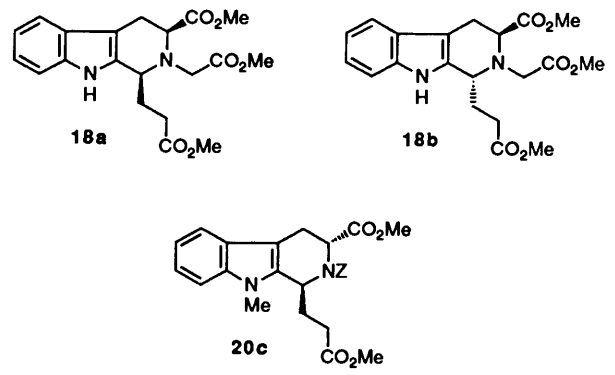
Scheme 1



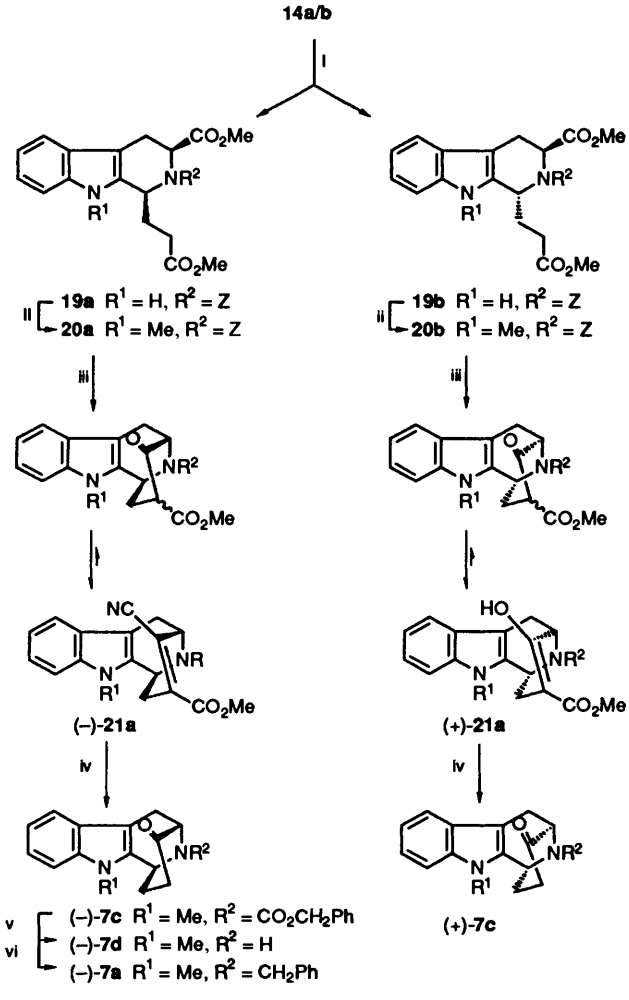
Scheme 2

60% yield of the tetrahydro-β-carbolines **14a/b** in a pleasing *cis*:*trans* ratio of 4:1, and without any competitive formation of the tri-ester **15**.

For subsequent synthetic steps, we were certain that protection of the N(2) nitrogen would be necesssary. We wondered, however, whether it might be possible to do so using a group that could subsequently become incorporated into natural product targets. To this end, treatment of **14a/b** with ethyl bromoacetate or (better) ethyl iodoacetate yielded the separable triesters **18a/b**. But, although attempted cyclisations on **18a** were unsuccessful, an additional problem had already been encountered; the formation of **18a** was incomplete and very sluggish, with the *trans*-isomer **14b** reacting more rapidly with the alkylating agent. Thus, the disappointing 50% yield (at best) for these reactions was accompanied by a reduction in the diasteroisomeric excess, making this approach unattractive. Using benzyl bromide as the alkylating agent also gave the same problems of yield and selectivity, and we therefore tried the more reactive benzyl chloroformate instead. This successfully led to benzyloxycarbonylation of the N(2)-nitrogens (77% yield) without any discrimination between the *cis* and *trans* isomers, and the diastereoisomers **19a/b** were readily separated by flash chromatography. Although only the *cis*-isomer had the correct absolute stereochemistry for subsequent natural product synthesis, the *trans*-isomer **19b** was to be of use later in assessing the optical purity of the bridged ketone **7c** (see below).



There are many indole alkaloids that are methylated on the indole nitrogen (*e.g.* ajmaline **2** and suavoline **6**), and we initially decided to develop a synthetic route to advanced intermediates suitable for these targets (Scheme 3). Thus, N^{in}-methylation (MeI/NaH) of the major *cis*-isomer **19a** gave the fully protected

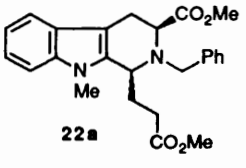


Scheme 3 *Reagents and conditions:* i, $PhCH_2OCOCl$, $NaHCO_3$, CH_2Cl_2, room temp.; ii, MeI, NaH, DMF, 0 °C; iii, NaH (2.2 equiv.), MeOH (0.1 equiv.), DMF, room temp.; iv, NaCl (1.2 equiv.), H_2O (2 equiv), DMF, 130 °C; v, H_2, 10% Pd–C, MeOH; vi, $PhCH_2Br$, $NaHCO_3$, CH_2Cl_2, reflux.

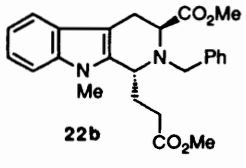
cis-diester **20a**. When this was treated with sodium hydride in DMF under rigorously aprotic conditions, no Dieckmann cyclisation was observed; instead, after work-up, a mixture of starting material and its C(3)-epimer **20c** was recovered. However, when a catalytic quantity of methanol was added to the *cis*-diester **20a** (or to the *cis*/*trans* mixtue **20a**/**c**) in the presence of sodium hydride (2.2 equiv.), the desired Dieckmann cyclisation took place, giving the enolic form (−)-**21a** of the β-keto ester in 70% yield. Hydrolytic decarboxylation was achieved smoothly using Krapcho's procedure[8] [DMF–H_2O (2 equiv.)/NaCl (1.2 equiv.)/130 °C], giving the bridged ketone (−)-**7c** in 73% yield.

At this stage, we decided to check the optical integrity of the advanced intermediate (−)-**7c**. The advantage with determining the enantiomeric excess at this relatively late stage was that racemisation of the bicyclic structure during any subsequent synthetic steps seemed virtually impossible – if optical purity could be demonstrated for (−)-**7c**, then optically pure final products would be virtually guaranteed. There were two reactions at which racemisation had been deemed a serious risk: firstly, during the initial Pictet–Spengler reaction. However, although racemisation is common when such reactions are carried out at high temperature, we had observed no evidence for racemisation when model reactions were conducted at or below room temperature.[7] Secondly, the Dieckmann cyclisation had been believed to proceed *via* epimerisation at C(3) (see below), and any concurrent epimerisation at C(1) would have resulted in racemisation. In the event, the C(3)-epimerisation observed during the Dieckmann cyclisation was both proved, and used to advantage in the following way: taking the minor *trans*-diester **19b** (see above) through the same sequence as the *cis*-isomer (N^{in}-methylation, Dieckmann cyclisation, hydrolytic decarboxylation) gave the bridged ketone (+)-**7c**. Assuming that epimerisation only occurred at C(3) during Diekmann cyclisation, this should be antipodal to (−)-**7c** derived from the *cis* Pictet–Spengler adduct **19a**, and indeed these compounds did show equal and opposite optical rotations. With samples of both absolute stereochemistry in hand, it was possible to find conditions under which the two enantiomers were resolved on a 3,5-dinitrobenzoylphenylglycine derived chiral HPLC column.[9] Both (−)-**7c** and (+)-**7c** were found to be optically pure within our detection limits (<95% ee).

In earlier work with related *cis* and *trans*-1,3-disubstituted tetrahydro-β-carbolines **22a** and **22b**, Yoneda *et al.*[10] and Cook *et al.*[11] both claimed that only the *trans* isomer **22b** would



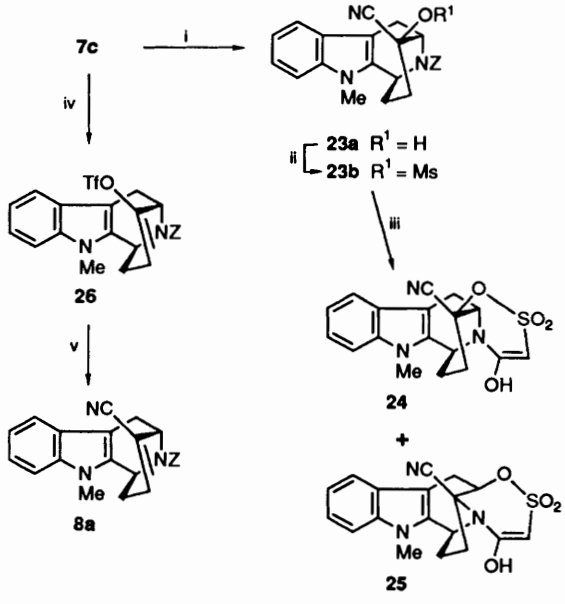
22a



22b

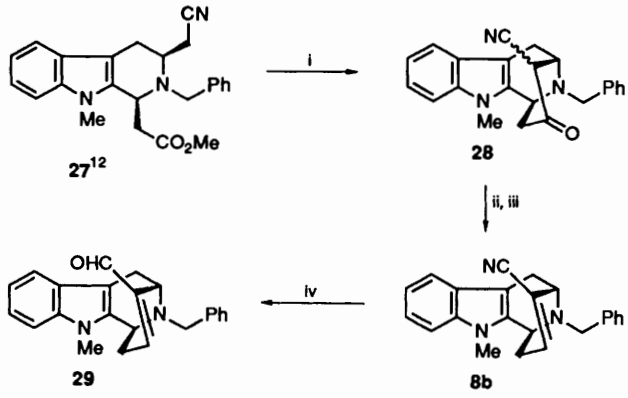
undergo Dieckmann cyclisation. This result is very surprising, for the *trans* isomer can clearly undergo cyclisation only after it has been epimerised to the *cis* isomer. In our hands, however, both the *cis* and *trans* isomers **19a** and **19b** separately underwent Dieckmann cyclisation at comparable rates and (judging by TLC before cyclisation was complete) *via* *cis*/*trans* mixtures of **19a**/**b** of very similar composition. This finding is in agreement with that reported by Magnus[5] for similar systems.

With the optical integrity of (−)-**7c** now assured, we completed formal syntheses of (−)-ajmaline **2** and (−)-suavoline **6** by removal of the benzyloxycarbonyl protection (H_2/Pd–C), followed by benzylation with benzyl bromide, to generate the protected ketone **7a**. It is interesting to note that the benzylation of **7d** occurred quickly and efficiently, in contrast to the synthetic precursor **14a**; this must be due to substantially reduced steric interactions when the *cis* substituents are bridged. The (±)-form of this ketone was used by Mashimo and Sato[3] in their synthesis of racemic ajmaline (±)-**2**, and by Cook *et al.*[4] in their synthesis of racemic suavoline (±)-**6**, and our intermediate should, therefore, give access to these optically active natural products possessing the correct absolute stereochemistry.



Scheme 4 *Reagents and conditions:* i, KCN, MeOH, H_2O, sat. $Na_2S_2O_5$; ii, CH_3SO_2Cl, DMAP, CH_2Cl_2, reflux; iii, NaH, DMF, room temp.; iv, $(CF_3SO_2)_2NPh$, NaH, THF, room temp.; v, LiCN, PhH, $Pd(PPh_3)_4$-(cat.), 12-crown-4 (cat.), room temp.

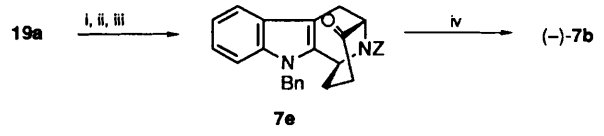
Conversion of **7c** into the α,β-unsaturated nitrile **8a** was unexpectedly difficult. Formation of the cyanohydrin **23a** was readily achieved [KCN/MeCN/$Na_2S_2O_5$(aq)], but numerous attempts at elimination of water to give **8a** were unsuccessful; for example, heating with strong acids, or with thionyl or phosphoryl chloride, all gave complex mixtures of products, whilst derivatisation of the hydroxy group as the xanthate, thiocarbamate, tosylate or triflate proved impossible. We were eventually able to derivatise the hydroxy group of the cyanohydrin as the mesylate **23b** (stereochemistry assigned by NOESY), but attempted emination using a range of bases (NaOEt, NaH, KOBu^t, DBU, DBN) gave mainly **24** and (tentatively) **25** in a 3:1 ratio; if structure **25** is indeed correct, it must have been formed *via* an extraordinary rearrangement. The desired α,β-unsaturated nitrile **8a** was eventually formed



Scheme 5 *Reagents and conditions:* i, $LiNEt_2$, THF, −78 °C; ii, $NaBH_4$, MeOH, room temp.; iii, $POCl_3$, pyr, PhH, reflux; iv, DIBAL, CH_2Cl_2, −78 °C. Details of these synthetic steps will be published shortly.

via the enol triflate **26**, as indicated in Scheme 4. This advanced intermediate **8a**, and the benzyl protected analogue **8b** accessible by the route shown in Scheme 5, are currently being assessed as precursors to bridged indole alkaloids of the sarpagine family. Indeed, reduction of **8b** with DIBAL yielded the α,β-unsaturated aldehyde **29**, the racemic form of which was also an intermediate in Cook's synthesis of suavoline **6**.[4] For completion of their synthesis, the remaining C_4-fragment was introduced *via* a Claisen rearrangement, although Michael-type chemistry on **8b** or **29** would, in theory at least, also generate the correct skeleton for most of the sarpagine family of alkaloids.

Returning to our final target molecule (−)-**7b**, we were simply able to N^{in}-benzylate the diester **19a** that we had prepared earlier, and then repeat the cyclisation and hydrolytic decarboxylation as before to give the fully protected ketone (−)-**7e** (Scheme 6). Catalytic hydrogenation over palladium on



7e

Scheme 6 *Reagents and conditions:* i, $PhCH_2Br$, NaH, DMF, 0 °C; ii, NaH (2.2 equiv.), MeOH (0.1 equiv.), DMF, room temp.; iii, NaCl (1.2 equiv.), H_2O (2 equiv.), DMF, 130 °C; iv, H_2, 10% Pd–C, MeOH

charcoal led to selective removal of the benzyloxycarbonyl protection, yielding (−)-**7b**, the antipode of the ketone used by Magnus *et al.* in their syntheses of (+)-koumine, (+)-taberpsychine and (+)-koumidine.[5] Our work therefore constitutes formal syntheses of these compounds with the natural configuration [*i.e.* the (−)-isomers].

In summary, we have shown that the kinetically controlled Pictet–Spengler reaction developed by us can be used in the synthesis of indolic natural products. Of particular importance is that the use of proteinogenic L-tryptophan gives access to natural products with the correct absolute stereochemistry. The high optical purity of the key bridged ketone (−)-**7c** confirms that kinetically controlled Pictet–Spengler reactions take place with no sign of racemisation, and this is the first example of the use of this stereocontrolled reaction for the introduction of the intact L-tryptophan skeleton into indolic natural products of the correct configuration.

Experimental

Melting points were determined on a Reichert microscope hot-stage apparatus, and are uncorrected. NMR spectra were recorded on a JEOL FX90Q at 90 MHz (^1H) and 22.5 MHz (^{13}C), or a Bruker MSL300 spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), unless otherwise stated. Chemical shifts were measured in ppm on the δ scale downfield from tetramethylsilane as internal standard; *J* values are recorded in Hz. All ^{13}C data are quoted with ^1H multiplicities (off resonance results in brackets), although this multiplicity was usually inferred from DEPT experiments. Where appropriate, NMR data in brackets refers to the minor diastereoisomer or minor rotamer. Infrared spectra were recorded on a Pye–Unicam SP3-200 or a Perkin-Elmer 1420 spectrophotometer. Mass spectra were obtained by electon impact at 70 eV on an AEI MS-3074 spectrometer, unless otherwise stated. Optical rotations were measured using a Perkin-Elmer 141 polarimeter; $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was carried out on Merck aluminium sheet silica gel 60 F_{254} plates (thickness 0.2 mm). Spots were visualised with a UV hand lamp or iodine vapour. Flash chromatography[13] was performed using silica gel 60 (230–400 mesh) as the stationary phase, purchased from Camlab. HPLC was performed on a Bio-Rad 1330 HPLC with UV detector using a Spherisorb capped SiO_2 column, or a 5 μm DNBPG covalent chiral column.

Unless otherwise indicated all reactions were carried out under an atmosphere of dry nitrogen or argon.

(1S,3S)- *and* (1R,3S)-*Methyl* 1-(2-*Methoxycarbonylethyl*)-1,2,3,4-*tetrahyrdo*-9H-*pyrido*[3,4-b]*indole*-3-*carboxylate* **14a**/**14b**.—L-Tryptophan methyl ester (3.75 g, 17.2 mmol, 1.5 equiv.) in an anhydrous benzene was heated to reflux in a Dean–Stark apparatus under an inert atmosphere. The solution was stirred rapidly and methyl 4-oxobutanoate (1.33 g, 11.5 mmol, 1 equiv.) in anhydrous benzene was added in one portion at reflux. Heating was continued for 15 min when *ca.* 0.2 cm^3 of water had collected, indicating that the imine formation was complete. The reaction mixture was then cooled and the solvent evaporated. The residue was taken up in anhydrous dichloromethane and the resultant solution cooled to 0 °C. Trifluoroacetic acid (2.6 g, 22.8 mmol, 2 equiv.) was added and the reaction mixture was stirred at this temperature for 2 h when TLC showed that cyclisation was complete. The reaction mixture was then poured into water and made alkaline with an excess of aqueous NaOH (2 mol dm^{-3}). The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica (mainly to remove excess of L-tryptophan methyl ester) eluted with ethoxyethane–trichloromethane (1:9) afforded **14a**/**14b** as an inseparable mixture of diastereoisomers as a white foam (2.2 g, 60%) in the ratio of 4:1. R_f on silica 0.2 (ethoxyethane–trichloromethane, 1:9); ν_{max}($CHCl_3$)/cm^{-1} 3470, 3010, 2960, 1730, 1440, 1270, 1175, 800 and 675; δ_H(300 MHz; $CDCl_3$) 1.88–2.63 (4 H, m, $CH_2CH_2CO_2CH_3$), 2.72–2.95 (1 H, m, $ArCH_2$), 3.00–3.14 (1 H, m, $ArCH_2$), 3.59–3.90 [7 H, m, comprising of 4 sharp singlets δ 3.79 (3.72) and 3.62 (3.64) due to CO_2CH_3, and $ArCH_2CH$], 4.12–4.23 (1 H, m, ArCH), 7.03–7.16 (2 H, m, ArH), 7.18–7.27 (1 H, m, ArH) 7.42–7.48 (1 H, m, ArH) and 8.63 (8.55) (1 H, br s, indole NH), δ_C(75 MHz; $CDCl_3$) 25.75 (25.20) (t), 29.29 (30.04) (t), 29.47 (30.52) (t), 51.77 (q), 52.04 (49.71) (d), 52.21 (q), 56.28 (52.15) (d), 108.36 (106.98) (s), 111.02 (d), 117.92 (d), 119.42 (119.28) (d), 121.71 (d), 127.00 (126.80) (s), 134.36 (134.61) (s), 136.14 (135.97) (s), 173.56 (174.19) (s) and 174.62 (174.78) (s), *m/z* 316 (M^+, 28%), 257 (10), 229 (100) and 169 (48) (Found: M^+, 316.1420. $C_{17}H_{20}N_2O_4$ requires M^+, 316.1423).

(1S,3S)- *and* (1R,3S)-*Methyl* 2-(*Ethoxycarbonylmethyl*)-1-(2-*methoxycarbonylethyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]-*indole*-3-*carboxylates* **18a**/**18b**.—The *cis*/*trans* mixture of 1,3-disubstituted tetrahydro-β-carboline derivatives **14a**/**14b** (200 mg, 0.63 mmol), ethyl iodoacetate (270 mg, 150 mm^3, 1.26 mmol, 2 equiv.) and triethylamine (128 mg, 176 mm^3, 1.26 mmol, 2 equiv.) were stirred in DMF at 60 °C for 3 h. The solvent was removed under reduced pressure, the residue taken up into ethyl acetate and the solution washed with hydrochloric acid (2 mol dm^{-3}) and saturated brine (×2). The organic layer was then dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with ethoxyethane–trichloromethane (1:1 g) afforded the mixture of diastereoisomers **18a**/**18b** (127 mg, 50%) as a white form; R_f on silica 0.22 (ethoxyethane–trichloromethane, 1.19); ν_{max}($CHCl_3$)/cm^{-1} 3470, 3000, 2960, 1735, 1440 and 1175; δ_H(300 MHz; $CDCl_3$) 1.10–1.40 (3 H, m, $CO_2CH_2CH_3$), 1.83–2.77 (4 H, m, $CH_2CH_2CO_2CH_3$), 2.90–3.18 (2 H, m, $ArCH_2$), 3.53–3.78 [7 H, m, comprising of 4 resolved singlets δ 3.74 (3.67) and 3.62 (3.64), $CH_2CH_2CO_2CH_3$, $CHCO_2CH_3$ and $ArCH_2CH$], 3.93–4.44 (5 H, m, $CH_2CO_2CH_2CH_3$ and ArCH), 6.94–7.57 (4 H, m, ArH) and 8.14 (8.19) (1 H, br s, indole NH); δ_C(75 MHz; $CDCl_3$) 14.14 (q), 24.16 (22.27) (t), 28.77 (27.79) (t), 29.25 (28.98) (t), 51.52 (q), 51.84 (q),

52.17 (51.95) (d), 56.72 (56.02) (t), 57.37 (56.72) (t), 60.51 (60.40) (d), 107.59 (107.21) (s), 110.95 (d), 117.94 (d), 119.35 (d), 121.68 (d), 126.71 (126.61) (s), 133.59 (133.00) (s), 136.36 (s), 171.14 (171.46) (s), 173.41 (173.09) (s) and 174.71 (174.93) (s); *m/z* 402 (M^+, 11%), 343 (8), 315 (100) and 255 (9) (Found: M^+, 402.1785. $C_{21}H_{26}N_2O_6$ requires M^+, 402.1785).

(1S,3S)- *and* (1R,3S)-*Methyl* 2-*Benzyl*-1-(2-*methoxycarbonylethyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indoles*-3-*carboxylate* **22a**/**22b**.—The *cis*/*trans* mixture of 1,3-disubstituted tetrahydro-β-carboline derivatives **14a**/**14b** (200 mg, 0.63 mmol) and benzyl bromide (217 mg, 150 mm^3, 1.26 mmol, 2 equiv.) were refluxed together in dichloromethane over solid $NaHCO_3$ for 48 h. The solution was cooled, filtered, and evaporated. Flash chromatography of the residue on silica eluted with ethoxyethane–trichloromethane (1:19) afforded a mixture of the diastereoisomers **22a**/**22b** (123 mg, 48%) as a white foam: R_f on silica 0.2 (ethoxyethane–trichloromethane, 1:9); $\nu_{max}(CHCl_3)$/cm^{-1} 3470, 3010, 2950, 1730, 1440, 1360, 1325, 1270 and 1175; δ_H(300 MHz; $CDCl_3$) 1.71–2.05 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.23–2.57 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.94–3.27 (2 H, m, $ArCH_2$), 3.55 (3.48) (3 H, s, CO_2CH_3), 3.59 (3.71) (3 H, s, CO_2CH_3), 3.75–4.00 (4 H, m, $PhCH_2$, $ArCH_2CH$ and ArCH), 7.05–7.54 (9 H, m, ArH) and 8.19 (8.22) (1 H, br s, indole NH); δ_C(75 MHz; $CDCl_3$) 19.57 (21.23) (t), 29.24 (28.68) (t), 30.26 (29.71) (t), 51.55 (51.48) (q), 51.83 (51.88) (q), 56.04 (54.88) (d), 58.62 (56.63) (d), 59.36 (53.33) (t), 106.17 (107.18) (s), 110.87 (110.95) (d), 118.19 (118.06) (d), 119.29 (119.36) (d), 121.64 (d), 126.88 (s), 127.27 (127.05) (d), 128.33 (129.04) (d), 133.30 (134.19) (s), 136.10 (136.21) (s), 138.94 (139.29) (s), 173.90 (173.43) (s) and 174.67 (174.40) (s); *m/z* 406 (M^+, 6%), 347 (8), 319 (100), 169 (13) and 91 (58) (Found: M^+, 406.1888. $C_{24}H_{26}N_2O_4$ requires M^+, 406.1893).

(1S,3S)- *and* (1R,3S)-2-*Benzyl* 3-*Methyl* 1-(2-*Methoxycarbonylethyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-*b*]*indole*-2,3-*dicarboxylate* **19a**/**19b**.—The *cis*/*trans* mixture of 1,3-disubstituted tetrahydro-β-carboline derivatives **14a**/**14b** (3.63 g, 11.5 mmol) was dissolved in anhydrous dichloromethane and stirred over solid $NaHCO_3$ (*ca.* 2 g, >2 equiv.). Benzyl chloroformate (1.96 g, 1.64 cm^3, 11.5 mmol, 1 equiv.) was then added and the solution stirred at ambient temperature for 4 h. The solution was filtered and washed with water. The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with ethoxyethane–trichloromethane, 1:19, allowed separation to afford the *cis*-isomer **19a** (3.2 g, 62%), and the *trans*-isomer **19b** (775 mg, 15%) both as white foams.

Data for *cis* isomer **19a**: R_f on silica 0.5 (ethoxyethane–trichloromethane, 1:19); $[\alpha]_D^{22}$ +80.0 (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 3360, 3020, 2960, 1730, 1690, 1440, 1415, 1325, 1045, 910 and 705; δ_H(300 MHz; $CDCl_3$) 2.01–2.33 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.42–2.94 (2 H, m, $CH_2CH_2CO_2CH_3$), 3.06 (3.00) (1 H, d, *J* 7.1, ArCH), 3.30–3.75 [7 H, m, comprising of 4 resolved singlets at δ 3.60 (3.64) and 3.58 (3.52) due to $CH_2CH_2CO_2CH_3$, $CHCO_2CH_3$, and ArCH), 5.08–5.62 (4 H, m, $PhCH_2OCO$, $ArCH_2CH$ and ArCH), 7.02–7.54 (9 H, m, ArH) and 8.79 (9.02) (1 H, br s, indole NH); δ_C(75 MHz; $CDCl_3$) 22.31 (21.74) (t), 31.09 (t), 31.33 (t), 51.02 (51.26) (d), 51.67 (q), 52.56 (q), 52.70 (52.26) (d), 68.19 (67.85) (t), 105.54 (104.79) (s), 111.06 (d), 118.21 (118.06) (d), 119.37 (d), 121.97 (121.85) (d), 126.25 (s), 127.73 (d), 128.22 (d), 128.51 (d), 132.26 (133.00) (s), 136.15 (135.80) (s), 136.15 (s), 156.04 (156.38) (s) and 172.29 (s); *m/z* 450 (M^+, 17%), 363 (7), 315 (43), 169 (19) and 91 (100) (Found: M^+, 450.1791. $C_{25}H_{26}N_2O_6$ requires M^+, 450.1791).

Data for *trans* isomer **19b**: R_f on silica 0.3 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{22}$ +20.0 (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 3360, 3010, 2950, 1735, 1700, 1450, 1400, 1310, 1175, 910 and 700; δ_H(300 MHz; $CDCl_3$) 2.04–2.70 (4 H, m, $CH_2CH_2CO_2CH_3$), 3.13 (3.07) (1 H , d, *J* 5.2, ArCH), 3.30–3.67 (7 H, m, $CH_2CH_2CO_2CH_3$, $CHCO_2CH_3$ and ArCH), 4.74–4.93 (1 H, m, $ArCH_2CH$), 5.10–5.39 (3 H, m, $PhCH_2OCO$ and ArCH), 7.03–7.53 (9 H, m, ArH), and 8.86 (8.68) (1 H, br s, indole NH); δ_C(75 MHz; $CDCl_3$) 23.11 (22.71) (t), 29.23 (t), 30.35 (30.72) (t), 51.61 (q), 52.31 (q), 52.56 (52.31) (d), 55.48 (d), 67.84 (t), 106.09 (106.87) (s), 111.22 (d), 117.97 (d), 119.48 (d), 121.88 (d), 126.09 (s), 128.05 (d), 128.17 (d), 128.48 (d), 133.28 (s), 135.96 (s), 136.28 (s), 156.98 (s), 172.07 (171.85) (s), 173.96 (s); *m/z* 450 (M^+, 50%), 363 (35), 315 (90), 169 (26) and 91 (100) (Found: M^+, 450.1788. $C_{25}H_{26}N_2O_6$ requires M^+, 450.1791).

(1S,3S)-2-*Benzyl* 3-*Methyl* 1-(2-*Methoxycarbonylethyl*)-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-2,3-*dicarboxylate* **20a**.—Sodium hydride (80% dispersion in oil; 145 mg, 4.83 mmol, 1.05 equiv.) was added to a stirred solution of **19a** (2.07 g, 4.60 mmol) and iodomethane (685 mg, 300 mm^3, 4.83 mmol, 1.05 equiv.) in anhydrous DMF at 0 °C. The mixture was stirred at this temperature for 1 h and then at ambient temperature for a further 30 min. The solvent was removed under reduced pressure, the residue taken up into ethyl acetate and the solution washed with water and saturated brine. The oganic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (1:19) afforded **20a** (1.75 g, 82%) as a cream foam; R_f on silica 0.69 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{25}$ +7.9 (*c* 1.26 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3020, 2950, 1730, 1695, 1470, 1440, 1410, 1315, 1280, 1040 and 910; δ_H(300 MHz; $CDCl_3$) 1.62–1.87 (1 H, m, $CH_2CH_2CO_2CH_3$), 2.07–2.24 (1 H, m, $CH_2CH_2CO_2CH_3$), 2.42–2.61 (1 H, m, $CH_2CH_2CO_2CH_3$), 2.66–2.82 (1 H, m, ArCH), 3.33–3.74 (10 H, m, comprising 4 resolved singlets at δ 3.71, 3.68, 3.60 and 3.43 due to $CH_2CH_2CO_2CH_3$, $CHCO_2CH_3$ and NCH_3 and ArCH), 4.98–5.69 (4 H, m, $PhCH_2OCO$, $ArCH$ and $ArCH_2CH$) and 7.53–7.04 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 21.95 (21.13) (t), 29.88 (29.57) (t), 29.75 (q), 29.97 (30.41) (t), 49.22 (d), 51.52 (51.35) (q), 52.15 (52.24) (q), 52.94 (51.98) (d), 68.03 (67.87) (t), 103.84 (104.41) (s), 109.13 (109.01) (d), 117.97 (118.17) (d), 119.32 (d), 121.70 (121.55) (d), 125.68 (125.83) (s), 127.94 (127.81) (d), 128.05 (128.14) (d), 128.40 (128.49) (d), 134.19 (135.19) (s), 136.14 (135.95) (s), 137.19 (137.39) (s), 156.31 (156.21) (s), 172.92 (172.76) (s) and 173.70 (173.55) (s); *m/z* 464 (M^+, 37%), 377 (55), 333 (67), 283 (78), 223 (33), 183 (30) and 91 (100) (Found: M^+, 464.1947. $C_{26}H_{28}N_2O_6$ requires M^+, 464.1947).

(6S,10S)-12-*Benzyl* 8-*Methyl* 5-*Methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8,12-*dicarboxylate* (−)-**21a**.—The *cis* tetrahydro-β-carboline **20a** (2.25 g, 4.85 mmol) was dissolved in anhydrous DMF. Sodium hydride (80% dispersion in oil; 320 mg, 10.7 mmol, 2.2 equiv.) was added and the reaction mixture stirred for 1 h at ambient temperature. Methanol (15.5 mg, 19.6 mm^3, 0.485 mmol, 0.1 equiv.) was then added and stirring was contained at this temperature for a further 5 h when TLC indicated the cyclisation to be complete. The solvent was removed under reduced pressure, aqueous citric acid (0.5 mol dm^{-3}) was added and the residue extracted into ethyl acetate. The organic layer was then separated, washed with saturated brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (1:1) afforded the β-keto ester (−)-**21a** (1.46 g, 70%) as a white foam: R_f on silica 0.8 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{25}$ −24.7 (*c* 2.23 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 1695, 1660, 1620, 1440, 1330, 1290, 1255 and 1100; δ_H(300 MHz; $CDCl_3$) 2.41 (2.37) (1 H, d, *J*

15.8, ArCHC*H*H), 2.85–2.98 (1 H, m, ArCHC*H*H), 3.05–3.29 (2 H, m, ArCH_2), 3.65 (3.63) (3 H, s, NCH_3),3.67 (3.64) (3 H, s, CO_2CH_3), 5.07–5.26 (3 H, m, PhCH_2OCO and ArCH_2C*H*), 5.65 (5.51) (1 H, d, *J* 5.2, ArC*H*), 7.06–7.50 (9 H, m, ArH) and 12.09 (12.07) (1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 25.38 (24.78) (t), 28.31 (28.85) (t), 29.54 (q), 44.80 (45.50) (d), 50.35 (49.89) (d), 51.63 (q), 67.63 (t), 94.60 (94.19) (s), 106.11 (106.77) (s), 108.94 (d), 118.16 (118.33) (d), 119.37 (119.45) (d), 121.65 (121.75) (d), 126.24 (s), 127.98 (d), 128.20 (d), 128.56 (d), 133.91 (133.49) (s), 136.11 (136.26) (s), 136.94 (s), 153.98 (153.83) (s), 169.71 (170.33) (s) and 172.21 (172.06) (s); *m/z* 432 (M^+, 33%), 400 (16), 297 (7), 265 (27), 237 (18), 183 (27), 149 (38) and 91 (100) (Found: M^+, 432.1684. $C_{25}H_{24}N_2O_5$ requires M^+, 432.1685).

(−)-(6S,10S)-*Benzyl* 5-*Methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-12-*carboxylate* (−)-**7c**.—The β-keto ester (−)-**21a** (1.83 g, 4.24 mmol) was dissolved in DMF degassed with argon. Sodium chloride (297 mg, 5.08 mmol, 1.2 equiv.) and water (153 mg, 153 mm^3, 8.47 mmol, 2 equiv.) were then added and the mixture was heated (under an atmosphere of argon) at 130 °C for 6 h. The solvent was removed under reduced pressure, the residue taken up into ethyl acetate and the solution washed twice with saturated brine. The organic layer was then separated, dried ($MgSO_4$) and evaporated. Flash chromatography on silica eluted with hexane–trichloromethane (3:7) afforded the protected ketone (−)-**7c** (1.16 g, 73%) as a white foam: R_f on silica 0.55 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{25}$ −40.0 (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3000, 1700, 1470, 1430, 1420, 1295 and 1105; δ_H(300 MHz; $CDCl_3$) 2.03–2.27 (2 H, m, CH_2CH_2CO), 2.45–2.66 (2 H, m, CH_2CH_2CO), 2.89–3.05 (1 H, m, ArC*H*H), 3.15–3.29 (1 H, m, ArC*H*H), 3.71 (3.68) (3 H, s, NCH_3), 4.96–5.31 (3 H, m, PhCH_2OCO and ArCH_2C*H*), 5.72 (5.59) (1 H, br s, ArC*H*) and 7.07–7.52 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 25.31 (24.76) (t), 28.75 (29.19) (t), 29.67 (q), 34.48 (t), 45.38 (46.00) (d), 59.64 (59.13) (d), 67.78 (t), 106.74 (107.45) (s), 109.06 (d), 118.28 (118.46) (d), 119.57 (d), 122.02 (d), 126.09 (s), 127.97 (d), 128.29 (d), 128.60 (d), 133.16 (132.85) (s), 136.00 (136.17) (s), 137.34 (s), 154.46 (154.31 (s) and 208.41 (s); *m/z* 374 (M^+, 24%), 239 (27), 202 (100), 183 (26), 159 (23) and 91 (37) (Found: M^+, 374.1624. $C_{23}H_{22}N_2O_3$ requires M^+, 374.1630).

(1R,3S)-2-*Benzyl* 3-*Methyl* 1-(2-*Methoxycarbonylethyl*)-9-*methyl*-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-2,3-*dicarboxylate* **20b**.—Sodium hydride (80% dispersion in oil; 34.5 mg, 1.15 mmol, 1.1 equiv.) was added to a stirred solution of **19b** (470 mg, 1.04 mmol) and iodomethane (163 mg, 71 mm^3, 1.15 mmol, 1.1 equiv.) in anhydrous DMF at 0 °C. The mixture was stirred at this temperature for 1 h and then at ambient temperature for a further 30 min. The work-up procedure was the same as for the *cis* isomer **20a**. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (1:9) afforded **20b** (303 mg, 63%) as a cream foam: R_f on silica 0.60 (ethoxyethane–trichloromethane, 1:9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3000, 2950, 1730, 1700, 1470, 1435, 1395, 1310 and 1040; δ_H(300 MHz; $CDCl_3$) 2.02–2.64 (4 H, m, CH_2CH_2CO_2CH_3) 3.25 (3.20) (1 H, d, *J* 5.2, ArC*H*H), 3.42–3.88 (10 H, m, comprising 4 resolved singlets at δ 3.78, 3.74, 3.51 and 3.47 due to $CH_2CH_2CO_2CH_3$, $CHCO_2CH_3$, NCH_3 and ArC*H*H), 4.75–4.98 (1 H, m, ArCH_2C*H*), 5.15–5.40 (2 H, m, PhCH_2-OCO), 5.47–5.62 (1 H, m, ArC*H*) and 7.14–7.63 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 23.20 (22.58) (t), 28.72 (t), 29.16 (29.31) (t), 29.77 (q), 51.46 (d) and (q), 52.22 (q), 55.28 (54.96) (d), 67.79 (t), 105.78 (106.64) (s), 109.13 (d), 118.08 (d), 119.36 (d), 121.64 (d), 125.62 (125.78) (s), 127.92 (d), 128.15 (d), 128.48 (d), 134.29 (s), 135.00 (s), 137.56 (s), 156.83 (156.71) (s), 171.92 (171.36) (s) and 173.30 (s); *m/z* 464 (M^+, 15%), 377 (28), 333 (42), 183 (17) and 91 (100) (Found: M^+, 464.1947. $C_{26}H_{28}N_2O_6$ requires M^+, 464.1947).

(+)-(6S,10S)-12-*Benzyl* 8-*Methyl* 5-*Methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-8,12-*dicarboxylate* (+)-**21a**.—The *trans*-tetrahydro-β-carboline **20b** was cyclised following the same procedure carried out on the *cis* tetrahydro-β-carboline **20a**. The β-keto ester (+)-**21a** obtained was identical in all respects with (−)-**21a** obtained previously apart from its optical rotation $[\alpha]_D^{25}$ +24.0 (*c* 2.23 in $CHCl_3$).

(+)-(6S,10S)-*Benzyl* 5-*Methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-12-*carboxylate* (+)-**7c**.—This compound was prepared in exactly the same way as (−)-**7c**, starting from (+)-**21a** following the above procedure, $[\alpha]_D^{25}$ +38.9 (*c* 0.5 in $CHCl_3$).

(−)-(6S,10S)-5-*Methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole* (−)-**7d**.—The protected ketone (−)-**7c** (153 mg, 0.41 mmol) was dissolved in anhydrous methanol and subjected to catalytic hydrogenolysis over 10% palladium on activated charcoal for 2 h. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. Flash chromatography of the residue on silica eluted with methanol–trichloromethane (1:19) afforded the deprotected ketone (−)-**7d** (75.7 mg, 77.1%) as a white foam: R_f on silica 0.5 (ethanol–trichloromethane, 1:9); $[\alpha]_D^{22}$ −115.2 (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-3}$ 3320, 2940, 1710 and 1470; δ_H(300 MHz; $CDCl_3$) 2.01–2.17 (2 H, m, CH_2CH_2CO), 2.36–2.49 (2 H, m, CH_2CH_2CO), 2.78 (1 H, d, *J* 16.5, ArC*H*H), 3.08 (1 H, dd, *J* 16.5, 6.8, ArC*H*H), 3.58 (3 H, s, NCH_3), 3.89 (1 H, d, *J* 6.8, ArCH_2C*H*), 4.32 (1 H, br s, ArC*H*), 7.05–7.32 (3 H, m, ArH) and 7.48–7.40 (1 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 25.76 (t), 29.22 (q), 31.29 (t), 34.87 (t), 44.78 (t), 59.59 (d), 106.32 (s), 108.84 (d), 118.05 (d), 119.21 (d), 121.53 (d), 126.43 (s), 135.09 (s), 136.88 (s) and 210.68 (s); *m/z* 240 (M^+, 32%), 183 (100), 168 (20), 140 (5), 115 (6) and 91 (22) (Found: M^+, 240.1269. $C_{15}H_{16}N_2O$ requires M^+, 240.1263).

(+)-(6S,10S)-5-*Methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole* (+)-**7d**.—This compound was prepared in exactly the same way as (−)-**7d**, except starting from (+)-**7c**; $[\alpha]_D^{22}$ +114.1 (*c* 0.5 in $CHCl_3$).

(−)-(6S,10S)-12-*Benzyl*-5-*methyl*-9-*oxo*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole* (−)-**7a**.—The protected ketone (−)-**7c** (290 mg, 1.21 mmol) and benzyl bromide (310 mg, 214 mm^3, 1.26 mmol, 1.8 equiv.) were refluxed together in dichloromethane over solid $NaHCO_3$ for 24 h. The solution was cooled, filtered, and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (3:7) afforded the ketone (−)-**7a** (181 mg, 71%) as a white foam [see refs. 3 and 4 for data on (±)-**7a**]: δ_H(300 MHz; $CDCl_3$) 1.87–2.20 (2 H, m, CH_2CH_2CO), 2.37–2.51 (2 H, m, CH_2CH_2CO), 2.67 (1 H, d, *J* 7.0, ArC*H*H), 3.23 (1 H, dd, *J* 17.0, 7.0, ArC*H*H), 3.56 (3 H, s, NCH_3), 3.63–3.77 (3 H, m, PhCH_2 and ArCH_2C*H*), 4.03–4.08 (1 H, m, ArC*H*) and 7.52–7.00 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 20.96 (t), 29.85 (q), 30.28 (t), 34.88 (t), 49.38 (d), 56.72 (t), 65.33 (d), 106.20 (s), 109.48 (d), 118.74 (d), 119.48 (d), 122.06 (d), 126.97 (s), 127.89 (d), 128.99 (d), 129.19 (d), 133.67 (s), 137.71 (s), 138.76 (s), 210.65 (s); *m/z* 330 (M^+, 40%), 302 (8), 273 (100), 183 (20), 168 (23) and 91 (51) (Found: M^+, 330.1735. $C_{22}H_{22}N_2O$ require M^+, 330.1732).

Synthesis using (−)-Series of Compounds.

The following syntheses were carried out using the (−) series of compounds which are required for the synthesis of the naturally occurring target molecules.

(6S,10S)-*Benzyl* 9-*Cyano*-9-*hydroxy*-5-*methyl*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-12-*carboxylate* **23a**.—The protected ketone **7c** (154 mg, 0.41 mmol) was dissolved in acetonitrile (2 cm^3) and added to a solution of potassium cyanide (30.8 mg, 0.47 mmol) in water (1 cm^3). Saturated aqueous sodium metabisulphite (2 cm^3) was then added dropwise over a period of 5 min. The reaction mixture was stirred at ambient temperature for 4 h and then poured into water and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried ($MgSO_4$) and evaporated to afford the cyanohydrin **23a** (152.9 mg, 93%) as a white foam, which was used without further purification: R_f on silica 0.17 (ethoxyethane–trichloromethane); $\nu_{max}(CHCl_3)$/cm^{-1} 3340, 3020, 2960, 1700, 1480, 1440, 1430 and 1310; δ_H(300 MHz; $CDCl_3$ at room temp.) 1.62–1.80 [2 H, m, C*H*HCH$_2$C(OH)CN and CH$_2$C*H*HC(OH)CN], 1.86–2.00 (1 H, m, CH$_2$C*H*HC(OH)CN), 2.26–2.37 [1 H, m, C*H*HCH$_2$-C(OH)CN], 2.95–3.20 (2 H, m, ArCH_2), 3.63 (3.57) (3 H, s, NCH_3), 4.23 (4.51) (1 H, br s, OH), 4.95–5.08 (1 H, m, ArCH$_2$C*H*), 5.12–5.21 (2 H, m, PhCH_2OCO), 5.59 (5.45) (1 H, s, ArC*H*) and 7.06–7.46 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$ at room temp.) 19.06 (18.34) (t), 28.31 (28.10) (t), 28.81 (28.67) (t), 29.30 (29.20) (q), 44.64 (45.35) (d), 53.29 (52.84) (d), 68.12 (t), 70.54 (s), 107.02 (107.62) (s), 109.16 (109.06) (d), 118.17 (118.38) (d), 119.34 (119.48) (d), 121.46 (s), 121.71 (121.84) (d), 125.80 (s), 127.77 (d), 127.89 (d), 128.18 (d), 128.55 (d), 132.66 (132.55) (s), 135.92 (s), 137.02 (s) and 154.70 (s); *m*/*z* no molecular ion, 374 (36%), 273 (9), 239 (32), 183 (35), 91 (100) and 44 (30).

NMR data for cyanohydrin **23a** recorded at 70 °C in $(CD_3)_2SO$: δ_H(300 MHz) 1.43–1.56 [1 H, m, C*H*HCH$_2$-C(OH)CN], 1.81–1.97 [2 H, m, CH$_2$CH_2C(OH)CN], 2.10–2.25 [1 H, m, C*H*HCH$_2$C(OH)CN], 2.96 (1 H, dd, *J* 7.5, 18, ArC*H*H), 3.09 (1 H, d, *J* 18, of ArC*H*H), 3.64 (3 H, s, NCH_3), 4.87 (1 H, d, *J* 7.5, ArCH$_2$C*H*), 5.16 (2 H, s, PhCH_2OCO), 5.54 (1 H, br s, ArC*H*) and 6.98–7.47 (9 H, m, ArH); δ_C(75 MHz), 22.04 (t), 31.47 (t), 32.03 (t), 32.56 (q), 48.49 (d), 56.76 (d), 70.53 (t), 73.59 (s), 110.30 (s), 113.04 (d), 121.38 (d), 122.52 (d), 124.83 (d), 125.60 (s), 129.23 (s), 130.87 (d), 131.37 (d), 131.90 (d), 136.78 (s), 140.15 (s), 140.58 (s) and 157.73 (s).

(6S,10S)-*Benzyl* 9-*Cyano*-5-*methyl*-9-*methylsulphonyloxy*-6,7,8,9,10,11-*hexahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-12-*carboxylate* **23b**.—The cyanohydrin **23a** (160 mg, 0.40 mmol) was dissolved in anhydrous dichloromethane. Methanesulphonyl chloride (54.8 mg, 37.1 mm^3, 0.48 mmol, 1.2 equiv.) followed by 4-dimethylaminopyridine (58.5 mg, 0.48 mmol, 1.2 equiv.) were then added to the reaction mixture which was then heated at reflux for 2.5 h. After this it was allowed to cool to room temperature when it was washed with 5% aqueous citric acid and saturated brine. The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (1:9) afforded the cyanomesylate **23b** (142 mg, 74.3%) as a white foam: R_f on silica 0.51 (ethoxyethane–trichloromethane, 1:9); ν_{max}-$(CHCl_3)$/cm^{-1} 3010, 1720, 1485, 1435, 1390, 1200, 970 and 850; δ_H(300 MHz; $CDCl_3$ at room temp.) 1.85–1.98 [1 H, m, C*H*HCH$_2$C(OMs)CN], 2.08–2.20 [1 H, m, CH$_2$C*H*H-C(OMs)CN], 2.35–2.56 [2 H, m, CH$_2$C*H*HC(OMs)CN and C*H*HCH$_2$C(OMs)CN], 3.20–3.28 (2 H, m, ArCH_2), 3.32 (3.33) (3 H, s, SO_2CH_3), 3.72 (3.71) (3 H, s, NCH_3), 5.15–5.33 (2 H, s, PhCH_2OCO), 5.44–5.51 (1 H, m, ArCH$_2$C*H*), 5.71 (5.55) (1 H, br s, ArC*H*) and 7.16–7.58 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$ at room temp.) 19.94 (19.31) (t), 27.83 (27.70) (t), 28.79 (28.34) (t), 29.34 (q), 40.22 (q), 44.24 (45.15) (d), 52.66 (52.13) (d), 68.26 (t), 78.77 (s), 106.41 (106.99) (s), 109.20 (d), 116.75 (s), 118.31 (118.44) (d), 119.62 (119.71) (d), 122.06 (122.15) (d), 125.61 (s), 127.92 (d), 128.24 (d), 128.57 (d), 132.08 (131.91) (s), 135.79 (s), 137.07 (s) and 154.21 (s); *m*/*z* 479 (M^+, 10%), 388 (8), 374 (9), 239 (10), 183 (18), 149 (12) and 91 (100) (Found: M^+, 479.1507. $C_{25}H_{25}N_3O_5S$ requires M^+, 479.1515). NMR data for the cyanomesylate **23b** recorded at 70 °C in $(CD_3)_2SO$: δ_H(300 MHz) 1.81–1.94 [1 H, m, C*H*HCH$_2$C(OMs)CN], 1.95–2.07 (1 H, m, CH$_2$C*H*HC(OMs)CN], 2.17–2.28 (1 H, m, CH$_2$C*H*HC(OMs)CN], 2.29–2.40 [1 H, m, C*H*HCH$_2$C-(OMs)CN], 3.20–3.02 (2 H, m, ArCH_2), 3.44 (3 H, s, SO_2CH_3), 3.67 (3 H, s, NCH_3), 5.18 (2 H, ABq, *J* 10, PhCH_2OCO), 5.29 (1 H, d, *J* 7.5, ArCH$_2$C*H*), 5.61 (1 H, br s, ArCH) and 7.00–7.53 (9 H, m, ArH); δ_C(75 MHz) 19.30 (t), 27.19 (t), 27.97 (t), 29.04 (q), 40.39 (q), 44.67 (d), 55.22 (d), 67.24 (t), 77.74 (s), 105.76 (s), 109 (d), 116.76 (d), 117.96 (d), 119.07 (d), 121.50 (d), 125.36 (s), 127.24 (d), 127.85 (d), 128.32 (d), 132.62 (s), 136.28 (s), 136.97 (s) and 153.86 (s).

Preparation of the Heterocyclic Caged Molecules **24** *and* **25**.—The cyanomesylate **23b** (100 mg, 0.209 mmol) was dissolved in anhydrous DMF and sodium hydride (80% dispersion in oil; 6.9 mg, 0.23 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at ambient temperature for 2 h when TLC showed total consumption of starting material. The solvent was removed under reduced pressure, the residue taken up into ethyl acetate and the solution washed with water and saturated brine. The organic layer was separated, dried ($MgSO_4$) and evaporated to give a mixture of two compounds in the ratio of 3:1 in which the lower running component was prominent by TLC (total yield 55 mg, 71%). Separation by flash chromatography on silica eluted with ethoxyethane–trichloromethane (1:9) afforded the lower runner **24** (34 mg) and the higher runner **25** (10 mg).

Data for higher runner **24**. R_f on silica 0.15 (ethoxyethane–trichloromethane, 1:9); $\nu_{max}(CHCl_3)$/cm^{-1} 3430, 3200, 1750 and 1670; δ_H(300 MHz; $CDCl_3$) 1.95–2.14 (2 H, m, CHC*H*HCH$_2$ and CHCH$_2$*H*H), 2.52–2.64 (1 H, m, CHCH$_2$-C*H*H), 2.69–2.76 (1 H, m, CHC*H*HCH$_2$), 3.05 (1 H, dd, 15.3, 11.0, ArC*H*HCH), 3.57 (1 H, dd, *J* 15.4, 5.3, ArC*H*HCH), 3.75 (3 H, s, NCH_3), 4.92 (1 H, dd, *J* 10.9, 5.2, ArCH$_2$C*H*), 5.36 (1 H, d, *J* 8.2, ArC*H*), 5.77 [1 H, s, C(OH)C*H*SO$_3$], 7.07–7.47 (4 H, m, ArH) and 8.05 (1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 25.71 (t), 28.77 (t), 30.04 (q), 33.39 (t), 51.55 (d), 69.54 (s), 81.61 (d), 96.77 (d), 102.26 (s), 109.84 (d), 118.12 (d), 120.22 (d), 122.45 (d), 127.24 (s), 135.54 (s), 140.11 (s), 149.24 (s) and 158.59 (s); *m*/*z* (FAB) 371 (M^+, 75%), 372 ($M + 1$)$^+$ (95) 182 (27), 170 (30) and 91 (100) [Found: ($M + 1$)$^+$, 372.1020. $C_{18}H_{18}N_3O_4S$ requires M^+, 372.1018].

Data for lower runner **25**: R_f on silica 0.10 (ethoxyethane–trichloromethane, 1:9); $\nu_{max}(CHCl_3)$/cm^{-1} 3390, 3200, 1700 and 1650; δ_H(300 MHz; $CDCl_3$) 1.66–1.73 (1 H, m, CHCH$_2$C*H*H), 2.00–2.37 (3 H, m, CHC*H*HCH$_2$ and CHCH$_2$-CH_2), 3.07–3.24 (2 H, m, ArCH_2CH), 3.61 (3 H, s, NCH_3), 3.99 (1 H, m, ArCH$_2$C*H*), 4.98 (1 H, d, *J* 3.1, ArC*H*), 6.08 [1 H, s, C(OH)C*H*SO$_3$], 7.12–7.42 (4 H, m, ArH) and 9.30 (1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 19.05 (t), 26.18 (t), 29.07 (t), 29.24 (q), 49.71 (d), 53.45 (d), 82.43 (s), 96.58 (d), 105.20 (s), 109.22 (d), 118.46 (d), 119.72 (d), 122.32 (d), 125.33 (s), 130.50 (s), 137.33 (s), 151.52 (s) and 159.64 (s); *m*/*z* (FAB) 371 (M^+, 100%), 372 ($M + 1$)$^+$ (97%), 306 (35), 183 (50) (Found: M^+, 371.0986. $C_{18}H_{17}N_3O_4S$ requires M^+, 371.0940).

(6S,10S)-*Benzyl* 5-*Methyl*-9-*trifluoromethylsulphonyloxy*-6,7,10,11-*tetrahydro*-6,10-*imino*-5H-*cyclooct*[b]*indole*-12-*carboxylate* **26**.—The protected ketone **7c** (242 mg, 0.65 mmol) was dissolved in anhydrous tetrahydrofuran and sodium hydride (80% dispersion in oil; 21.4 mg, 0.71 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at ambient temperature for 1 h after which *N*-phenyltrifluromethanesulphonimide (254 mg, 0.71 mmol, 1.1 equiv. was added; stirring was then maintained at this temperature for a further 2 h. After this the

solvent was removed and the residue was taken up into ethyl acetate and the solution washed with water and saturated brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (1:1) afforded the enol triflate **26** (173.3 mg, 53%) as a white foam: R_f on silica 0.65 (ethoxyethane–trichloromethane, 1:9); ν_{max}($CHCl_3$)/cm^{-1} 3010, 1700, 1420, 1295, 1140, 1050, 985 and 855; δ_H(300 MHz; $CDCl_3$) 2.30 [1 H, dd, *J* 17.4, 5.8 Hz, CHC*H*HCHC(OTf)], 2.95–3.28 [3 H, m, ArCH_2 and CHC*H*HCHC(OTf)], 3.69 (3.65) (3 H, s, NCH_3), 5.11–5.30 (3 H, m, $ArCH_2CH$ and $PhCH_2OCO$), 5.61 (5.47) (1 H, d, *J* 5.4, ArC*H*), 5.70–5.76 [1 H, m, $CHCH_2CHC(OTf)$] and 7.08–7.51 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 24.43 (23.78) (t), 29.63 (q), 30.11 (30.70) (t), 43.78 (44.55) (d), 49.67 (49.08) (d), 67.90 (t), 105.25 (105.92) (s), 109.07 (d), (112.07, 116.31, 120.56, 124.81 making up the quartet due to CF_3), 115.35 (114.48) (d), 118.24 (118.39) (d), 119.59 (d), 121.96 (122.03) (d), 126.29 (s), 127.66 (d), 128.28 (d), 128.61 (d), 133.29 (132.95) (s), 135.98 (s), 137.07 (s), 146.60 (147.11) (s) and 153.89 (153.72) (s); *m/z* 506 (M^+, 5%), 315 (3), 279 (4), 167 (13), 149 (52) and 91 (100%) (Found: M^+, 506.1119. $C_{25}H_{25}N_3O_5S$ requires M^+, 506.1123).

(6S,10S)-*Benzyl 9-Cyano-5-methyl-6,7,10,11-tetrahydro-6,10-imino-5H-cyclooct*[b]*indole-12-carboxylate* **8a**.—The enol triflate **26** (67.6 mg, 0.13 mmol) dissolved in anhydrous benzene (4 cm^3) was added to a mixture of anhydrous lithium cyanide (8.8 mg, 0.27 mmol, 2 equiv.), tetrakis(triphenylphosphine)palladium(0) (10.8 mg, 9.4 μmol, 0.07 equiv.) and 12-crown-4 (1.6 mg, 1.5 mm^3, 9.4 μmol, 0.07 equiv.) under an atmosphere of argon. The reaction mixture was stirred at ambient temperature for 2 h. TLC analysis showed the reaction to be incomplete and a further palladium catalyst (3 × 0.07 equiv.) was added at 1 h intervals to achieve complete conversion. Water (5 cm^3) was then added and the phases were separated. The aqueous phase was washed with light petroleum and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with pure trichloromethane afforded the α,β-unsaturated nitrile **8c** (27.5 mg, 52%) as a white foam: R_f on silica 0.55 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{25}$ −27.3 (*c* 0.5 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3010, 2220, 1700, 1470, 1430, 1420, 1335, 1315, 1305, 1140 and 1005; δ_H(300 MHz; $CDCl_3$) 2.14–2.32 [1 H, m, CHC*H*HCHC(CN)], 2.70–2.98 [2 H, m, ArC*H*H and CHC*H*HCHC(CN)], 3.06–3.26 (1 H, m, ArC*H*H), 3.60 (3.57) (3 H, s, NCH_3), 5.00–5.29 (3 H, m, $ArCH_2CH$ and PhC*H*HOCO), 5.60 (5.45) (1 H, d, *J* 5.8, ArC*H*), 6.57–6.42 [1 H, m, $CHCH_2CHC(CN)$] and 6.97–7.47 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 24.58 (23.99) (t), 28.58 (q), 29.48 (29.83) (t), 42.44 (43.18) (d), 47.68 (47.34) (d), 66.92 (66.84) (t), 103.93 (104.61) (s), 108.05 (d), 113.90 (114.46) (s), 116.18 (116.10) (s), 117.31 (117.47) (d), 118.63 (d), 121.02 (121.10) (d), 125.23 (s), 127.08 (d), 127.39 (d), 127.65 (d), 132.41 (132.01) (s), 134.84 (134.94) (s), 136.07 (s), 140.71 (139.98) (s) and 152.81 (152.71) (s); *m/z* 383 (M^+, 100%), 292 (10), 262 (38), 248 (50), 221 (10), 183 (14) and 91 (56) (Found: M^+, 383.1633. $C_{24}H_{21}N_3O_2$ requires M^+, 383.1634).

(6S,10S)-5-*Benzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct*[b]*indole* (−)-**7b**.—(i) *Benzylation of indole nitrogen*. Sodium hydride (80% dispersion in oil; 70.3 mg, 2.34 mmol, 1.05 equiv.) was added to a stirred solution of **19a** (1.00 g, 2.23 mmol) and benzyl bromide (401 mg, 279 mm^3, 2.34 mmol, 1.05 equiv.) in anhydrous DMF at 0 °C. The mixture was stirred at this temperature for 1 h and then at ambient temperature for a further 30 min. After this it was evaporated under reduced pressure and the residue taken up into ethyl acetate and the solution washed with water and saturated brine. The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with ethoxyethane–trichloromethane (3:97) afforded the N^{in}-benzylated *cis* tetrahydro-β-carboline (845 mg, 70%) as a white foam: R_f on silica 0.67 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{22}$ −38.6 (*c* 0.259 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3010, 2950, 1735, 1690, 1495, 1455, 1410, 1280, 1175 and 1030; δ_H(300 MHz; $CDCl_3$) 1.59–1.81 (1 H, m, one proton of $CH_2CH_2CO_2CH_3$), 1.88–2.22 (1 H, m, one proton of $CH_2CH_2CO_2CH_3$), 2.29–2.53 (1 H, m, one proton of $CH_2CH_2CO_2CH_3$), 2.58–2.76 (1 H, m, one proton of $CH_2CH_2CO_2CH_3$), 3.22–3.82 [8 H, m, comprising of 4 sharp singlets at δ 3.73 (3.64) and 3.33 (3.61), 2 × CO_2CH_3 and $ArCH_2$], 4.87–5.72 (6 H, m, comprising of $PhCH_2OCO$, $PhCH_2N$, ArC*H* and $ArCH_2CH$) and 7.07–7.58 (14 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 21.25 (22.07) (t), 29.63 (29.96) (t), 30.20 (30.59) (t), 46.66 (46.94) (t), 49.27 (49.31) (d), 51.35 (51.46) (q), 52.24 (51.55) (d), 52.36 (52.10) (q), 67.99 (67.78) (t), 105.27 (104.68) (s), 109.95 (110.24) (d), 118.35 (118.13) (d), 119.69 (d), 122.06 (121.92) (d), 125.92 (d), 126.03 (d), 126.25 (s), 127.34 (d), 127.74 (d), 127.90 (d), 128.05 (d), 128.12 (d), 128.48 (d), 128.71 (d), 134.44 (s), 135.58 (s), 135.52 (s), 135.88 (s), 135.96 (s), 136.19 (s), 136.99 (s), 137.21 (s), 137.35 (s), 137.54 (s), 156.26 (156.18) (s), 172.97 (173.04) (s) and 173.37 (173.59) (s); *m/z* 540 (M^+, 14%), 453 (16) 409 (23), 259 (8), 168 (10) and 91 (100) (Found: M^+, 540.2259. $C_{32}H_{32}N_2O_6$ requires M^+, 540.2260).

(ii) *Dieckmann cyclisation*. The *cis*-tetrahydro-β-carboline (800 mg, 1.48 mmol) was dissolved in anhydrous DMF. Sodium hydride (80% dispersion in oil; 98 mg, 3.26 mmol, 2.2 equiv.) was added and the reaction mixture stirred for 1 h at ambient temperature. Methanol (4.8 mg, 6.0 mm^3, 0.148 mmol, 0.1 equiv.) was then added and stirring was maintained at this temperature for a further 5 h when TLC indicated the cyclisation to be complete. The solvent was removed under reduced pressure and aqueous citric acid (0.5 mol dm^{-3}) was added to the residue which was then extracted into ethyl acetate and washed with saturated brine. The organic layer was then separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (6:5) afforded the protected β-keto ester (527 mg, 71%) as a white foam: R_f on silica 0.83 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{22}$ −52.4 (*c* 0.382 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3010, 1700, 1665, 1625, 1445, 1335, 1295, 1105 and 1025; δ_H(300 MHz; $CDCl_3$) 2.18–2.37 (1 H, m, ArCHC*H*H), 2.69–2.82 (1 H, m, ArCHC*H*H), 3.08–3.38 (2 H, m, $ArCH_2$), 3.57 (3.59) (3 H, s, CO_2CH_3), 4.95–5.43 (5 H, m, comprising of $PhCH_2OCO$, $PhCH_2N$ and $ArCH_2CH$), 5.62 (5.45) (1 H, d, *J* 4.9, ArC*H*), 6.84–7.57 (14 H, m, ArH) and 12.06 (1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 25.52 (24.89) (t), 28.21 (28.88) (t), 45.03 (45.63) (d), 46.77 (46.68 (t), 50.38 (49.86) (d), 51.48 (q), 67.63 (67.44) (t), 94.70 (94.24) (s), 106.96 (107.67) (s), 109.77 (109.56) (d), 118.22 (118.42) (d), 119.68 (119.74) (d), 121.99 (121.07) (d), 125.83 (d), 125.97 (d), 126.55 (s), 126.92 (d), 127.40 (d), 127.56 (d), 127.85 (d), 127.99 (d), 128.07 (d), 128.21 (d), 128.56 (d), 128.76 (d), 133.83 (133.43) (s), 136.75 (136.08) (s), 137.13 (s), 153.92 (153.73) (s), 169.58 (170.18) (s) and 172.16 (172.03) (s); *m/z* 508 (M^+, 24%), 476 (23), 450 (7), 341 (19), 313 (20), 259 (12), 168 (13) and 91 (100) (Found: M^+, 508.2000. $C_{31}H_{28}N_2O_5$ requires M^+, 508.1998).

(iii) *Hydrolytic decarboxylation*. The protected β-keto ester (675 mg, 1.33 mmol) was dissolved in DMF degassed with argon. Sodium chloride (93 mg, 1.59 mmol, 1.2 equiv.) and water (48 mg, 48 mm^3, 2.66 mmol, 2 equiv.) were then added and the mixture was heated (under an atmosphere of argon) at 130 °C for 8 h. The solvent was removed under reduced pressure, the residue taken up into ethyl acetate and the solution washed twice with saturated brine. The organic layer was then separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with hexane–trichloromethane (1:4) afforded the protected ketone **7e** (406

mg, 68%) as a white foam: R_f on silica 0.75 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{22}$ −73.1 (*c* 0.342 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3010, 1700, 1500, 1425, 1295, 1105 and 1050; δ_H(300 MHz; $CDCl_3$) 1.65–1.85 (1 H, m, one proton of CH_2CH_2CO), 2.05–2.18 (1 H, m, one proton of CH_2CH_2CO), 2.23–2.44 (2 H, m, two protons of CH_2CH_2CO), 2.88–3.00 (1 H, m, ArC*H*H), 3.13–3.32 (1 H, m, ArC*H*H), 4.96–5.36 (5 H, m, comprising of $PhCH_2OCO$, $PhCH_2N$ and $ArCH_2CH$), 5.67 (5.50) (1 H, br s, ArC*H*) and 6.87–7.50 (14 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 25.43 (24.81) (t), 28.62 (29.14) (t), 34.39 (t), 45.48 (46.03) (d), 46.71 (t), 59.55 (58.99) (d), 67.70 (65.02) (t), 107.50 (108.20) (s), 109.82 (109.65) (d), 118.30 (118.49) (d), 119.86 (d), 122.35 (d), 125.76 (d), 126.26 (s), 126.84 (d), 127.40 (d), 126.70 (d), 127.93 (s), 128.23 (d), 128.40 (d), 128.53 (d), 128.86 (d), 133.03 (132.74) (s), 135.94 (136.05) (s), 137.14 (s), 154.30 (154.16) (s) and 208.35 (s); *m/z* 450 (M^+, 32%), 349 (7), 315 (14), 259 (9), 168 (12) and 91 (100) (Found: M^+, 450.1897. $C_{29}H_{26}N_2O_3$ requires M^+, 450.1899).

(iv) *Hydrogenolysis.* The protected ketone **7e** (87.6 mg, 0.19 mmol) was dissolved in anhydrous methanol and subjected to catalytic hydrogenolysis over 10% palladium on activated charcoal for 4 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue on silica eluted with triethylamine–ethyl acetate (1:99) afforded the deprotected ketone **7b** (40 mg, 65%) as a white foam: R_f on silica 0.45 (ethoxyethane–trichloromethane, 1:9); $[\alpha]_D^{22}$ −104.2 (*c* 0.228 in CH_2Cl_2) {lit.,[5] for the (+)-isomer; $[\alpha]_D^{22}$ +98 (*c* 1.08 in CH_2Cl_2)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3010, 2940, 1710, 1465 and 1455; δ_H(300 MHz; $CDCl_3$) 1.83–1.90 (1 H, m, one proton of CH_2CH_2CO), 2.04–2.20 (2 H, m, one proton of CH_2CH_2CO and N^b–*H*), 2.27–2.45 (2 H, m, two protons of CH_2CH_2CO), 2.86 (1 H, d, *J* 16.6, ArC*H*H), 3.18 (1 H, dd, *J* 16.6, 6.9, ArC*H*H), 3.94 (1 H, d, *J* 6.9, $ArCH_2CH$), 4.29 (1 H, br s, ArC*H*), 5.29 (2 H, ABq, *J* 17.1, $PhCH_2N$), 6.92–6.96 (2 H, m, ArH), 7.09–7.33 (6 H, m, ArH), and 7.48–7.54 (1 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 25.93 (t), 31.53 (t), 34.92 (t), 45.01 (d), 46.51 (t), 59.69 (d), 107.36 (s), 109.55 (d), 118.23 (d), 119.62 (d), 122.00 (d), 125.71 (d), 126.72 (s), 127.54 (d), 128.88 (d), 135.09 (s), 136.84 (s), 137.55 (s) and 210.58 (s); *m/z* 316 (M^+, 52%), 259 (100), 204 (23), 168 (64), 105 (86) and 91 (97) (Found: M^+, 316.1576. $C_{21}H_{20}N_2O$ requires M^+, 316.1576).

Acknowledgements

We thank Dr. G. K. Barlow, Mrs. B. Chamberlain, Dr. T. A. Dransfield and Mr. B. R. Glennie for NMR & mass spectra, and the Yorkshire Cancer Research Campaign for a career development award (to P. D. B).

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Paper 2/05144C
Received 25*th September* 1992
Accepted 10*th November* 1992