Enantiospecific Synthesis with Amino Acids. Part 1. Tryptophan as a Chiron for the Synthesis of α-Substituted Tryptophan Derivatives

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N_α-Methoxycarbonyl-(*S*)-tryptophan methyl ester is cyclised with 85% phosphoric acid to give (2*S*,3a*R*,8a*S*)-1,2-bis(methoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole which on reaction with toluene-*p*-sulphonyl chloride gives (2*S*,3a*R*,8a*S*)-1,2-bis(methoxycarbonyl)-8-(*p*-tolylsulphonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole. This compound undergoes deprotonation with lithium diisopropylamide to the corresponding enolate which is quenched with a variety of alkylating agents resulting in alkylation, with retention of configuration, at C-2 of the pyrroloindole system. Subsequent treatment with trifluoroacetic acid brings about cycloreversion affording essentially optically pure α-alkylated tryptophan derivatives. The process is also applied in the *R*-series.

The asymmetric synthesis of α-amino acids, both essential and 'non-proteinogenic', has been the subject of extensive interest in recent years resulting in the development of several elegant procedures.[1] α-Disubstituted amino acids are of particular interest owing to the increased resistance to hydrolysis, both chemical and enzymatic, which they confer on the peptide bond when incorporated into simple peptides,[2,3] and to the increased lipophilicity of such derivatives over the simple parent amino acids facilitating greater penetration of cell walls.[4] A further, and most important, feature of α-disubstituted amino acids is the reduction of conformational space available to any peptide containing such a residue,[2] a good example of which is the stabilisation of conformation afforded to 3_{10}/α-helical regions by the α-aminoisobutyric acid residue.[5] Another major interest in α-disubstituted amino acids is their potential for use as enzyme inhibitors[6] as evidenced by the inhibition of aromatic acid decarboxylase by α-methyl-dopa.[7]

The asymmetric synthesis of α-substituted derivatives of tryptophan occupies an unusual position in so far as it has received relatively little attention. Indeed, to our knowledge, only two enantiospecific syntheses of α-methyltryptophan[8,9] and one of α-2-methylthioethyltryptophan are known, an earlier report[10] having been shown[8] to be erroneous. This relative paucity of synthetic activity, we speculate, is in part due to the incompatibility of the reactive indole nucleus with various literature methods. In contrast to this diminished effort a considerable amount is known about the biological activity and pharmaceutical potential of such α-substituted tryptophan derivatives when prepared in racemic form by more classical procedures[11] and used as such or resolved chemically or enzymatically.[12] Thus 'dipeptoid'[13] derivatives of α-methyltryptophan have been shown to be effective analogues of the cholecystokinin(30–33) tetrapeptide.[14] Furthermore, (±)-α-methyltryptophan and (±)-α-monofluoromethyltryptophan are substrates for tryptophan hydroxylase and (±)-5-hydroxy-α-monofluoromethyltryptophan is a time dependent inhibitor of aromatic acid decarboxylase.[15] (±)-α-Methyltryptophan is also known to have antihypertensive and noradrenaline depleting effects in the rat[16] and its 5-hydroxy derivative to be a potent inhibitor, *in vivo*, of tyrosine hydroxylase.[17]

Stimulated by this catalogue of useful activity and by the evident challenge of the synthesis of tryptophan derivatives we have initiated a program on the enantiospecific synthesis of α-substituted tryptophan derivatives in which tryptophan itself is used as the original source of chirality. In this paper we report in full[18] on the initial phase of this investigation aimed at the development of a general synthetic method for the preparation of homochiral α-substituted tryptophan 'peptoids.'

The synthetic route envisaged required the reaction of an appropriately protected L-tryptophan derivative **1** with a suitable electrophile E^+ to give one or other or both of the hexahydropyrrolo[2,3-*b*]indoles **2** and **3** *via* the respective indolenium ions which would be separated either by crystallisation or chromatography. Deprotonation of **2** followed by quenching with a suitable alkyl halide from the less hindered *exo*-face of the bicyclic system would result in overall substitution with retention of configuration giving **4** whereas application of the same procedure to **3** would result in substitution with inversion of configuration giving **5**. Cleavage of the pyrroloindoles **4** and **5** by a mechanism evidently dependent on the nature of the initial electrophile E^+ would provide the enantiomers **6** and **7** respectively of the desired product in protected form (Scheme 1). This scheme was attractive in view of its simplicity, its potential for the preparation of either enantiomer given the correct choice of E^+ and reaction conditions, and the advantage it takes of the reactive indole moiety.

Hexahydropyrrolo[2,3-*b*]indoles with various substitution patterns occur widely in Nature as evidenced by physostigmine,[19] chimonanthine,[19] folicanthine,[19] the 3a-hydroxypyrroloindoles,[20] the 3a-alkylpyrroloindoles,[21] the sporidesmins[22] and the brevianamides.[23] Ring closure of tryptophan and tryptamine derivatives to the hexahydropyrroloindole nucleus as envisaged in Scheme 1 is well documented for a variety of electrophiles including protons,[24,25,26] positive halogen donors,[27] singlet oxygen,[20,28] positive oxygen donors[29] and carbon electrophiles.[30] In the event we chose to avail ourselves of the procedure of Hino[24] in which N_α-methoxycarbonyl-(*S*)-tryptophan methyl ester **8** is suspended in 85% phosphoric acid giving high yields of the pyrroloindole **9**, in our hands essentially free of contamination by its diastereoisomer **12** (Scheme 2). The *endo*-configuration of the methoxycarbonyl group in **9** was assigned by Hino[24] on the basis of the close similarity in the chemical shifts of various protons in its acetamide derivative with those of the 3a-hydroxy derivative **13** whose structure had been determined[31] crystallographically. The absolute configuration of **9** was

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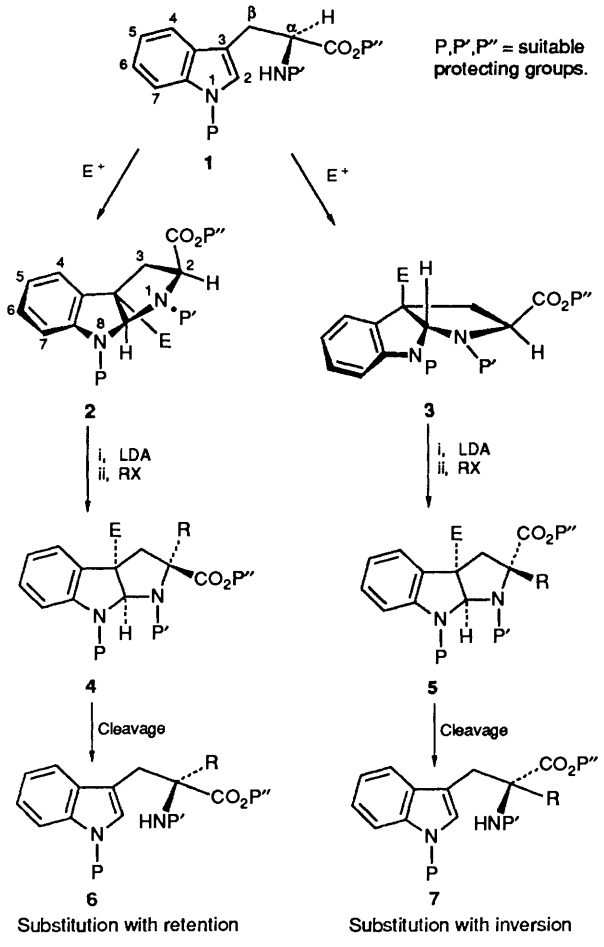


Scheme 1

Table 1 Alkylation of pyrroloindoles **11** and **31**

Entry	Electrophile	Product	Yield (%)	δ Ester CH_3	$[\alpha]_D^{25}$ [a]
1	Allyl bromide	**16**	79	3.02	+73
2	Methyl iodide	**17**	80	3.03	+108
3	Benzyl bromide	**18**	71	3.09	+113
4	Methylthioethyl iodide	**19**	33[b]	3.03	+51
5	Methyl bromoacetate	**20**	83	3.02	+111
6	SEM-Cl	**21**	78	3.06	+62
7	Methyl iodide	**32**	72[c]	3.03	−108

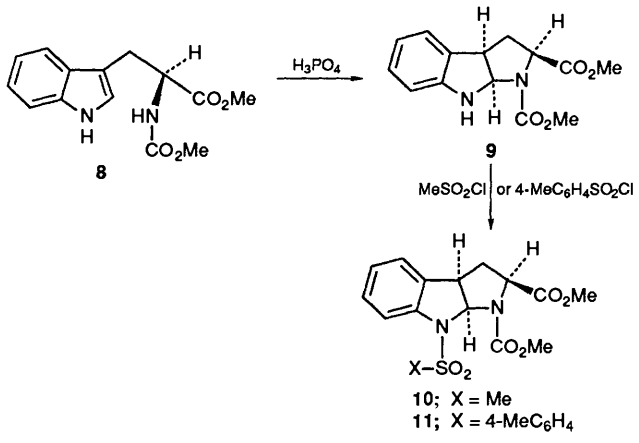
[a] Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. [b] 44% Based on recovered starting material. [c] By alkylation of **31**.

Table 2 Regeneration of tryptophans from pyrroloindoles

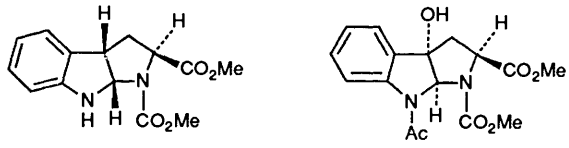
Entry	Substrate	Product	Yield (%)	$[\alpha]_D^{25}$ [a]
1	**16**	**22**	85	+38
2	**17**	**23**	90	+46
3	**18**	**24**	93	+13
4	**19**	**25**	84	+28
5	**20**	**26**	97	+47
6	**21**	**27**	61	+31
7	**32**	**33**	83	−44

[a] Optical rotations are given in 10^{-1} deg cm^2 g^{-1}.

confirmed when a derivative was converted back into (*S*)-tryptophan.[24] The preferential formation of **9** with the methoxycarbonyl group *endo* to the diazabicyclo[3.3.0] octane



Scheme 2



12 **13**

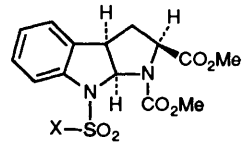
skeleton rather than **12** under the equilibrating conditions of ring closure[24] is crucial to the outcome of the project and worthy of consideration. Two possibilities suggest themselves: (i) the existence of a stabilising non-bonding secondary orbital interaction between the *endo*-ester function and the aromatic nucleus in **9** and (ii) reduced torsional strain in **9**. Both experimental and theoretical studies, the results of which will be reported in due course, are currently being made in this laboratory to enable differentiation between these two hypotheses.

The general reaction plan (Scheme 1) now called for the introduction of a third protecting group at N-8 that would be compatible with the proposed enolate chemistry. Various attempts at benzylation and silylation led to the formation of only ring-opened tryptophan derivatives, eventually however the derivative **10** was obtained in high yield by reaction of **9** with methanesulphonyl chloride in pyridine.

It is appropriate at this point to draw attention to salient features of the ^{1}H NMR spectrum of **10** as typical of those of the entire series of pyrroloindoles reported on here. Slow rotation about the N-1 to CO_2Me and N-8 to SO_2 bonds results in considerable broadening of spectral lines at room temperature. This problem is readily solved by acquiring the spectrum at 50 °C in deuteriochloroform. A particularly useful feature of the spectrum is the unusual, somewhat upfield chemical shift of the ester OMe group at δ 3.12 reflecting its shielding by the diatropic ring current. This latter feature is common to all of the derivatives prepared so far and serves as a simple, ready diagnostic tool for the stereochemical outcome of any reactions at C-2.

Treatment of the methanesulphonamide **10** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C followed by quenching with allyl bromide gave, not the expected product of substitution at C-2, but rather that, **14**, of substitution in the sulphonamide group. Clearly an alternative protecting group was required. This was achieved by the use of the toluene-*p*-sulphonyl group resulting in the derivative **11**. Although this substance proved satisfactory for the present study, its considerable reluctance to crystallise made it less than ideal and in subsequent work[32] we have preferred the highly crystalline benzenesulphonamide **15** (m.p. 165–167 °C) prepared in an exactly analogous manner. Deprotonation of **11** with LDA in THF at −78 °C and quenching with allyl bromide gave

the desired product **16** in high yield (Table 1, entry 1) as a single diastereoisomer within the limits of detection by ^{1}H NMR at 400 MHz. The *exo*-nature of the allyl group was assigned, by the unusual chemical shift of the ester OMe group (δ 3.02) alluded to above and by the observation of NOEs between the allyl CH_2 and 3a-H.



14; X = $CH_2CH_2CH{=}CH_2$
15; X = Ph

The overall aim of the project being the enantiospecific synthesis of tryptophan derivatives substituted at the α-centre with groups corresponding to the side chains of other essential amino acids we now turned to the examination of other electrophiles. Deprotonation of **11** with LDA followed by quenching with methyl iodide enabled the introduction of the alanine side chain (Table 1, entry 2) whilst use of benzyl bromide provided the phenylalanine side chain (Table 1, entry 3). The methionine side chain was introduced with the aid of 2-methylthioethyl iodide (Table 1, entry 4) and that of aspartic acid by means of methyl bromoacetate* (Table 1, entry 5).

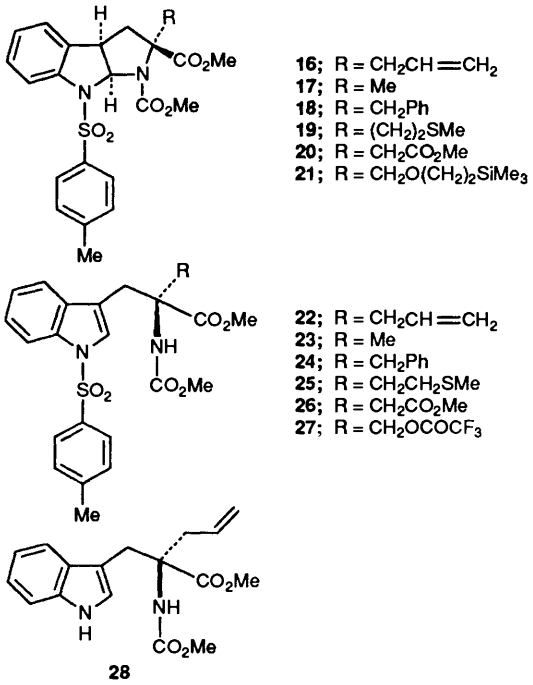
Finally, with regard to the introduction of the hydroxymethyl side chain of serine, we chose trimethylsilylethoxymethyl chloride (SEM-Cl) as electrophile (Table 1, entry 6), its use being considerably more convenient than that of gaseous formaldehyde[33] or of the trioxane–titanium tetrachloride combination advocated[34] by Mukaiyama. In the course of this investigation Paquette also reported the use of SEM-Cl as a formaldehyde equivalent for reaction with enolates.[35] Subsequently we,[36] and Topgi,[37] have reported further related examples of this convenient procedure.

We now turned to the problem of regeneration of the tryptophan skeleton. After considerable experimentation it was found that standing of the pyrroloindole **16** in trifluoroacetic acid (TFA) overnight at room temperature followed by concentration under reduced pressure and filtration on silica gel gave the (*S*)-α-allyltryptophan derivative **22** in 85% yield (Table 2, entry 1). This same straightforward process was then applied to the pyrroloindoles **17**–**20** giving the corresponding seco-derivatives **23**–**26** respectively in high yield (Table 2, entries 2–5). Treatment of **21** with TFA in the same manner resulted both in ring opening and concomitant replacement of the β-trimethylsilylethyl protecting group by the trifluoroacetate group giving **27** (Table 2, entry 6). The use of TFA to bring about ring opening is worthy of comment especially in the light of the use, by Hino,[24] of this same reagent to affect the closure of **8** to **9**. The evident difference between the two systems is the sulphonamide group which clearly shifts the equilibrium in favour of the ring-opened product by reducing the tendency of the indole nucleus to undergo protonation at C-3.

Finally, we investigated removal of the sulphonamide protecting group. Thus, treatment of **22** in refluxing liquid ammonia with sodium metal and subsequent quenching with methanol and ammonium chloride resulted in clean deprotection to give the derivative **28** in 96% isolated yield. The yield of this reaction was crucially dependent on the dryness of the reaction conditions and fell markedly when proper precautions were not taken to exclude water during the condensation of the ammonia into the reaction vessel. Treatment of the pyrroloindole **16** with sodium in liquid ammonia led directly to the tryptophan derivative **28** but only in 37% yield. All attempts to improve on this yield failed and consequently we prefer the two-step procedure.

The optical purity of **28** was confirmed by ^{19}F NMR of its (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide derivative, prepared in the NMR tube according to Mosher,[38] which exhibited a single peak.

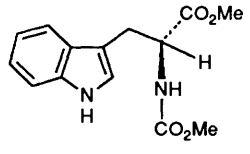
With a view to the preparation of certain derivatives in the enantiomeric series (*R*)-tryptophan was converted into the diprotected derivative **29** which was cyclized with phosphoric acid to **30** followed by sulphonylation to give the pyrroloindole **31** in an exactly analogous manner to that employed for the preparation of **11** in the *S*-series. Deprotection of **31** with LDA and quenching with methyl iodide gave **32**, again in excellent yield and diastereoselectivity (Table 1, entry 7). Ring opening with TFA gave **33** (Table 2, entry 7), the enantiomer of **23**, which was treated with sodium in liquid ammonia to provide **34**. Finally complete deprotection of **34** was achieved by refluxing in 5 mol dm^{-3} potassium hydroxide solution followed by neutralisation and ion exchange chromatography. In this manner (*R*)-α-methyltryptophan **35** was obtained as a white solid. The enantiomeric purity of this substance was demonstrated by HPLC on an α-cyclodextrin column which



16; R = $CH_2CH{=}CH_2$
17; R = Me
18; R = CH_2Ph
19; R = $(CH_2)_2SMe$
20; R = CH_2CO_2Me
21; R = $CH_2O(CH_2)_2SiMe_3$

22; R = $CH_2CH{=}CH_2$
23; R = Me
24; R = CH_2Ph
25; R = CH_2CH_2SMe
26; R = CH_2CO_2Me
27; R = CH_2OCOCF_3

28



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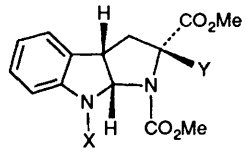
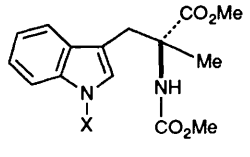
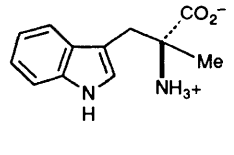


30; X = Y = H
31; X = $SO_2C_6H_4Me$, Y = H
32; X = $SO_2C_6H_4Me$, Y = Me



33; X = $SO_2C_6H_4Me$
34; X = H



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resolved completely a sample of the racemate under identical conditions.

Experimental

M.p.s are uncorrected and were determined with a Kofler hot stage microscope. Optical rotations were measured with an Optical Activity AA-10 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as chloroform solutions with a Perkin-Elmer 983 spectrophotometer. ^1H NMR spectra were obtained at 200, 300 or 400 MHz as deuteriochloroform solutions, unless otherwise stated, with Varian XL 200, Bruker AM300 and Varian VXR 400 instruments respectively. ^{13}C NMR spectra were obtained at 50 MHz with the Varian XL 200 instrument. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard and J values are given in Hz. 70 eV EIMS were recorded with a VG 7070H mass spectrometer. All solvents were dried and distilled by standard techniques. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl immediately prior to use. Ether refers to diethyl ether and light petroleum to the fraction boiling in the range 40–60 °C.

Dimethyl (2S,3aR,8aS)-1,2,3,3a,8,8a-*Hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **9**.—85% Phosphoric acid (43.4 cm^3; 3 mmol) was added to N_b-methoxycarbonyl-L-tryptophan methyl ester **8**[39] (4.00 g, 14.46 mmol) at room temperature and the mixture stirred for 3 h until a clear solution was obtained. This solution was then added dropwise to a vigorously stirred two-phase system consisting of 15% aqueous sodium carbonate (1.3 dm^3; 90 cm^3/mmol) and dichloromethane (400 cm^3) in such a manner as to prevent build-up of local regions of acid pH; the pH of the mixture was >8 throughout the addition. The two phases were separated and the aqueous layer re-extracted with chloroform (2 × 20 cm^3). The combined organic phases were dried ($CaCl_2$) and concentrated under reduced pressure to give an oil which solidified when set aside for 14 d at 0 °C to give crude **9** (3.40 g, 85%). (In subsequent preparations seeding resulted in solidification in a matter of hours.) The so-prepared pyrroloindole **9** had m.p. 78–79 °C (lit.,[24] 85–86 °C); δ(200 MHz, two rotamers) 3.13 and 3.16 (3 H, 2 s, 2-OMe), 3.57 (2 H, m, 3-CH_2), 3.66 and 3.79 (3 H, 2 s, 1-OMe), 3.85 (1 H, m, 3a-H), 4.41 and 4.55 (1 H, 2 m, 2-H), 5.00 (1 H, br s, NH), 5.55 (1 H, d, J 6.7, 8a-H), 6.55 (2 H, m, 5-H + 7 H) and 6.99 (2 H, m, 4-H + 6-H).

Dimethyl (2S,3aR,8aS)-8-*Methylsulphonyl*-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **10**.—Methanesulphonyl chloride (0.86 cm^3, 11.0 mmol) was added slowly to a stirred solution of the hexahydropyrroloindole **9** (276 mg, 1.00 mmol) in pyridine (5 cm^3) at 0 °C. Stirring was continued overnight at ambient temperature before the pyridine was removed under reduced pressure. The resulting residue was subjected to flash chromatography [eluent ethyl acetate–light petroleum (3:2)] to give a white crystalline solid which was crystallised from ether to provide the *title compound* **10** as needles (230 mg, 65%), m.p. 164–165 °C; δ(400 MHz, 50 °C) 2.53 (1 H, m, 3-H), 2.65 (1 H, d, J 13.3, 3-H), 3.12 (3 H, s, 2-OMe), 3.30 (3 H, br s, SO_2Me), 3.71 (3 H, s, 1-OMe), 4.11 (1 H, br t, J 6.9, 3a-H), 4.58 (1 H, d, J 8.7, 2-H), 6.38 (1 H, d, J 6.7, 8a-H) and 6.9–7.05 (1 H, m, dt, J 5.7, 1.6, 4-H + 6 H); δ_C 33.8 (3-C), 42 (2-C), 45.5 (SO_2Me), 52.0 (2-OMe), 53.0 (1-OMe), 58.9 (3a-C), 79.4 (8a-C), 116.5 (7-C), 124.0 (4-C), 124.4 (6-C), 128.8 (5-C), 131.5 (3b-C), 142.2 (7a-C), 154.9 (1-CO_2) and 171.2 (2-CO_2); ν_{max}/cm^{-1} 3546, 2945, 2424, 1732, 1447, 1361 and 1154; m/z 354 ($M^{+\cdot}$), 295, 275, 243, 216, 184, 157, 130, 103 and 59 (Found: C, 50.9; H, 5.2; N, 7.8; S, 9.3. $C_{15}H_{18}N_2O_6S$ requires C, 50.84; H, 5.12; N, 7.90; S, 2.95%).

Dimethyl (2S,3aR,8aS)-8-p-*Tolylsulphonyl*-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **11**.—Toluene-*p*-sulphonyl chloride (8.39 g, 44.0 mmol) was added to a solution of the hexahydropyrroloindole **9** (6.09 g, 22.0 mmol) in pyridine (30 cm^3) at 0 °C. The reaction mixture was stirred overnight at room temperature before the solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (40 cm^3). This solution was washed with hydrochloric acid (2 mol dm^{-3}, 3 × 20 cm^3) and brine (3 × 20 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The product was isolated by flash chromatography [eluent ethyl acetate–light petroleum (2:3)] to furnish the title compound **11** as a viscous oil (8.10 g, 85%); $[\alpha]_D$ +94 (*c* 1, $CHCl_3$); δ(400 MHz, 50 °C) 2.32 (3 H, s, SO_2Me), 2.40 (1 H, m, 3-H), 2.53 (1 H, d, J 13.2, 3-H), 3.10 (3 H, s, 2-OMe), 3.58 (1 H, br s, 3a-H), 3.60 (3 H, s, 1-OMe), 4.54 (1 H, br d, J 9.0, 2-H), 6.20 (1 H, d, J 6.4, 8a-H), 7.00 (2 H, m, 7-H + 5-H), 7.16 (2 H, d, J 8.2, 2′-H + 6′-H), 7.18 (1 H, m, 6-H), 7.43 (1 H, d, J 8.1, 4-H) and 7.55 (2 H, d, J 8.2, 3′-H + 5′-H); δ_C 21.4 (Ar-Me), 33.5 (C-3), 52.0 (2-OMe), 52.7 (1-OMe), 58.7 (3a-C), 79.9 (8a-C), 118.6 (7-C), 124.3 (4-C), 125.6 (6-C), 126.5 (2′-C), 128.8 (5-C), 129.4 (3′-C), 133.0 (3b-C), 136.0 (4′-C), 142.5 (7a-C), 143.6 (1′-C) and 171.4 (2-CO_2); ν_{max}/cm^{-1} 3025, 1708, 1598, 1447, 1384 and 1164 cm^{-1}; m/z 430,1154 ($M^{+\cdot}$, $C_{21}H_{22}N_2O_6S$ requires 430.1199), 371, 275, 243, 216, 130, 91 and 49.

Standard Method for the Deprotonation and Alkylation of **11** *and* **31**.—*Dimethyl* (2S,3aR,8aS)-2-*Allyl*-8-(p-*tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **16**. A solution of LDA was prepared by the dropwise addition of butyllithium (1.38 mol dm^{-3} in hexane; 3.03 cm^3, 4.18 mmol) to diisopropylamine (0.59 cm^3, 4.18 mmol) in THF (10 cm^3) at 0 °C under nitrogen. The solution was stirred for 0.5 h before being cooled to −78 °C and then added, *via* a syringe, to a stirred solution of **11** (1.5 g, 3.50 mol) in THF (30 cm^3) under nitrogen at −78 °C. After the dark orange mixture had been stirred for 1 h at −78 °C allyl bromide (0.36 cm^3, 4.18 mmol) was added dropwise to it. After a further 2 h at −78 °C moist chloroform (50 cm^3) was added before the volatile components were removed under reduced pressure. The resulting oil was dissolved in ethyl acetate (50 cm^3) and the solution washed with hydrochloric acid (2 mol dm^{-3}, 2 × 30 cm^3). The organic layer was dried ($MgSO_4$), concentrated and the residue purified by chromatography on silica gel [eluent ethyl acetate–light petroleum (3:7)]. ^1H NMR and HPLC at this stage indicated the presence of a single diastereoisomer. Crystallisation from ether gave the *title compound* **16** (1.30 g, 79%) as large needles, m.p. 179–180 °C; $[\alpha]_D$ +73 (*c* 1, $CHCl_3$); δ(400 m Hz, 35 °C), 2.31 (3 H, s, ArMe), 2.38 (1 H, dd, J 13.5, 7.2, 3-H), 2.44 (1 H, dd, J 13.5, 1.6, 3-H), 2.50 (1 H, dd, J 14.6, 8.3, $CH_2CH{=}CH_2$), 3.02 (3 H, s, 2-OMe), 3.51 (1 H, br d, J 14.6, $CH_2CH{=}CH_2$), 3.28 (1 H, dd, J 6.3, 7.2, 3a-H), 3.68 (3 H, s, 1-OMe), 5.10–5.18 (2 H, m, $CH{=}CH_2$), 5.57 (1 H, m, $CH{=}CH_2$), 6.12 (1 H, d, J 6.3, 8a-H), 6.93 (1 H, d, J 7.5, 7-H), 7.04 (1 H, m, 5-H), 7.11 (2 H, d, J 8.6), 7.20 (1 H, m, 6-H), 7.45 (2 H, d, J 8.4) and 7.48 (1 H, d, J 8.0, 4-H); δ_C 21.5 (ArMe), 37.9 ($CH_2CH{=}CH_2$), 38.5 (2-C), 42.8 (3-C), 52.1 (2-OMe), 52.31 (1-OMe), 68.3 (3a-C), 81.8 (8a-C), 119.5 (7-C), 120.6 ($CH_2CH{=}CH_2$), 124.0 (4-C), 125.6 (6-C), 126.8 (5-C), 129.4 (3′-C), 131.8 ($CH_2CH{=}CH_2$), 134.5 (3b-C), 135.8 (4′-C), 142.4 (7a-C), 143.7 (1′-C), 153.9 (1-CO_2) and 173.6 (2-CO_2); ν_{max}/cm^{-1} 3538, 2945, 1912, 1715, 1595, 1441, 1357, 1277 and 1157; m/z 470 (M − H), 411, 397, 315, 283, 266, 181, 155, 130.91, 84 and 48 (Found: 61.2; H, 5.4; N, 5.9; S,

* In the preliminary communication[18] this electrophile and subsequent derivatives were erroneously recorded as the ethyl ethers.

7.1. $C_{24}H_{26}N_2O_6S$ requires C, 61.26; H, 5.57; N, 5.95; S, 6.81%).

Dimethyl (2S,3aR,8aS)-2-*Methyl*-8-(p-*tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **17**. The *title compound* was prepared by the standard procedure from **11** (2.05 g, 4.76 mmol) and methyl iodide (0.44 cm^3, 7.14 mmol). It was isolated by chromatography, on silica gel with ethyl acetate–light petroleum (3:7) as eluent, as a white powder (1.70 g, 80%), m.p. 87–88 °C; $[\alpha]_D$ +108 (*c* 1, $CHCl_3$); δ(400 MHz, 35 °C) 1.67 (3 H, s, 2-Me), 2.17 (1 H, dd, *J* 7.3, 13.3, 3-H), 2.34 (3 H, s, ArMe), 2.72 (1 H, br d, *J* 13.3, 3-H), 3.03 (3 H, s, 2-OMe), 3.36 (1 H, br t, *J* 7, 3a-H), 3.65 (3 H, s, 1-OMe), 6.24 (1 H, d, *J* 6.3, 8a-H), 6.97 (1 H, d, *J* 7.6, 7-H), 7.05 (1 H, m, 5-H), 7.13 (2 H, d, *J* 8.4), 7.22 (1 H, m, 6-H), 7.48 (2 H, d, *J* 8.2) and 7.48 (1 H, d, *J* 8.0, 4-H); ν_{max}/cm^{-1} 3589, 2945, 1912, 1715, 1595, 1441, 1357, 1277 and 1157; *m/z* 444 ($M^{+\bullet}$), 385, 289, 257, 230, 130 and 91 (Found: C, 59.2; H, 5.4; N, 6.0; S, 7.4. $C_{22}H_{24}N_2O_6S$ requires: C, 59.45; H, 5.44; N, 6.30; S, 7.21%).

Dimethyl (2S,3a,R,8aS)-2-*Benzyl*-8-(p-*tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **18**. The *title compound* was prepared by the standard procedure from **11** (2.10 g, 4.88 mmol) and benzyl bromide (0.89 cm^3, 7.32 mmol). It was isolated by chromatography, on silica gel with ethyl acetate–light petroleum (1:1) as eluent, as a white powder (1.70 g, 71%), m.p. 79–81 °C; $[\alpha]_D$ +113 (*c* 1, $CHCl_3$); δ(400 MHz, 35 °C) 2.30 (3 H, s, ArMe), 2.35 (2 H, m, 3-H), 3.00 (1 H, bs, CH_2Ph), 3.09 (3 H, s, 2-OMe), 3.10 (1 H, br m, 3a-H), 3.85 (3 H, s, 1-OMe), 3.97 (1 H, br s, CH_2Ph), 5.83 (1 H, d, *J* 6.3, 8a-H), 6.91 (1 H, d, *J* 7.5, 7-H), 7.00–7.41 (11 H, m) and 7.53 (1 H, d, *J* 8.0, 4-H); δ_C 14.2, 21.4, 36.0, 38.0, 42.7, 52.4, 60.2, 69.7, 81.8, 119.3, 124.0, 125.5, 126.8, 128.3, 129.3, 131.1, 134.4, 134.5, 142.3, 143.7, 154.4 and 173.8; ν_{max}/cm^{-1} 3546, 2945, 1411, 1715, 1595, 1444, 1367, 1271 and 1164; *m/z* 494 ($M^{+\bullet}$), 487, 461, 429, 397, 274, 155, 130 and 91 (Found: C, 64.4; H, 5.6; N, 5.1; S, 6.1. $C_{28}H_{28}N_2O_6S$ requires C, 64.60; H, 5.42; N, 5.38; S, 6.16%).

Dimethyl (2S,3aR,8aS)-2-(2-*Methylthioethyl*)-8-(p-*tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **19**. The *title compound* was prepared by the standard procedure from **11** (1.00 g, 2.32 mmol) and 2-methylthioethyl iodide (0.51 g). It was isolated, followed by unchanged starting material **11** (262 mg), by chromatography on silica gel with ethyl acetate–light petroleum (35:65) as eluent, as an off-white solid (383 mg, 33%), m.p. 150–151 °C; $[\alpha]_D$ +51 (*c* 1, $CHCl_3$); δ(400 MHz, 35 °C) 2.09 (3 H, s, SMe), 2.13–2.50 (4 H, m, CH_2CH_2SMe), 2.20 (1 H, m, 3-H), 2.34 (3 H, s, ArMe), 2.56 (1 H, d, *J* 13.5, 3-H), 3.03 (3 H, s, 2-OMe), 3.33 (1 H, dd, *J* 6.5, 7.2, 3a-H), 3.70 (3 H, s, 1-OMe), 6.19 (1 H, d, *J* 6.5, 8a-H), 6.98 (1 H, d, *J* 7.6), 7.07 (1 H, m, 5-H), 7.14 (2 H, d, *J* 8.0), 7.25 (1 H, m, 6-H), 7.47 (2 H, d, *J* 8.3) and 7.51 (1 H, d, *J* 8.1, 4-H); δ_C 15.5, 21.5, 28.1, 34 (br s), 38 (br s), 43.0, 52.1, 68.6, 119.4, 124.1, 125.6, 126.9, 128.6, 129.4, 134.1, 136.0, 142.6, 143.7, 154.0 and 173.1; ν_{max}/cm^{-1} 2939, 2251, 1715, 1595, 1441, 1368, 1271, 1164, 1087 and 904; *m/z* 504 ($M^{+\bullet}$), 445, 430, 349, 290, 284, 243, 229, 155, 130, 91, 75, 65 and 61 (Found: C, 57.1; H, 5.4; N, 5.5; S, 12.8. $C_{24}H_{28}N_2O_6S_2$ requires C, 57.12; H, 5.59; H, 5.55; S, 12.71%).

Dimethyl (2S,3aR,8aS)-2-*Methoxycarbonylmethyl*-8-(p-*tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **20**. The *title compound* was prepared by the standard procedure from **11** (2.10 g, 4.88 mmol) and methyl bromoacetate (0.69 cm^3, 7.32 mmol). It was isolated by chromatography, on silica gel with ethyl acetate–light petroleum (2:3) as eluent, as a white solid (1.75 g, 83%), m.p. 175–177 °C; $[\alpha]_D$ +110 (*c* 1, $CHCl_3$); δ(400 MHz, 35 °C) 2.31 (3 H, s, ArMe), 2.55 (1 H, br d, *J* 13.5, 3-H), 2.75 (1 H, dd, *J* 13.5, 7.9, 3-H), 2.88 (1 H, d, *J* 16.9, 2-CH_2), 3.02 (3 H, s, 2-Me), 3.31 (1 H, br t, *J* 7.2, 3a-H), 3.42 (1 H, br d, *J* 16.9, 2-CH_2), 3.65 (3 H, s, 1-OMe), 3.70 (3 H, s, CH_2CO_2Me), 6.19 (1 H, d, *J* 6.3, 8a-H), 6.93 (1 H, d, *J* 7.5, 7-H), 7.05 (1 H, m, 5-H), 7.11 (2 H, d, *J* 8.0), 7.21 (1 H, m, 6-H), 7.43 (2 H, d, *J* 8.4) and 7.53 (1 H, d, *J* 8.0, 4-H); δ_C 21.4, 25.5, 39.1, 43.1, 51.7, 52.3, 52.4, 66.2, 82.0, 119.6, 123.8, 125.6, 126.9, 128.4, 129.4, 134.8, 135.5, 142.2, 144.7, 167.7, 170.3 and 172.6; ν_{max}/cm^{-1} 3546, 2945, 1912, 1725, 1598, 1441, 1357 and 1164; *m/z* 502 ($M^{+\bullet}$), 443, 430, 397, 347, 288, 275, 255, 216, 155, 144, 130, 91, 84, 77, 65, 59 and 49 (Found: C, 57.5; H, 4.9; N, 5.3; S, 6.4. $C_{24}H_{26}N_2O_8S$ requires C, 57.36; H, 5.21; N, 5.57; S, 6.38%).

Dimethyl (2S,3aR,8aS)-8-(p-*Tolylsulphonyl*)-2-(2-*trimethylsilylethoxymethyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole* 1,2-*dicarboxylate* **21**. The *title compound* was prepared by the standard procedure from **11** (1.28 g, 2.97 mmol) and 2-trimethylsilylethoxymethyl chloride (1.05 cm^3, 5.94 mmol). It was isolated by chromatography, on silica gel with ethyl acetate–light petroleum (1:3) as eluent as a white solid (1.30 g, 78%), m.p. 50–51 °C; $[\alpha]_D$ +62° (*c* 1, $CHCl_3$); δ(400 MHz, 35 °C) 0.00 (9 H, s, $SiMe_3$), 0.87 (2 H, t, *J* 8.0, $SiCH_2$), 2.33 (3 H, s, ArMe), 2.37 (1 H, d, *J* 13.2, 3-H), 2.72 (1 H, dd, *J* 13.2, 7.8, 3-H), 3.06 (3 H, s, 2-OMe), 3.30 (1 H, t, *J* 7.2, 3a-H), 3.53 (3 H, m, 1 × $CH_2OCH_2CH_2$ + 2 × OCH_2CH_2), 3.70 (3 H, s, 1-OMe), 4.13 (1 H, br d, $CH_2OCH_2CH_2$), 6.17 (1 H, d, *J* 8.0, 8a-H), 6.96 (1 H, d, *J* 7.5, 7-H), 7.04 (1 H, m, 5-H), 7.11 (2 H, d, *J* 8.0), 7.23 (1 H, m, 6-H), 7.45 (2 H, d, *J* 8.1) and 7.54 (1 H, d, *J* 8.1, 4-H); δ_C 0.0, 18.0, 21.5, 36.9, 43.0, 52.1, 52.2, 68.2, 68.5, 69.2, 119.6, 123.8, 125.7, 126.9, 128.4, 129.4, 135.0, 135.7, 142.3, 143.7, 154.0 and 172.4; ν_{max}/cm^{-1} 3539, 2945, 1912, 1711, 1598, 1444, 1364, 1287, 1164 and 1111; *m/z* 560 ($M^{+\bullet}$), 429, 397, 284, 274, 155, 130, 91 and 73 (Found: C, 57.4; H, 4.7; N, 4.7; S, 6.0. $C_{27}H_{36}N_2O_7SSi$ requires C, 57.83; H, 6.47; N, 4.99; S, 5.72%).

Standard Method for the Ring Opening of Hexahydropyrroloindoles with Trifluoroacetic Acid.—N_b-(αS)-α-*Allyl*-N_b-*methoxycarbonyl*-1-(p-*tolylsulphonyl*)*tryptophan methyl ester* **22**. The hexahydropyrroloindole **16** (1.60 g, 3.41 mmol) was dissolved in trifluoroacetic acid (TFA) (7 cm^3) and the solution stirred overnight at room temperature. Concentration under reduced pressure yielded an oil which was taken up in chloroform (20 cm^3) and treated with an excess of powdered sodium carbonate (1–2 g) before being filtered through a pad of silica gel. The chloroform was then evaporated under reduced pressure and the residue purified by chromatography on silica gel [eluent ethyl acetate–light petroleum (1:4)] to give the *title compound* **22** as a viscous oil (1.41 g, 88%), $[\alpha]_D$ +38. (*c* 1, $CHCl_3$); δ(400 MHz) 2.34 (3 H, s, ArMe), 2.63 (1 H, dd, *J* 13.8, 7.5, $CH_2CH{=}CH_2$), 3.24 (1 H, d, *J* 14.5, β-CH_2), 3.29 (1 H, m, $CH_2CH{=}CH_2$), 3.45 (1 H, d, *J* 14.5, β-CH_2), 3.66 (3 H, s, OMe), 3.70 (3 H, s, NCO_2Me), 5.10 (2 H, m, $CH_2CH{=}CH_2$), 5.60 (1 H, m, $CH_2CH{=}CH_2$, 5.60 (1 H, br s, NH), 7.17–7.20 (5 H, m, 2-H + Ar-H), 7.42 (1 H, d, *J* 7.7, 7-H), 7.69 (2 H, d, *J* 8.4) and 7.92 (1 H, d, *J* 8.3, 4-H); δ_C 21.6, 30.4, 39.9, 52.0, 52.8, 64.7, 113.7, 117.3, 119.3, 119.4, 123.0, 124.7, 125.0, 126.7, 129.8, 131.3, 132.0, 134.8, 135.1, 144.9, 155.1 and 172.7; ν_{max}/cm^{-1} 3412, 2939, 1908, 1722, 1595, 1491, 1441, 1124, 1019 and 977; *m/z* 470.1558 ($M^{+\bullet}$, $C_{24}H_{26}N_2O_6S$ required 470.1512), 284, 240, 155, 130, 91, 84, 49 and 41.

(αS)-N_b-*Methoxycarbonyl*-α-*methyl*-1-(p-*tolylsulphonyl*)-*tryptophan methyl ester* **23**. This *derivative* was prepared from **17** (1.32 g, 2.97 mmol) by the standard procedure. After elution from silica gel with ethyl acetate–light petroleum (3:7) it was a white foam (1.18 g, 90%), m.p. 33–35 °C; $[\alpha]_D$ +46 (*c* 1, $CHCl_3$); δ(400 MHz) 1.61 (3 H, s, α-Me), 2.30 (3 H, s, ArMe), 3.27 (1 H, d, *J* 14.6, β-CH_2), 3.53 (1 H, d, *J* 14.6, β-CH_2), 3.64 (3 H, s, OMe), 3.66 (3 H, s, OMe), 5.44 (1 H, s, NH), 7.17–7.20 (5 H, m, 2-H + Ar-H), 7.40 (1 H, d, *J* 7.8, 7-H), 7.68 (2 H, d, *J* 8.3) and 7.92 (1 H, d, *J* 8.3, 4-H); δ_C 21.4, 23.7, 31.2, 51.8, 52.6, 60.3, 113.6, 117.3, 119.4, 123.0, 124.6, 125.0, 126.6, 129.7, 131.3, 134.8,

135.1, 144.8, 155.3 and 173.9; ν_{max}/cm^{-1} 3412, 2938, 1908, 1722, 1594, 1495, 1444, 1368 and 977; *m/z* 444.1332 ($M^{+\cdot}$, $C_{22}H_{24}N_2O_6S$ requires 444.1355), 284, 230, 155, 130, 91 and 43.

(αS)-α-*Benzyl*-N_b-*methoxycarbonyl*-1-(p-*tolylsulphonyl*)-*tryptophan methyl ester* **24**. This *derivative* was prepared from **18** (1.14 g, 2.19 mmol) by the standard procedure. After elution from silica gel with ethyl acetate–light petroleum (1:4) it was a white foam (1.06 g, 93%), m.p. 69–71 °C; $[\alpha]_D$ +13 (*c* 1, $CHCl_3$); δ(400 MHz) 2.31 (3 H, s, ArMe), 3.25 (1 H, d, *J* 13.6, CH_2Ph), 3.35 (1 H, d, *J* 14.5, β-CH_2), 3.62 (3 H, s, OMe), 3.75 (3 H, s, NCO_2Me), 3.89 (1 H, d, *J* 13.6, CH_2Ph), 3.98 (1 H, d, *J* 14.5, β-CH_2), 5.53 (1 H, s, NH), 7.05 (2 H, d, *J* 7.5 Hz), 7.17–7.20 (9 H, m), 7.47 (1 H, d, *J* 7.8, 7-H), 7.67 (2 H, d, *J* 8.4) and 7.93 (1 H, d, *J* 8.2, 4-H); ν_{max}/cm^{-1} 3406, 2938, 1738, 1711, 1598, 1495, 1444, 1364 and 1167; *m/z* 520 ($M^{+\cdot}$) 284, 155, 130, 91, 83 and 43 (Found: C, 64.4; H, 5.6; N, 5.3; S, 6.1. $C_{28}H_{28}N_2O_6S$ requires C, 64.60; H, 5.42; N, 5.38; S, 6.16%).

(αS)-N_b-*Methoxycarbonyl*-α-(2-*methylthioethyl*)-1-(p-*tolylsulphonyl*)*tryptophan methyl ester* **25**. This *derivative* was prepared from **19** (135 mg, 0.27 mmol) by the standard procedure. It was a white foam (112 mg, 84%), m.p. 49–52 °C; $[\alpha]_D$ +28 (*c* 1, $CHCl_3$); δ(400 MHz) 2.05 (3 H, s, SMe), 2.22 (1 H, m, CH_2CH_2SMe), 2.31 (3 H, s, ArMe), 2.45 (2 H, m, CH_2CH_2SMe), 2.89 (1 H, m, CH_2CH_2SMe), 3.15 (1 H, d, *J* 14.4, β-CH_2), 3.62 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.70 (1 H, d, *J* 14.2 β-CH_2), 5.68 (1 H, s, NH), 7.13–7.25 (5 H, m), 7.36 (1 H, d, *J* 7.8, 7-H), 7.77 (2 H, d, *J* 8.4) and 7.89 (1 H, d, *J* 8.4, 4-H); ν_{max}/cm^{-1} 3406, 2938, 1712, 1595, 1495, 1365, 1274, 1167, 1121 and 974; *m/z* 504.1382 ($M^{+\cdot}$, $C_{24}H_{28}N_2O_6S_2$ requires 504.1388), 284, 155, 130, 91, 65 and 61.

(αS)-α-*Methoxycarbonylmethyl*-N_b-*methoxycarbonyl*-1-(p-*tolylsulphonyl*)*tryptophan methyl ester* **26**. This *derivative* was prepared from **20** (670 mg, 1.30 mmol) by the standard procedure. It was a white foam (650 mg, 97%), m.p. 59–61 °C; $[\alpha]_D$ +47 (*c* 1, $CHCl_3$); δ(400 MHz) 2.33 (3 H, ArMe), 3.06 (1 H, d, *J* 16.5, CH_2CO_2Me), 3.15 (1 H, d, *J* 14.4, β-CH_2), 3.61 (3 H, s, OMe), 3.65 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.72 (1 H, br m, CH_2CO_2Me), 3.78 (1 H, d, *J* 14.5, β-CH_2), 5.84 (1 H, s, NH), 7.17–7.20 (5 H, m), 7.38 (1 H, d, *J* 7.8, 7-H), 7.70 (2 H, d, *J* 8.4) and 7.92 (1 H, d, *J* 8.4, 4-H); ν_{max}/cm^{-1} 3406, 2945, 1912, 1735, 1598, 1495, 1438, 1361, 1324, 1274, 1167 and 1117; *m/z* 502.1450 ($M^{+\cdot}$, $C_{24}H_{26}N_2O_8S$ requires 502.1409), 427, 284, 155, 130 and 91.

(αS)-N_b-*Methoxycarbonyl*-1-(p-*tolylsulphonyl*)-α-*trifluoroacetoxymethyltryptophan methyl ester* **27**. This *derivative* was prepared from **21** (0.51 g, 0.90 mmol) by the standard procedure. After elution from silica gel with ethyl acetate–light petroleum (3:7) it was a white foam (310 mg, 61%), m.p. 58–61 °C; $[\alpha]_D$ 31 (*c* 1, $CHCl_3$); δ(400 MHz) 2.33 (3 H, s, ArMe), 3.18 (1 H, d, *J* 14.4, β-CH_2), 3.63 (3 H, s, OMe), 3.67 (1 H, m, β-CH_2), 3.70 (3 H, s, OMe), 4.76 (1 H, d, *J* 10.9, CH_2O), 5.18 (1 H, br d, *J* 10.9, CH_2O), 5.61 (1 H, s, NH), 7.18–7.30 (5 H, m), 7.36 (1 H, d, *J* 7.7, 7-H), 7.68 (2 H, d, *J* 8.4) and 7.93 (1 H, d, *J* 8.3, 4-H); ν_{max} 3406, 3306, 2945, 1908, 1781, 1722, 1595, 1498, 1444, 1367 and 1164; *m/z* 556 ($M^{+\cdot}$), 460.1251 ($M + H - COCF_3^+$, $C_{22}H_{24}N_2O_7S$ requires 460.1303), 428, 385, 285, 248, 155, 130 and 91.

(αS)-α-*Allyl*-N_b-*methoxycarbonyltryptophan Methyl Ester* **28**.—Liquid ammonia (*ca.* 20 cm^3) was condensed onto a solution of the sulphonamide **22** (1.10 g, 2.34 mmol) in THF (4 cm^3) under nitrogen. Sodium metal (210 mg, 7.01 mmol) was added portionwise over a period of 1 h until a consistent blue colour was observed. Methanol (20 cm^3) and excess of solid ammonium chloride (1 g) were added and an air condenser fitted to the apparatus. The ammonia was allowed to evaporate overnight and the remaining volatile components were removed under reduced pressure. The solid residue was then dissolved in ethyl acetate (40 cm^3) and washed with water (3 × 20 cm^3), dried ($MgSO_4$) and the *title product* isolated by chromatography on silica gel [eluent ether–light petroleum (3:7)]. It was a viscous oil (0.70 g, 96%), $[\alpha]_D$ +63 (*c* 1, $CHCl_3$); δ(400 MHz) 2.74 (1 H, dd, *J* 7.4, 13.8, $CH_2CH{=}CH_2$), 3.30 (1 H, dd, *J* 7.4, 13.8, $CH_2CH{=}CH_2$), 3.35 (1 H, d, *J* 14.6, β-CH_2), 3.67 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.77 (1 H, br d, *J* 14.6, β-CH_2), 5.12 (2 H, m, $CH_2CH{=}CH_2$), 5.65 (1 H, s, NH), 5.71 (1 H, m, $CH_2CH{=}CH_2$), 6.91 (1 H, d, *J* 2.5, 2-H), 7.08 (1 H, m, 5-H), 7.14 (1 H, m, 6-H), 7.31 (1 H, d, *J* 8.1, 7-H), 7.54 (1 H, d, *J* 7.9, 4-H) and 8.24 (1 H, br s, NH); ν_{max}/cm^{-1} 3473, 3413, 2945, 1715, 1655, 1498, 1444, 1341, 1314, 1091, 1067 and 917; *m/z* 316 ($M^{+\cdot}$), 285, 211, 155, 131, 130, 117, 103, 77, 59 and 41 (Found: C, 64.3; H, 6.3; N, 9.0. $C_{17}H_{20}N_2O_4$ requires C, 64.54; H, 6.37; N, 8.85%).

Dimethyl (2R,3aS,8aR)-1,2,3,3a,8,8a-*Hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **30**—This pyrroloindole was prepared (85%) in a manner exactly similar to that employed for its enantiomer **9** from N_b-methoxycarbonyl-D-tryptophan methyl ester. It was a white solid, m.p. 87–88 °C and its spectral data were in full agreement with those of its enantiomer.

Dimethyl (2R,3aS,8aR)-8-(p-*Tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **31**.—This *pyrroloindole* was prepared (92%) analogously to its enantiomer **11**. It was a white solid, m.p. 43.5 °C; $[\alpha]_D$ −94° (*c* 1, $CHCl_3$) (Found: C, 58.7; H, 4.9; N, 6.5; S, 7.5. $C_{21}H_{22}N_2O_6S$ requires C, 58.59; H, 5.27; N, 6.40; S, 7.34%). Its spectral data were in accord with those of **11**.

Dimethyl (2R,3aS,8aR)-2-*Methyl*-8-(p-*tolylsulphonyl*)-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **32**.—This *substance* was prepared by the standard procedure for deprotonation and alkylation of pyrroloindoles from **31** (2.50 g, 5.81 mmol) and methyl iodide. It was a crystalline solid (2.37 g, 72%), m.p. 87–88 °C; $[\alpha]_D$ −108° (*c* 1, $CHCl_3$) (Found: C, 59.5; H, 5.7; N, 6.2; S, 7.3. $C_{22}H_{24}N_2O_6S$ requires C, 59.45; H, 5.44; N, 6.30; S, 7.21%). It had spectra identical with those of its enantiomer **17**.

(αR)-N_b-*Methoxycarbonyl*-α-*methyl*-1-(p-*tolylsulphonyl*)-*tryptophan Methyl Ester* **33**.—This *tryptophan derivative* was prepared (83%) from **32** by treatment with TFA according to the standard procedure. It was isolated as a white foam, m.p. 33–35 °C; $[\alpha]_D$ −44 (*c* 1, $CHCl_3$) (Found: C, 59.6; H, 5.6; N, 6.2; S, 7.1. $C_{22}H_{24}N_2O_6S$ requires C, 59.45; H, 5.44; N, 6.30; S, 7.21%). Spectral data were identical with those of its enantiomer **23**.

(αR)-N_b-*Methoxycarbonyl*-α-*methyltryptophan Methyl Ester* **34**.—Application of the protocol for desulphonylation of **22** as described for the preparation of **28** above, to the sulphonylamide **33** (1.00 g, 2.25 mmol) gave the *title compound* as a white solid (0.60 g, 92%) after chromatography on silica gel [eluent ethyl acetate–hexane (3:7)], m.p. 135–136 °C; $[\alpha]_D$ −51 (*c* 1, $CHCl_3$); δ(300 MHz) 1.69 (3 H, s, α-Me), 3.36 (1 H, d, *J* 14, β-CH_2), 3.44 (1 H, d, *J* 14, β-CH_2), 3.67 (3 H, s, OMe), 3.68 (3 H, s, OMe), 5.45 (1 H, br s, NH), 6.94 (1 H, d, *J* 2, 2-H), 7.08–7.20 (2 H, m, 5-H + 6-H), 7.33 (1 H, d, *J* 8, 7-H), 7.54 (1 H, d, *J* 8, 4-H), 8.26 (1 H, br s, NH); ν_{max}(film)/cm^{-1} 3404, 2946 and 1708 (Found: C, 61.9; H, 6.4; N, 9.5. $C_{15}H_{18}N_2O_4$ requires C, 62.05; H, 6.25; N, 9.65%).

(αR)-α-*Methyltryptophan* **35**.—The tryptophan derivative **34** (0.60 g, 2.1 mmol) was dissolved in aqueous potassium hydroxide (5 mol dm^{-3}, 15 cm^3) and heated to reflux for 24 h. After cooling and neutralisation with hydrochloric acid (1 mol dm^{-3}, 75 cm^3) the solution was passed through Amberlite

120 (H) and lyophilised to give the crude product which was subject to purification by reverse phase chromatography on LiChromprep® RP-18 [eluent water–methanol (5:1)] to provide the title compound as a white solid (0.40 g, 87%), m.p. 235–237 °C; $[\alpha]_D$ +16 (*c* 1, MeOH), lit.,[4] for the (*S*)-enantiomer: −10.6 (*c* 0.9, water); δ(300 MHz, [$^2H_6$]-DMSO) 1.34 (3 H, s, 2-Me), 3.07 (1 H, d, *J* 15, β-CH_2), 3.18 (1 H, d, *J* 15, β-CH_2), 6.95 (1 H, t, *J* 7, 6-H), 7.03 (1 H, t, *J* 7, 5-H), 7.27 (1 H, s, 2-H), 7.34 (1 H, d, *J* 7, 7-H), 7.64 (1 H, d, *J* 7, 4-H), 11.19 (1 H, br s, NH). By HPLC on 10% α-cyclodextrin on silica [eluent 0.1% Et_3N in H_2O) **35** was judged to have an enantiomeric excess of >95%.

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