Cyclic Tautomers of Tryptophan: Enantio- and Diastereoselective Synthesis of β-Substituted and α,β-Disubstituted Derivatives of Tryptophan

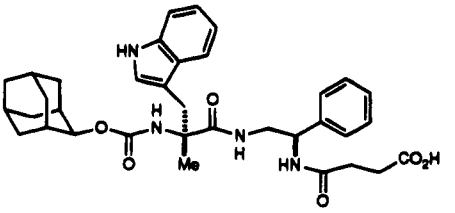
Milan Bruncko and David Crich*

University of Illinois at Chicago, Department of Chemistry (M/C111), 845 W. Taylor Street, Chicago, Illinois 60607-7061

Received February 1, 1994®

A method is presented for the synthesis of enantiomerically pure erythro-β-alkylated derivatives of L-tryptophan from L-tryptophan itself via the intermediacy of cyclic tryptophan tautomers. Dehydrogenation of the cyclic tryptophan tautomer **2** to **3** is achieved via either the 2-phenylseleno derivative **6** or its 2-phenylthio counterpart **7** by oxidation to the corresponding selenoxide or sulfoxide and formal syn-elimination. Evidence is provided that this elimination proceeds, at least in part, by a stepwise rather than a concerted pericyclic mechanism. Soft nucleophiles, including thiolates, amines, and higher order cuprates, add to **3** in conjugate fashion in high yield and with excellent diastereoselectivity from the exo-face of the bicyclic system. The enolate anion resulting from conjugate addition is likewise quenched with high selectivity from the exo face either by simple protonation or by alkylation with methyl iodide. The tetrahydropyrroloindole **3** also reacts with cyclopentadiene in a Diels–Alder reaction with excellent selectivity to give **29**. Sulfur ylide chemistry enables the formation of the cyclopropane adduct **27**. After conjugate addition, cycloreversion to the tryptophan skeleton is achieved by dissolution in trifluoroacetic acid. The rate of ring opening is strongly dependant on the steric bulk and orientation of the substituent at C-3, with large exo-substituents strongly retarding ring opening and endo-substituents favoring ring opening. Desulfonylation is achieved by photolysis with ascorbic acid and anisole and final deprotection by heating to reflux with 6 M hydrochloric acid. Desulfonylation of the 2,3-methano derivative **37** resulted in degradation of the cyclopropane ring. Use of a (4-methoxyphenyl)sulfonyl group in place of the phenylsulfonyl group, as in **11** and **22**, enables one-step desulfonylation and ring opening by treatment with methanesulfonic acid.

In this laboratory we have been interested in the chemistry of cyclic tryptophan tautomers and in particular in their use as intermediates in the enantiospecific synthesis of α-alkylated tryptophan derivatives from tryptophan itself without the requirement of an external chiral auxiliary.[1] This series of investigations was prompted by the well-known ability of α-substituted amino acid residues to impart advantageous properties, particularly enhanced resistance to exogenous and endogenous peptidases and restriction of conformational mobility,[2] to peptides and/or peptoids[3] in which they are included, and by the paucity of suitable synthetic routes to such tryptophan derivatives.[4] L-Tryptophan is an essential residue in numerous peptide hormones and its replacement by its antipode or by conformationally restricted analogues has considerable potential.[5] The development of CI-988 (**1**) with its nanomolar affinity for the cholecystokinin-B binding site is an extreme example of the kind.[6] Alternative approaches to conformationally



1

restricted tryptophans have involved the construction of cyclic derivatives.[7] Enantiomerically and diastereomerically pure β-substituted amino acids might reasonably be expected to have similar properties[8] although, with the exception of the β-hydroxy-α-amino acids,[9,10] much less synthetic work has been conducted in this area and

® Abstract published in *Advance ACS Abstracts,* July 1, 1994.

(1) (a) Crich, D.; Davies, J. W. *J. Chem. Soc., Chem. Commun.* **1989**, 1418. (b) Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1693. (c) Chan, C.-O.; Crich, D.; Natarajan, S. *Tetrahedron Lett.* **1992**, *33*, 3405. (d) Crich, D.; Lim, L. B. L. *Heterocycles* **1993**, *36*, 1199. (e) Bruncko, M.; Crich, D.; Samy, R. *Heterocycles* **1993**, *36*, 1735. (f) Crich, D.; Chan, C.-O.; Davies, J. W.; Natarajan, S.; Vinter, J. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2233. (g) Crich, D.; Chan, C.-O.; Cooksey, C. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 777. (h) Crich, D.; Pastrana-Gress, I.; Quintero-Cortes, L.; Sandoval-Ramirez, J. *Heterocycles* **1994**, *37*, 719.

(2) For a recent overview see: Rees, D. C. *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic: San Diego, 1993; Vol. 28, 59.

(3) Horwell, D. C. in *Topics in Medicinal Chemistry*; Leeming, P. R., Ed.; Spec. Pub. R. Soc. Chem., 1988; Vol. 65, 62.

(4) Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413. (b) Gandor-Coquez, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224.

(5) For example: (a) Oxytocin: Flouret, G.; Brieher, W.; Majewski, T.; Mahan, K.; Wilson, L. *J. Med. Chem.* **1991**, *34*, 2089 and references therein. (b) Endothelin: Doherty, A. *J. Med. Chem.* **1992**, *35*, 1493 and references therein. (c) Somatostatin: Brady, S. F.; Freidinger, R. M.; Palevada, W. J.; Colton, C. D.; Homnick, C. F.; Whitter, W. L.; Curley, P.; Nutt, R. F.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764. (d) Gonadotropin releasing hormone: Rizo, J.; Koerber, S. C.; Bienstock, R. J.; Rivier, J.; Hagler, A. T.; Gierasch, L. M. *J. Am. Chem. Soc.* **1992**, *114*, 2852.

(6) (a) Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. *J. Med. Chem.* **1991**, *34*, 404. (b) Bock, G. M. *Chemtracts: Org. Chem.* **1991**, 216.

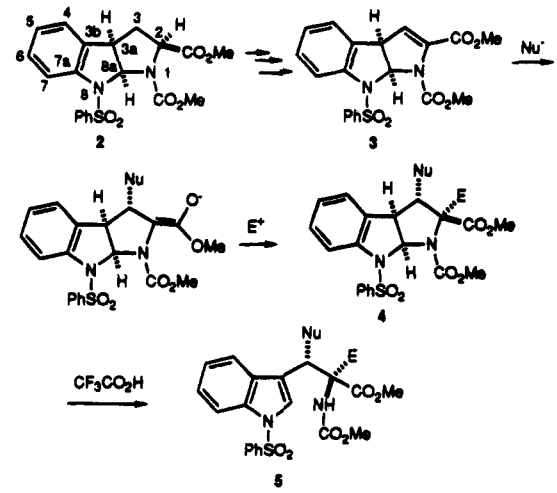
(7) (a) Chung, J. Y. L.; Wasicak, J. T.; Nadzau, A. M. *Synth. Commun.* **1992**, *22*, 1039. (b) Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pelliciarri, R. *Tetrahedron Lett.* **1993**, *34*, 3185.

(8) For example see: (a) Hruby, V. J.; Al-Obedi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249. (b) Kazmierski, W. M.; Yamamura, H. I.; Hruby, V. J. *J. Am. Chem. Soc.* **1991**, *113*, 2275.

0022-3263/94/1959-4239$04.50/0

it is only relatively recently that asymmetric syntheses have begun to appear.[11] 2,3-Methano or cyclopropa amino acids, long of interest in this context,[12] continue to be pursued with vigor.[13] Although (2S,3R)-β-methyltryptophan is known to be the biosynthetic precursor of both Streptonigrin[14] and Lavendomycin,[15] is a component of the antibiotic Telomycin,[16] and is a competitive inhibitor of tryptophanase,[17] until recently[18] there existed no asymmetric synthesis of β-alkylated tryptophans of any configuration, with the only source being separation of diastereomeric mixtures.[19] Very recently the importance of diastereo- and enantiomerically pure β-substituted tryptophan derivatives has been considerably enhanced by Corey's demonstration of their use as chiral ligands in Lewis acid-mediated Diels–Alder reactions.[20] In this paper we describe in full the extension of our cyclic

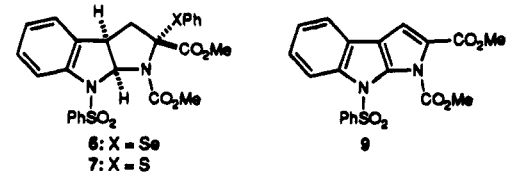
Scheme 1



tryptophan tautomer method to the asymmetric synthesis of β-substituted and α,β-disubstituted tryptophan derivatives.[21,22] Hruby has recently described an alternative asymmetric approach to the some of the same derivatives using Evans methodology.[11h]

On the basis of our earlier work[1a,b,d] with the alkylation of the hexahydropyrroloindole **2** which was found to occur, within the limits of high field NMR detection, exclusively from the *exo*-face of the diazabicyclo[3.3.0]-octane system, we envisaged that nucleophilic attack on the hypothetical 2,3-dehydro-system **3** would take place with similar selectivity from the *exo*-face and furthermore that the resulting enolate would be likewise trapped from the *exo*-face to give **4**. Acid-assisted tautomerization would then yield the β-substituted tryptophan **5** with high diastereomeric purity (Scheme 1). As **2** is available in excellent yield from tryptophan as an enantiomerically pure crystalline solid[1,23] this sequence would provide, after deprotection, an attractive and versatile entry into a number of β-substituted and α,β-disubstituted tryptophans of high diastereo- and enantiomeric purity.

Sequential treatment of **2** with LDA and then phenylselenyl chloride in THF at −78 °C afforded the phenylselenide **6** in 70% isolated yield as a white crystalline solid. This selenide was a single diastereomer resulting



from the anticipated *exo*-face quenching. That the reaction had occurred on the *exo*-face was readily discernible from the chemical shift (δ_H 3.15, $CDCl_3$) of the ester methyl group indicative of its *endo*-face position where it suffers shielding by the ring current of the A-ring. Pertinent and diagnostic ^1H chemical shifts and ^3J

(9) For recent reports see: (a) Sardina, F. J.; Paz, M. M.; Fernandez-Megia, E.; de Boer, R. F.; Alvarez, M. P. *Tetrahedron Lett.* **1992**, *33*, 4637. (b) Lowe, C.; Pu, Y.; Vederas, J. C. *J. Org. Chem.* **1991**, *56*, 10. (c) Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067. (d) Akasaka, T.; Sakurai, A.; Ando, W. *J. Am. Chem. Soc.* **1991**, *113*, 2696. (e) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240. (f) Easton, C. J.; Hutton, C. A.; Tiekink, E. R. T. *Tetrahedron Lett.* **1990**, *31*, 7059. (g) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677. (h) Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genet, J. P. *Synlett* **1993**, 475. (i) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Synlett.* **1992**, 249. (j) Blank, S.; Seebach, D. *Liebigs Ann. Chem.* **1993**, 889. (k) Corey, E. J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735.

(10) For earlier reports see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989. Cintas, P. *Tetrahedron* **1991**, *47*, 6079. Tetrahedron Symposium in Print, no. 33, O'Donnell, M. J., Ed.: *Tetrahedron*, **1988**, *44*, 5253 and references therein.

(11) (a) β-Methylaspartic acid: Hanessian, S.; Sumi, K.; Vanasse, B. *Synlett* **1992**, 33. Palomo, C.; Aizpurua, J. M.; Ontoria, J. M.; Iturburu, M. *Tetrahedron Lett.* **1992**, *33*, 4823. (b) β-Alkyl- and arylcysteines: Lago, M. A.; Samanen, J.; Elliott, J. D. *J. Org. Chem.* **1992**, *57*, 3493. Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291. (c) β-Methyl-γ-hydroxy-α-amino acids: Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063. (d) β-Alkylglutamic acid: Jajo, I.; Uiber, P.; Mann, A.; Wermuth, C.-G. *J. Org. Chem.* **1991**, *56*, 5729. Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379. (e) β-Methylvinyl glycine: Griesbeck, H. G.; Mauder, H. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 73. (f) β-methylphenylalanine: Dharanipragada, R.; Nicolas, E.; Toth, G.; Hruby, V. J. *Tetrahedron Lett.* **1989**, *30*, 6841. Seebach, D.; Bürger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669. (g) β-Methyltyrosine and analogues: Nicolas, E.; Dharanipragada, R.; Toth, G.; Hruby, V. J. *Tetrahedron Lett.* **1989**, *30*, 6845. Li, G.; Russell, K. C.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2565. Nicolas, E.; Russel, K. C.; Knollenberg, J.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 7565. (h) β-Methyltryptophan: Boteju, L. W.; Wegner, K.; Hruby, V. J. *Tetrahedron Lett.* **1992**, *33*, 7491. (i) Cyclically constrained aspartic acid derivatives: Sasaki, N. A.; Pauly, R.; Fontaine, C.; Chiaroni, A.; Riche, C.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 241. (j) α,β-Dimethylphenylalanine: Kazmierski, W. M.; Urbanczyk-Lipkowska, Z.; Hruby, V. J. *J. Org. Chem.* **1994**, *59*, 1789.

(12) Stammer, C. H. *Tetrahedron* **1990**, *40*, 2231.

(13) For recent reports see: (a) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796. (b) Chincilla, R.; Najera, C.; Garcia-Grando, S.; Menendez-Velazquez, A. *Tetrahedron Lett.* **1993**, *34*, 5799. (c) Fadel, A. *Synlett* **1993**, 503. (d) Koskinen, A. M. P.; Munoz, L. *J. Org. Chem.* **1993**, *58*, 879. (e) Kodama, H.; Matsui, S.; Kondo, M.; Stammer, C. H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2668. (f) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931. (g) Burgess, K.; Ho, K.-K. *Tetrahedron Lett.* **1992**, *33*, 5677. (h) Ahmad, S.; Phillips, R. S.; Stammer, C. H. *J. Med. Chem.* **1992**, *35*, 1410. (i) di Lugano, F. R.; Monteiro, J.; Fliche, C.; Braun, J.; Le Goffic, F. *Synth. Commun.* **1992**, *22*, 1155.

(14) Hartley, D. L.; Speedio, M. K. *Biochem. J.* **1984**, *220*, 309. Gould, S. J.; Chang, C. C.; Darling, D. S.; Roberts, J. D.; Squillacote, M. *J. Am. Chem. Soc.* **1980**, *102*, 1707.

(15) Doyle, T. W.; Balitz, D. M.; Glurich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.; Moews, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595.

(16) Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462; Kuma, N. G.; Urry, D. W. *Biochemistry* **1973**, *12*, 3811.

(17) Watanabe, T.; Snell, E. S. *J. Biochem.* **1977**, *82*, 733.

(18) An improved preparation of (±)-(2*S*,3*R*)-β-methyltryptophan was reported in 1988: Behforouz, M.; Zarrinmayeh, H.; Ogle, M. E.; Riehle, T. J.; Bell, F. W. *J. Heterocycl. Chem.* **1988**, *25*, 1627; application to the synthesis of lavendomycin: Behforouz, M.; West, S. J.; Chakrabarty, C.; Rusk, D. A.; Zarrinmayeh, H. *Heterocycles* **1992**, *34*, 483.

(19) (a) Preparation: Snyder, H. R.; Matteson, D. S. *J. Am. Chem. Soc.* **1957**, *79*, 2217. (b) Separation: Gould, S. J.; Darling, D. S. *Tetrahedron Lett.* **1978**, 3207.

(20) (a) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimiaora, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (b) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979.

(21) Preliminary communication: Bruncko, M.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 6251.

(22) A review on the preparation and reactions of dehydro amino acids: Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.

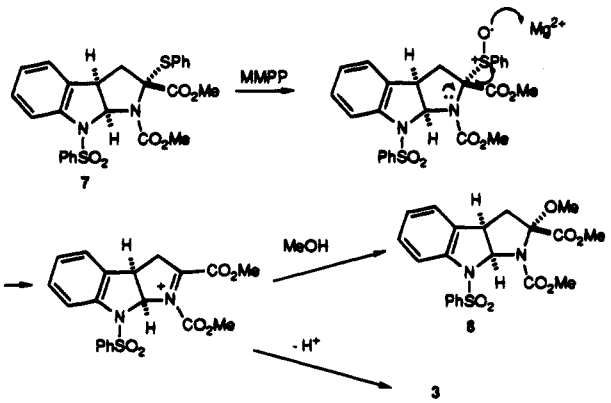
(23) Compound **2** is commercially available from Aldrich Chemical Co.

Table 1. Diagnostic ^{1}H-NMR Data for Hexa- and Tetrahydropyrroloindoles

entry	compd	δ CO_2Me (ester)	J (H2–H3exo), Hz	J (H2–H3endo), Hz	J (H3exo–H3a), Hz	J (H3endo–H3a), Hz
1	**2**	3.11	8.3	0.6	7.2	0
2	**3**	3.76	–	–	2.0[a]	
3	**6**	3.15	–	–	7.2	0
4	**7**	3.22	–	–	3.8	0
5	**11**	3.16	8.7	0	6.7	0
6	**12**	3.80	–	–	2.1[a]	
7	**16**	3.13	–	0	–	0
8	**17**	3.14	–	0	–	0
9	**18**	3.14	–	0	–	0
10	**19**	3.15	–	0	–	0
11	**20**	3.22	–	0	–	0
12	**21**	3.24	–	0	–	0
13	**22**	3.25	–	–	–	4.0
14	**23**	3.49	–	–	–	7.1
15	**24**	3.79	–	–	–	10.6
16	**25**	3.79	–	–	–	–
17	**26**	3.18	4.42	–	7.4	–
18	**27**	3.70	–	–	–	0
19	**29**	3.24	–	–	–	0

[a] Indicates olefinic H-3 in a tetrahydro series compound.

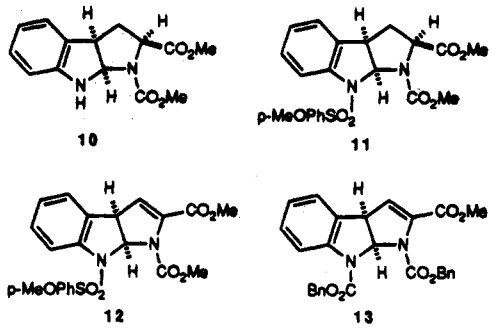
Scheme 2



couplings for all hexahydropyrroloindole derivatives described in this paper are collected in Table 1. The phenylthio analogue **7** was available on quenching the enolate with diphenyl disulfide. It too was obtained in good yield and as a single diastereomer. Treatment of **6** with a suspension of 2 mol equiv of MMPP in THF at room temperature followed by extractive workup gave a quantitative yield of the dehydro derivative **3**. The excess of oxidant was employed such that all arylselenium residues from the *syn*-elimination would be oxidized through to benzeneseleninic acid which could be removed extractively so simplifying the isolation procedure. Intriguingly, treatment of the phenylthio derivative **7** with MMPP in methanol at *room temperature* overnight also resulted in the isolation of **3** in 72% yield. The unexpectedly low temperature of this elimination prompts us to suggest that it does not occur by the anticipated pericyclic mechanism but rather that the sulfoxide group, possibly coordinated to magnesium, is expelled with the help of the ring nitrogen resulting in an aminium ion which then suffers deprotonation (Scheme 2). Indeed support for this hypothesis is found in the isolation of the methoxy derivative **8** as a byproduct of this sulfoxide reaction.[24] The same byproduct (**8**) was obtained as a 1:4 mixture with **3** from the selenide **6** when the MMPP oxidation was carried out in a 2:1 THF:MeOH mixture suggesting that the selenoxide elimination proceeds, at least in part, by a parallel mechanism.

(24) Kahne has observed a similar effect with glycosyl sulfoxides leading to glycosyl cations: Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

The tetrahydropyrroloindole **3** has defied all our attempts at crystallization and is isolated as a white foam. Nevertheless it shows no tendency to suffer aerial oxidation to the aromatic dihydro system **9** and can be readily stored under normal laboratory conditions without significant decomposition. In an attempt to prepare a crystalline congener of **3**, the hexahydropyrroloindole **10** was converted to a number of N-8 derivatives and these, via the 2-phenylseleno derivatives, to the corresponding 2,3-dehydro derivatives. In the event, only the anisylsulfonyl derivative **12** showed the desired combination of having both oxidation levels (**11** and **12**) crystalline. The bis(benzyloxycarbonyl) methyl ester **13** was also crystalline but its immediate precursor, saturated at C2 and C3, was a viscous oil which rendered purification tedious. Compound **13** was therefore not pursued any further.



With a ready preparation of **3**, and **12**, in hand, attention was turned to conjugate addition reactions. Close parallels were to be found in the work of Seebach who prepared the thiazoline **14** ($n = 0$) from cysteine and

(25) Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291.

(26) Conjugate addition to simple acyclic dehydro amino acids has previously been studied by a number of authors. See for example: (a) Wulff, G.; Bohne, H.; Klinken, H. *Liebigs Ann. Chem.* **1988**, 501. (b) Bajgrowicw, J. A.; Hallaoui, A. El.; Jaquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833. (c) Belokon, Y. N.; Sagyan, A. S.; Djamgaryan, S. M.; Bakhmutov, V. I.; Belikov, V. M. *Tetrahedron* **1988**, *44*, 5507. (d) Cardicellicchio, C.; Fiandanese, V.; Marchese, A.; Naso, F.; Ronini, L. *Tetrahedron Lett.* **1985**, *26*, 4387. (e) Hausler, J. *Liebigs Ann. Chem.* **1981**, 1073. (f) Crich, D.; Davies, J. W.; Negron, G.; Quintero, L. *J. Chem. Res. (S)* **1988**, 140. (g) Crich, D.; Davies, J. W. *Tetrahedron* **1989**, *45*, 5641. (h) Orlinski, R.; Stankiewicz, T. *Tetrahedron Lett.* **1988**, *29*, 1601. (i) Tarzia, G.; Balsamini, C.; Spadoni, G.; Durante, E. *Synthesis* **1988**, 514.

Scheme 3

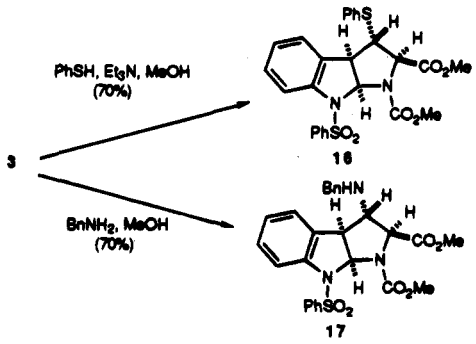
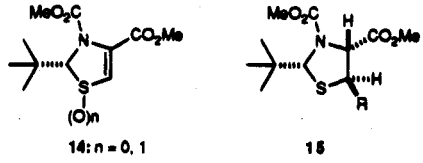


Table 2. Conjugate Addition Reactions

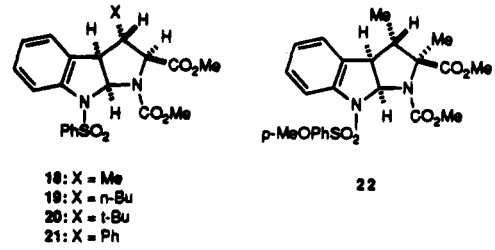
entry	substrate	product	% yield
1	**3**	**16**	70
2	**3**	**17**	70
3	**3**	**18**	79
4	**3**	**19**	60
5	**3**	**20**	70
6	**3**	**21**	65
7	**3**	**27**	56
8	**12**	**22**	78

found that it underwent conjugate addition with higher order cyanocuprates in the presence of BF_3OEt_2 with high diastereoselectivity to give **15** but only in modest yield.[25,26]

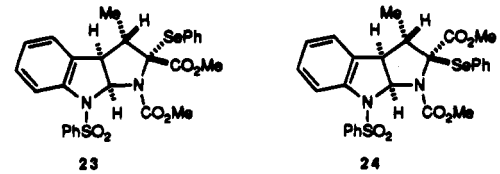


Treatment of **3** with thiophenol and triethylamine in methanol at room temperature smoothly gave **16** as a single diastereomer in 70% isolated yield. Similarly, with benzylamine in methanol at room temperature **3** gave **17** also in 70% yield and as a single diastereomer (Scheme 3). The ^{1}H-NMR spectra of **16** and **17** in $CDCl_3$ were instructive (Table 1, entries 7 and 8). In both compounds the ester methyl groups had δ_H 3.13 which pointed to the *endo*-ester configuration resulting from the usual *exo*-face quenching of the enolate. In **16** the remaining proton at C-3 resonated at δ_H 4.26 as a sharp singlet implying torsion angles of 90° with both H-2 and H-3a. In support of this, H-2 was also a sharp singlet and H-3a a simple doublet by virtue of its coupling to H-8a. This collection of data can only be accommodated by conjugate addition and enolate quenching occurring on the *exo*-surface of the bicyclic system and with the adduct adopting a conformation closely similar to that found in **2**. For comparison purposes the pertinent data on **2** are also presented in Table 1. Similarly in the amine adduct **17** H-2 was a singlet, H-3a a doublet, and the remaining H-3, in which coupling to the amine NH was not observed, a singlet. Unless otherwise stated, similar reasoning is used for assignment of configuration of all adducts throughout this paper with the important spectral data presented in Table 1. Clearly the fused bicyclic system present in **3**, effectively a ramified dehydroproline, provides excellent stereocontrol with nucleophilic attack and resultant enolate quenching, both taking place selectively from the *exo* face to give the overall cis adducts. The effect of the fused bicyclic system in controlling the overall stereochemistry of these additions is best seen by comparison with the addition of thiols to simple *N*-acetyl dehydroproline methyl ester which cleanly results in the anticipated trans-addition product.[26e]

Encouraged by the excellent diastereoselectivities with heteroatom nucleophiles attention was next focused on carbon nucleophiles. With assistance from TMSCl,[27] Lipshutz higher order cuprates[28] performed well and enabled the introduction of the β-Me, β-*n*-butyl, β-*tert*-butyl, and β-phenyl groups as in compounds **18**–**21**in



good yield and excellent diastereoselectivities (Table 2). Treatment of **12** with dilithium dimethylcyanocuprate at −70–0 °C followed by recooling to dry ice/acetone bath temperature and quenching with methyl iodide gave the double α,β-dimethyl adduct **22** in 78% yield and as a single diastereomer. Again, conjugate addition and enolate quenching were found to have occurred from the *exo*-face as confirmed by the chemical shift of the ester group (Table 1, entry 13). Additional confirmation was obtained by NOE experiments in which irradiation of either methyl substituent resulted in enhancement of both H-3a and H-8a. In order to prepare a 3-*endo*-methyl adduct, the 3-*exo*-methyl derivative **18** was treated with LDA followed by reaction with phenylselenyl chloride resulting in the isolation of the two diastereomeric phenylselenides **23** and **24** in 44 and 23% isolated yields, respectively. Evidently, the 3-*exo*-methyl group in the enolate derived from **18** blocks the *exo*-face sufficiently for quenching of the enolate from the concave surface to become competitive. This is the first example of a transformation of either the hexahydropyrrolindole **2** or its tetrahydro derivative **3** in which a measurable yield of a product resulting from reaction on the *endo*-surface was observed. Moreover, while the product of *exo*-face quenching **23** showed a shielded methyl ester (δ_H 3.49), albeit with the shielding moderated by the additional electron-withdrawing phenylselenide group, typical for its *endo*-location, the *endo*-adduct **24** had a very standard chemical shift

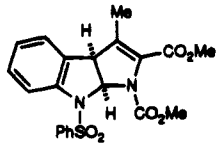


(δ_H 3.79) for the ester group (Table 1, entries 14 and 15). This provides a clear demonstration of the shielding effect encountered by the *endo-esters in this system in general* and nicely reinforces the assignments of configuration discussed above. Treatment of the *endo*-isomer **24** with

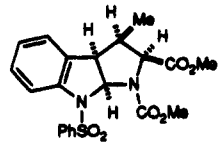
(27) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. (d) Johnson, C. R.; Marren, T. L. *Tetrahedron Lett.* **1987**, *28*, 27. (e) Bergdahl, M.; Linstedt, E. L.; Nilsson, M.; Kozlowski, J. A. *Tetrahedron* **1988**, *44*, 2055.

(28) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. Lipshutz, B. H.; Koermer, M. *Tetrahedron Lett.* **1987**, *28*, 945. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

MMPP in THF at room temperature resulted in the isolation of the α,β-unsaturated ester **25** in 78% yield. Hydrogenation of this substance at atmospheric pressure over palladium hydroxide on charcoal in methanol was sluggish but gave a 70% isolated yield of the 3-*endo*-methyl-2-*endo*-carbomethoxy derivative **26** after 2.5 days at room temperature.

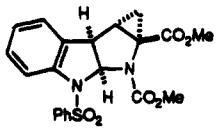


25

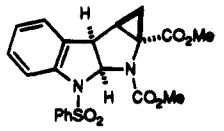


26

Cyclopropanation of **3** was readily achieved through standard sulfur ylide chemistry in DMSO at room temperature. The adduct **27** was isolated in 56% yield, again as a single diastereomer. The fused-cyclopropane dictated an alternative conformation of the hexahydropyrroloindole nucleus and an almost typical chemical shift for the ester Me group (Table 1, entry 18). Intriguingly, despite the nonstandard conformation indicated by the ester chemical shift in **27** (Table 1), H-3a exhibited near zero coupling to H-3endo. Of course, the ester



27



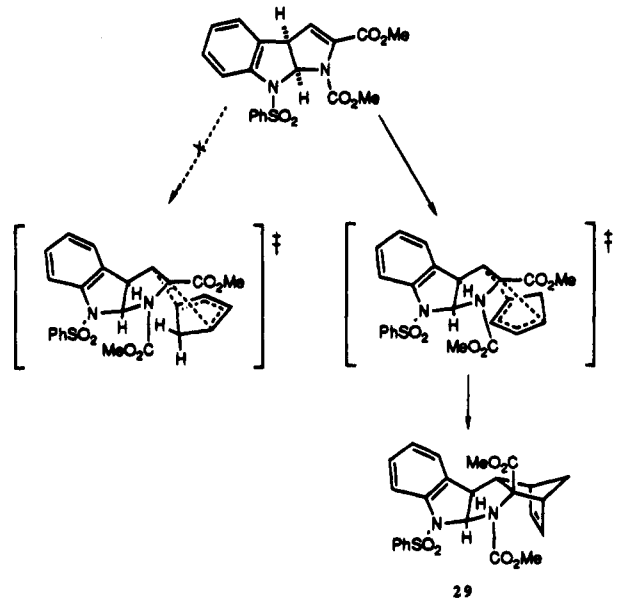
28

chemical shift could also be reconciled with the *endo*-adduct **28** and, consequently, clarification was sought through NOE experiments. Double irradiation of the cyclopropyl methylene hydrogen resonating at δ 1.08, identified with the aid of a $^{1}H-^{13}C$ heteronuclear correlation experiment, resulted in strong enhancement of H-3a and H-8a, clearly demonstrating the relative stereochemistry of the adduct to be as indicated in **27**.

Finally, in our study of **3** we turned to the Diels–Alder reaction. Heating **3** to reflux in dichloromethane with dicyclopentadiene for 24 h gave 71% of a single crystalline adduct **29** resulting from the anticipated reaction on the *exo*-surface of **3** in an *exo*-mode Diels–Alder reaction. The stereochemistry was assigned through the typical shielded ester methyl group (Table 1, entry 19) and a significant NOE between one of the olefinic hydrogens and H-8a. While the *exo*-selectivity of **3** requires no further comment, the very high preference for the *exo*-mode Diels–Alder reaction is most simply explained by invoking unfavorable steric interactions in the transition state leading to the *endo*-mode adduct between the bridgehead hydrogens in **3** and a methylene hydrogen in the diene (Scheme 4). This highly diastereoselective Diels–Alder reaction is to be contrasted to that of cyclopentadiene with dehydroalanine methyl esters whereby the *N*-acetyl derivative is reported to give poor *exo*/*endo* selectivity and, curiously, the *N*-methoxycarbonyl derivative only the *exo*-adduct.[29,30]

With a number of successful and highly diastereoselective conjugate and cycloadditions in hand, attention was turned to bringing about cycloreversion of the

Scheme 4



29

Table 3. Ring Opening Reactions

entry	substrate	conditions	time	product	% yield
1	**2**	100% TFA	2 h	**34**[a]	100
2	**18**	100% TFA	3–4 d	**30**[b]	93
3	**19**	100% TFA	3–4 d	**31**[c]	92
4	**20**	100% TFA	several months	**32**	0[d]
5	**21**	100% TFA	7 d	**33**[e]	92
6	**22**	100% TFA	1 d	**35**[a]	100
7	**26**	100% TFA	1 h	**36**	93
8	**27**	25% TFA in $CDCl_3$	0.5 h	**37**	81
9	**29**	100% TFA	several months		0[d]

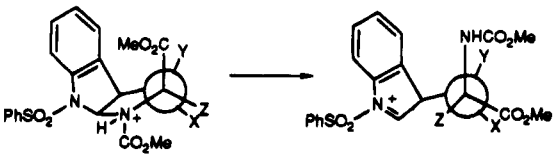
[a] NMR-scale expt only; sample not isolated. [b] A 14/1 mixture of **30/18**. [c] A 13/1 mixture of **31/19**. [d] The substrate was recovered unchanged. [e] A 15/1 mixture of **33/21**.

adducts to the tryptophan nucleus. In accordance with our earlier studies in the α-substituted series we had anticipated that brief treatment of the various β-substituted and α,β-disubstituted hexahydropyrrolindoles with trifluoroacetic acid at room temperature would affect clean and efficient ring opening to the corresponding substituted tryptophan derivatives. We were therefore surprised to discover that, in neat trifluoroacetic acid at ambient temperature, the β-methyl derivative **18** suffered ring opening at a much reduced rate such that a period of between three and four days was necessary to achieve conversion to an apparently equilibrated 14/1 mixture of **30** and starting material **18**. The same was true for the β-*n*-butyl derivative **19** (final ratio **31/19** = 13/1). The β-phenyl derivative **21** required approximately 7 days for essentially complete conversion (final ratio **33/21** = 15/1) while the β-*tert*-butyl derivative **20** was inert to these conditions being unchanged after standing for several months at room temperature in trifluoroacetic acid. In contrast the 3-*endo*-methyl derivative **26** was completely ring opened within 1 h at room temperature and the 2,3-*exo*-dimethyl derivative **22** within 1 day. The yields and times of ring openings of each of the β-substituted and α,β-substituted derivatives studied are collated, along with that of the simple unsubstituted system for comparison purposes, in Table 3. Evidently ring opening is severely retarded by substitution on the *exo*-face at C-3 of the pyrroloindole system and the effect increases with increasing steric bulk of the substituent. Inversion of configuration at C-3, as in **26**, reverses the effect and α,β-disubstitution as in **22** has a moderating effect. These

(29) (a) Horikawa, H.; Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyashi, M. *Tetrahedron Lett.* **1980**, *21*, 4101. (b) Boucher, J. L.; Stella, L. *Tetrahedron* **1985**, *41*, 875. (c) Catievela, C.; Lopez, P.; Mayoral, J. A. *Tetrahedron Asym.* **1990**, *1*, 379.

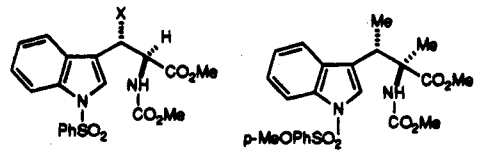
(30) Also see ref 25 for cycloadditions with **14**, $n = 1$.

Scheme 5



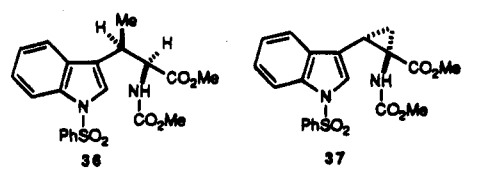
observations are best explained by a mechanism for ring opening involving protonation of the carbamate group (either on nitrogen or oxygen) followed by clockwise rotation about the C2—C3 bond (Scheme 5).

Rotation about the C2—C3 bond is indicated as it best approximates a stretching of the scissile C8a—N1 bond along the tetrahedral angle, whereas rotation about the C3—C3a bond requires a lateral movement of N1 away from the C8a—N1 bond. Clockwise rotation about C2—C3 rotates the ester group away from the face of the aromatic ring whereas counterclockwise rotation would have the effect of forcing the ester group into the concave surface of the molecule. Thus, clockwise rotation about C2—C3 brings the ester group into a gauche relationship with the substituent X at C3 and this conformation is progressively disfavored as the steric bulk of X increases. On the other hand, clockwise rotation about C2—C3 relieves the quasi-eclipsed relationship between the ester and the 3-*endo*-substituent Y: thus opening of the 3-*endo*-methyl derivative **26** is accelerated. Likewise, clockwise rotation relieves the torsional strain present between the C2-*exo*-group Z (usually a hydrogen atom) and the C3-*exo*-group. Hence the inclusion of a methyl group in the C3 *exo* position (**22**) has the effect of countering to some extent that of the 3-*exo*-methyl group. The incomplete conversion of **18**, **19**, and **21** to their ring-opened tautomers **30**, **31**, and **33**, respectively even after periods of several days in TFA suggests that the equilibrium mixture contains



30: X = Me
31: X = n-Bu
32: X = t-Bu
33: X = Ph
34: X = H

35



36

37

a minor amount of the ring-closed tautomer. To test this possibility a pure sample of **30** was eventually obtained after repeated preparative TLC of a mixture with **18**. In $CDCl_3$ this sample showed no tendency to undergo isomerization to **18**, but on standing in pure TFA at room temperature it was converted to a 13/1 mixture of **30** and **18**, indicating that the erythro substitution pattern does indeed favor, under acidic conditions, ring closure to a minor extent. This is evidently a consequence of the same conformational effect that retards the ring opening reaction. The inability to obtain, on a preparative scale, samples of **30**, **31**, and **33** completely free from traces of their ring-closed tautomers is not detrimental to the method as a whole as after desulfonylation (*vide infra*), purification is no longer a problem. In considering the accelerated ring opening of **22** it is interesting to note that, in common with **23** and **24** with which it shares a common substitution pattern, the highly substituted nature of the C2—C3 bond results in a modified conformation as evidenced by the ester chemical shift and the ^3J H-3endo-H-3a coupling (Table 1, entries 13—15). The cyclopentadienyl adduct **29** was found, like **20**, to be completely inert to trifluoroacetic acid. This is readily understood in terms of the rigid bicyclic system preventing rotation about the C2—C3 bond required for ring opening. Finally the cyclopropyl derivative **27** was extremely susceptible to ring opening requiring only treatment with a 25% solution of TFA in chloroform (or $CDCl_3$) for a few minutes at room temperature for complete conversion to **37**. As discussed above, ^{1}H-NMR spectroscopy of **27** indicates it to be in an atypical conformation for which the above model is no longer valid. Furthermore, opening of **27** is almost certainly accompanied by the relief of a substantial amount of strain present in the tetracyclic system. Despite the current widespread interest in cyclopropa amino acids, to our knowledge this is the first example of such a derivative of tryptophan.[12,13,31]

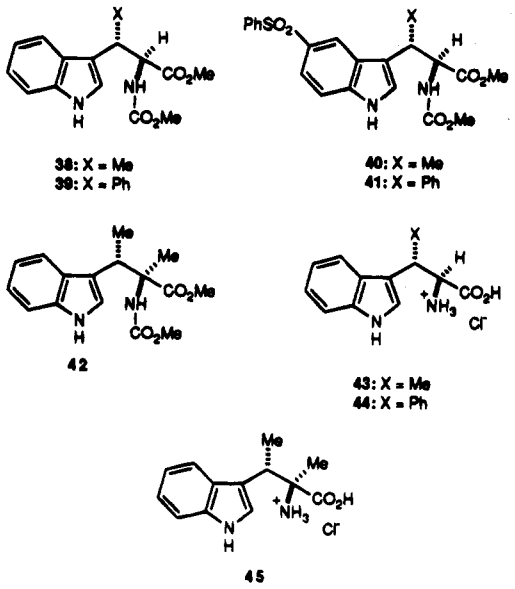
Deprotection of the sulfonamide in the original α-substituted series was routinely accomplished by treatment with sodium in liquid ammonia.[1] In the present series scramlbing of stereochemistry at the α-position, requiring only the presence of a catalytic amount of sodamide or water, was obviously a potential problem with this chemistry. An alternative system was therefore sought and found in the Yonemitsu protocol involving photolysis in the presence of anisole and ascorbic acid as reductants.[32] Thus, photolysis of **30** and **33** through Pyrex in the presence of ascorbic acid and anisole yielded **38** and **39** in 71 and 75% yields, respectively. ^{1}H and ^{13}C NMR spectroscopy indicated the two deprotected compounds to be single diastereomers within the limits of detection, indicating that no epimerization occurred in the deprotection step. The optical purity of **38** and **39** was determined to be >95% by ^{1}H-NMR analysis in the presence of chiral lanthanide shift reagents.[33] In each of these photolytic deprotection reactions we were unable to completely suppress the formation of a minor byproduct that was identified as arising from migration of the sulfonyl group from the indole N-1 position to indole C-5 as in **40** and **41**. Although we did not study this reaction in depth, it presumably arises by a mechanism somewhat analogous to those of the photo-Fries and photo-anilide reactions.[34] In the case of the 4-methoxybenzenesulfonamide **22**, cycloreversion to the tryptophan skeleton and desulfonylation could be achieved in a single step by treatment with methanesulfonic acid resulting in the isolation of **42** in 76% yield. Attempted photolytic deprotection of the cyclopropatryptophan **37** resulted only in extensive degradation, prompting the suggestion that such species in general will be somewhat unstable once the lone pair on the indole nitrogen is free to interact, vinylogously, with the cyclopropane.

(31) An alternative preparation of cyclopropatryptophan was reported recently: Frick, J. A.; Bathe, A.; Klassen, J. B.; Rapoport, H. in *Abstracts of Papers*, 206th American Chemical Society National Meeting, Chicago, IL, Aug 22—27, 1993, ORGN 43.

(32) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.

(33) Fraser, R. R. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, 173.

(34) Stenberg, V. I. in *Organic Photochemistry*; Chapman, O. L., Ed.; Dekker: New York, 1967; Vol. 1, 127.



Complete deprotection of **38** and **39** was achieved by heating to reflux in 6 M HCl, enabling the isolation of **43** and **44** in 93 and 92% yields, respectively.[35] ^{1}H- and ^{13}C-NMR spectroscopy revealed both **43** and **44**, isolated in the form of their amorphous hydrochloride salts, to be single diastereomers, indicating epimerization not to be a problem in this final deprotection step. In a similar manner, the α,β-dimethyl derivative **42** gave **45**, in the form of its hydrochloride salt, as a single diastereomer in 93% yield on heating to reflux in 6 M HCl.

In conclusion, we have established a method for the preparation of enantiomerically and diastereomerically pure *erythro*-β-alkylated tryptophan derivatives from tryptophan itself and have developed a method for deprotection of these substances which does not provoke epimerization. The method may be also extended to provide α,β-dialkylated derivatives of tryptophan and, by inverting the configuration at the β-center, to the *threo*-series.

Experimental Section

All solvents were dried and distilled by standard procedures. Unless otherwise stated all reactions were run under a dry nitrogen atmosphere. THF was distilled, under N_2, immediately prior to use from sodium benzophenone ketyl. ^{1}H- and ^{13}C-NMR spectra were ran in $CDCl_3$ at 300 and 75 MHz, respectively. Unless otherwise stated, IR spectra and specific rotations were recorded in $CHCl_3$ or CH_2Cl_2 solutions.

Dimethyl 2-(Phenylseleno)-8-(phenylsulfonyl)-1,2(*R*),3,3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (6). To a stirred solution of **2** (12.48 g, 30 mmol) in THF (250 mL) at −78 °C was added a solution of 1 M LDA in THF (37.5 mL, 37.5 mmol). After stirring for 30 min at −78 °C a solution of phenylselenyl chloride (7.57 g, 39.5 mmol) in THF (15 mL) was added dropwise. After a further 60 min the reaction mixture was allowed to warm to room temperature and then quenched by addition of saturated NH_4Cl (150 mL). The aqueous phase was further extracted with dichloromethane (2 × 50 mL) and the combined phases dried on $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave 12.00 g (70%) of **6** as a white crystalline solid: mp 161−162 °C (MeOH); $[\alpha]_D$ +86° (*c*, 1.0); δ_H 2.39 (d, 1H, J = 13.4 Hz, H-3endo), 2.50 (dd, 1H, J_{gem} = 13.4, $J_{3exo,3a}$ = 7.2 Hz, H-3exo), 3.15 (s, 3H, CO_2Me), 3.28 (t, 1H, J = 6.5 Hz, H-3a), 3.72 (s, 3H, NCO_2Me), 6.20 (d, 1H, J = 6.2 Hz, H-8a), 6.84 (d, 1H, J = 7.5 Hz, H-4), 7.01 (dt, 1H, J = 0.8, 7.5), 7.21 (t, 1H, J = 7.6 Hz, H-6), 7.30−7.36 (m, 4H), 7.41 (tt, 1H, J = 1.2, 7.5 Hz, H-4′), 7.43−7.48 (m, 2H, 2 × H-3′), 7.56−7.58 (m, 2H), 7.68−7.73 (m, 2H); δ_C 42.23 (C3a), 44.15 (C3), 52.41 (OMe), 52.67 (OMe), 64.40 (C2), 81.26 (C8a), 119.09, 124.47, 125.53, 126.59, 128.37, 128.68, 128.70, 128.79, 129.39, 132.71, 132.83, 138.15, 138.80, 141.86, 154.03 (NCO_2-Me), 171.49 (CO_2Me); ν 1710, 1447, 1375 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O_6SSe$: C, 54.64; H, 4.23; N, 4.90. Found: C, 54.43; H, 4.39; N, 4.97.

Dimethyl 2-(Phenylthio)-8-(phenylsulfonyl)-1,2(*R*),3,3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (7). **2** (0.208 g, 0.5 mmol) was dissolved in THF (7 mL) and cooled to −78 °C before dropwise addition of LDA in THF (1 M, 0.58 mL, 0.58 mmol) and subsequent stirring for 30 min. A solution of PhSSPh (0.12 g, 0.55 mmol) in THF (2.5 mL) was then added slowly to the reaction mixture, after which stirring was maintained at −78 °C for 1 h before the reaction mixture was allowed to come to ambient temperature and then poured into a mixture of water (50 mL) and ether (40 mL). The aqueous phase was separated and further ether extracted (2 × 30 mL), and the combined ether layers were dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on silica (eluent: petroleum ether/ethyl acetate 3/2) gave **7** (0.198 g, 76%) as a white foam which was crystallized from MeOH: mp 147−148 °C; $[\alpha]_D$ +114.6° (*c*, 0.5); δ_H 2.54 (s, 1H, H-3endo), 2.55 (d, 1H, J = 3.8 Hz, H-3exo), 3.14 (m, 1H, H-3a), 3.22 (s, 3H, 2-CO_2Me), 3.79 (s, 3H, NCO_2-Me), 6.02 (d, 1H, J = 6.3 Hz, H-8a), 6.87 (d, 1H, $J_{6,7}$ = 7.73 Hz, H-7), 7.01 (t, 1H, J = 7.5 Hz, H-5), 7.18−7.24 (m, 1H, H-6), 7.30−7.50 (m, 7H), 7.55−7.63 (m, 4H); δ_C 42.36, 43.45, 52.45, 52.65, 75.43, 81.85 (C8a), 118.88, 124.08, 125.43, 126.96, 128.62, 128.80, 128.92, 129.75, 131.24, 132.85, 133.54, 137.53, 138.94, 141.82, 153.61 (NCO_2Me), 170.40 (CO_2Me); ν 1725, 1605 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O_6S_2$: C, 59.53; H, 4.61, N, 5.34. Found: C, 59.40; H, 4.53, N, 5.33.

Dimethyl 8-(Phenylsulfonyl)-1,3a(*R*),8,8a(*S*)-tetrahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (3). Preparation from 6. To a stirred solution of **6** (2.00 g, 3.5 mmol) at room temperature in dry THF (100 mL) was added portionwise MMPP (3.46 g, 7.0 mmol). The solution was stirred for 3 h at that temperature after which the yellow coloration of diphenyl diselenide[36] was completely discharged. The reaction mixture was then poured into $CHCl_3$ (500 mL) and washed sequentially with saturated aqueous $NaHCO_3$ (4 × 200 mL) and water (5 × 250 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give pure **3** (1.435 g, 99%) as a white foam: $[\alpha]_D$ +211° (*c*, 1); δ_H 3.76 (s, 3H, CO_2Me), 3.80 (s, 3H, CO_2Me), 4.56 (dd, 1H, $J_{3a,3}$ = 2.0, $J_{3a,8a}$ = 7.5 Hz, H-3a), 5.94 (d, 1H, J = 2 Hz, H-3), 6.54 (d, 1H, J = 7.5 Hz, H-8a), 7.01 (dt, 1H, J = 0.9, 7.5 Hz, H-5), 7.14 (d, 1H, J = 7.4 Hz, H-4), 7.22 (dt, 1H, J = 1.3, 7.8 Hz, H-6), 7.44−7.52 (m, 2H, 2 × H-3′), 7.57 (tt, 1H, J = 2.2, 7.5 Hz, H-4′), 7.65 (d, 1H, J = 8.2 Hz, H-4), 7.97−8.01 (m, 2H, 2 × H-2′); δ_C 49.56 (C3a), 51.98 (OMe), 53.31 (OMe), 82.21 (C8a), 115.24, 122.95, 124.09, 124.61, 127.44, 128.24, 128.68, 128.91, 133.10, 136.43, 138.40, 141.18, 154.49 (NCO_2Me), 161.69 (CO_2Me); ν 1729, 1443, 1327 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_2O_6S$: C, 57.96; H, 4.38; N, 6.76. Found: C, 57.42; H, 4.62; N, 6.31. No further purification of **3**, which has defied all our attempts at crystallization, was normally required; however, if needs be, it can eluted from silica gel 3:1 hexane/ethyl acetate with no degradation.

Preparation of 3 from 7: Isolation of the 2-Methoxyhexahydropyrrolindole 8. To a stirred solution of **7** (0.1102 g, 0.21 mmol) in MeOH (7 mL) and THF (1 mL) at 0 °C was added MMPP (80%, 0.130 g, 0.21 mmol). The reaction mixture was allowed to warm gradually to room temperature and stirred overnight before it was poured into $CHCl_3$ (50 mL) and washed with $NaHCO_3$ solution (4 × 50 mL) and water (2 × 50 mL), dried ($MgSO_4$), and evaporated to dryness. Chromatography on silica gel (eluent: petroleum ether/ethyl acetate 2/1) gave **3** (63 mg, 72%). Further elution gave an impure sample

(35) Deprotection with BBr_3 as recommended by Phillips for related compounds was attempted but resulted only in complex reaction mixtures: Dua, R. K.; Phillips, R. S. *Tetrahedron Lett.* **1992**, *32*, 29. We thank Professor Phillips for the provision of an experimental part for this protocol.

(36) Diphenyl diselenide, resulting from disproportionation of phenylselenenic acid, is a standard byproduct of selenoxide eliminations. See: (a) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1046. (b) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250 and references therein.

of **8** in admixture with **3**. Complete purification of **8** from this mixture chromatographically was not successful. However a pure sample of **8** was obtained by treatment of the mixture with benzylamine, as described below in the preparation of **17**, followed by chromatographic separation. The adduct **8** was characterized by δ_H 2.33 (dd, 1H, J = 1.6, 13.1 Hz, H-3endo), 2.56 (dd, 1H, J = 8.2, 13.1 Hz, H-3exo), 2.98 (s, 3H, CO_2Me), 3.44 (t, 1H, J = 7.2 Hz, H-3a), 3.76 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.30 (d, 1H, J = 6.8 Hz, H-8a), 6.99 (d, 1H, J = 7.6 Hz), 7.11 (td, 1H, J = 7.5, 1.0 Hz), 7.23–7.30 (m, 1H), 7.36 (t, 2H, J = 7.4 Hz, 2 × H-3′), 7.48–7.53 (m, 1H), 7.60–7.68 (m, 3H).

Dimethyl 8-[(4-Methoxyphenyl)sulfonyl]-1,2(*S*),3,3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (11). The hexahydropyrroloindole **10** (5.79 g, 21 mmol) and DMAP (0.150 g) were dissolved in pyridine (100 mL) and after cooling to 0 °C were treated with *p*-methoxybenzenesulfonyl chloride (8.715 g, 42 mmol). The reaction mixture was allowed to come to ambient temperature and stirred for 16 h before it was poured into water (800 mL) and extracted with dichloromethane (2 × 150 mL). The extracts were washed with 10% HCl (250 mL) and then with saturated sodium hydrogen carbonate solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Crystallization of the residue from ethanol gave **11** (6.23 g, 67%) as a white crystalline solid with mp 103–105 °C; $[\alpha]_D$ +100.6° (*c* 2.1); δ_H 2.45 (ddd, 1H, $J_{2,3exo}$ = 8.7, J_{gem} = 13.0, $J_{3exo,3a}$ = 6.7 Hz, H-3exo), 2.58 (d, 1H, J_{gem} = 13.0 Hz, H-3endo), 3.16 (s, 3H, 2-CO_2Me), 3.64 (t, 1H, $J_{3exo,3a} = J_{3a,8a}$ = 6.7 Hz, H-3a), 3.70 (s, 3H, ArOMe), 3.82 (s, 3H, NCO_2Me), 4.60 (d, 1H, $J_{2,3exo}$ = 8.7 Hz, H-2), 6.26 (d, 1H, $J_{3a,8a}$ = 6.7 Hz, H-8a), 6.85 (d, 2H, J = 7.7 Hz, 2 × H-3′), 7.05 (m, 2H, H-4, H-6), 7.23 (m, 1H, H-5), 7.50 (d, 1H, J = 8.05 Hz, H-7), 7.67 (d, 2H, J = 7.7 Hz, 2 × H-2′); δ_C 33.49 (C3), 45.40 (C3a), 51.63 (CO_2Me), 55.41 (CO_2Me), 58.83 (C2), 80.11 (C8a), 113.93 (C3′), 118.45, 124.16, 125.01, 128.55, 128.82 (C2′), 131.19, 133.19, 142.65, 154.57 (NCO_2Me), 163.03 (C4′), 171.08 (CO_2Me); ν 1714 cm^{-1}; *m/z* 446 ($M^{+\bullet}$), 275 ($M^+ - MeOC_6H_4SO_2$), 216, 171, 130. Anal. Calcd for $C_{21}H_{22}N_2O_7S$: C, 56.49; H, 4.97; N, 6.27. Found: C, 56.4; H, 5.0; N, 6.3.

Dimethyl 8-[(4-Methoxyphenyl)sulfonyl]-1,3a(*R*)-8,8a(*S*)-tetrahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (12) and Dimethyl 8-[(4-Methoxyphenyl)sulfonyl]-2-(phenylseleno)-1,2(*R*),3,3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate. The 2-phenylselenide derivative of **11** was prepared from **11** analogously to the preparation of **6** from **2**. It was isolated, after chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) as an off-white foam (63%) which could be crystallized from methanol: mp 100–101 °C; $[\alpha]_D$ +90.4° (*c* 2.35); δ_H 2.37 (d, 1H, J = 12.8 Hz, H-3exo), 2.47 (dd, 1H, J_{gem} = 12.8, $J_{3endo,3a}$ = 6.8 Hz, H-3endo), 3.12 (s, 3H, CO_2Me), 3.20 (t, 1H, J = 6.3 Hz, H-3a), 3.74 (s, 3H, ArOMe), 3.80 (s, 3H, NCO_2Me), 6.12 (d, 1H, J = 6.1 Hz, H-8a), 6.74 (td, 2H, J = 2, 9 Hz, 2 × H-3′), 6.83 (d, 1H, J = 7.5 Hz, H-4), 7.00 (dt, 1H, J = 0.8, 7.5 Hz, H-5), 7.19 (t, 1H, J = 7.6 Hz, H-6′), 7.27–7.34 (m, 2H), 7.36–7.49 (m, 4H), 7.67–7.71 (m, 2H, 2 × H-2′); δ_C 42.17 (C3a), 44.10 (C3), 52.43 (OMe), 52.82 (OMe), 55.45 (OMe), 64.27 (C2), 81.30 (C8a), 113.86 (C3′), 119.46, 124.46, 125.62, 128.35, 128.67, 128.84, 129,37, 129.93, 132.98, 138.13, 141.97, 154.12 (NCO_2Me), 162.97 (C4′), 171.57 (CO_2Me); ν 1726, 1708, 1596, 1357, 1166 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_7SSe$: C, 53.91; H, 4.36; N, 4.66. Found: C, 53.56; H, 4.28; N, 4.44. **12** was prepared from the phenylselenide analogously to **3** from **6**. It was isolated after chromatography on silica gel (eluent: hexane/ethyl acetate 3/10 as a white foam (87%) which could be crystallized from ethanol: mp 163–164 °C; $[\alpha]_D$ +232 (*c* 1.36); δ_H 3.75 (s, 3H, OMe), 3.80 (s, 6H, 2 × CO_2Me), 4.52 (dd, 1H, $J_{3a,3}$ = 2.1, $J_{3a,8a}$ = 7.5 Hz, H-3a), 5.88 (d, 1H, J = 2.1 Hz, H-3), 6.51 (d, 1H, J = 7.5 Hz, H-8a), 6.90 (td, 2H, J = 2.1, 9.0 Hz, 2 × H-3′), 6.97 (dt, 1H, J = 0.9, 7.5 Hz, H-5), 7.08–7.12 (m, 1H, H-4), 7.14–7.22 (m, 1H, H-6), 7.61 (d, 1H, J = 8.2 Hz, H-7), 7.87 (td, 2H, J = 2.1, 9.0 Hz, 2 × H-2′); δ_C 49.56 (C3a), 51.99 (OMe), 53.34 (OMe), 55.49 (OMe), 82.27 (C8a), 114.22 (C3′), 115.32, 122.96, 123.99, 124.58, 128.27, 128.67, 129.73, 129.98, 136.54, 141.42, 154.57 (NCO_2Me), 161.80 (CO_2Me), 163.51 (C4′); ν 1730, 1596, 1375, 1325 cm^{-1}; ms 444 ($M^{+\bullet}$, 21%). Anal. Calcd for $C_{21}H_{20}N_2O_7S$: C, 56.75; H, 4.53; N, 6.30. Found: C, 56.83; H, 4.56; N, 6.15.

Dimethyl 8-(Phenylsulfonyl)-3-(phenylthio)-1,2(*R*),3-(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (16). A solution of **3** (0.414 g, 1 mmol), thiophenol (0.113 mL, 1.1 mmol), and a catalytic quantity of Et_3N were stirred in MeOH (20 mL) at room temperature for 24 h, diluted with $CHCl_3$ (30 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica gel (eluent hexane/ethyl acetate 3/1) gave **16** (0.368 g, 70%) as a white foam: $[\alpha]_D$ +7.4° (*c* 1), δ_H 3.13 (s, 3H, CO_2Me), 3.61 (s, 3H, NCO_2Me), 3.62 (d, 1H, $J_{3a,8a}$ = 6.4 Hz, H-3a), 4.26 (s, 1H, H-3), 4.61 (s, 1H, H-2), 6.28 (d, 1H, J = 6.4 Hz, H-8a), 6.99–7.07 (m, 2H), 7.18–7.25 (m, 1H), 7.31–7.41 (m, 5H), 7.43–7.51 (m, 4H), 7.69–7.74 (m, 2H, 2 × H-2′); δ_C 52.06 (C3a), 52.76 (OMe), 53.15 (OMe), 65.19, 79.71 (C8a), 118.44, 124.49, 125.11, 126.70, 128.35, 128.85, 129.38, 129.45, 131.02, 132.43, 132.77, 139.80, 142.55, 154.88 (NCO_2Me), 169.45 (CO_2Me); ν 1714, 1448, 1386, 1170 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O_6S_2$: C, 59.53; H, 4.61; N, 5.34. Found: C, 59.29; H, 4.74; N, 5.04.

Dimethyl 3-(Benzylamino)-8-(phenylsulfonyl)-1,2(*R*),3-(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (17). This substance was prepared analogously to **16** except that benzylamine was used as nucleophile in place of thiophenol. It was isolated as a glass in 70% yield after chromatography on silica gel, eluting with 3/1 hexane/ethyl acetate: $[\alpha]_D$ +12.7° (*c* 1); δ_H 3.14 (s, 3H, CO_2Me), 3.54 (d, 1H, J = 6.5 Hz, H-3a), 3.61 (s, 3H, CO_2Me), 3.85 (s, 1H, H-3), 3.86 (d, 1H, J = 13.3 Hz, 1 × CH_2Ph), 3.93 (d, 1H, J = 13.3 Hz, 1 × CH_2Ph), 4.58 (s, 1H, H-2), 6.42 (d, 1H, J = 6.5 Hz, H-8a), 6.95 (d, 1H, J = 7.5 Hz), 7.00 (dt, 1H, J = 1, 7.2 Hz), 7.18–7.52 (m, 10H), 7.72–7.77 (m, 2H, 2 × H-2′); δ_C 51.66 (CH_2Ph), 51.80, 52.60, 52.68, 65.16, 65.45, 79.69 (C8a), 118.30, 124.63, 124.91, 126.69, 127.43, 128.19, 128.61, 128.83, 129.08, 130.84, 132.66, 139.11, 140.09, 142.69, 155.21 (NCO_2Me), 169.75 (CO_2Me); ν 1711, 1448, 1387, 1170 cm^{-1}. Anal. Calcd for $C_{27}H_{27}N_3O_6S$: C, 62.17; H, 5.22; N, 8.06; S, 6.14. Found: C, 61.64; H, 5.34; N, 7.69; S, 6.27.

Preparation of Dimethyl 3-*n*-Butyl-8-(phenylsulfonyl)-1,2(*S*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (19): General protocol for Cuprate Addition to 3 and 12. A solution of dilithium 2-thienyl-*n*-butylcuprate was prepared by dropwise addition of a solution of *n*-butyllithium in hexanes (1.6 M, 1.68 mL, 2.7 mmol) to a stirred solution of lithium 2-thienylcuprate in Et_2O (0.25 M, 12 mL, 3 mmol) at −70 °C under Ar before warming to −55 °C and then recooling to −70 °C. To this solution was added TMSCl (0.164 mL, 0.9 mmol) and then, dropwise, a solution of **3** (0.248 g, 0.6 mmol) in THF (2 mL). The reaction mixture was allowed to come to room temperature over 4 h and then quenched by addition of saturated aqueous NH_4Cl (3 × 30 mL), and the combined phases were dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel (eluent: hexanes/ethyl acetate 3/1) gave **19** (0.170 g, 60%) as a white crystalline solid: mp 102–103 °C (EtOH); $[\alpha]_D$ +45° (*c* 1); δ_H 0.93 (t, 3H, J = 7.2 Hz, CH_3CH_2), 1.37–1.52 (m, 6H, $Me(CH_2)_3$), 2.73 (t, 1H, J = 7.0 Hz, H-3), 3.15 (s, 3H, CO_2Me), 3.43 (d, 1H, $J_{3a,8a}$ = 6.5 Hz, H-3a), 3.56 (s, 3H, CO_2Me), 4.33 (s, 1H, H-2), 6.30 (d, 1H, $J_{3a,8a}$ = 6.5 Hz, H-8a), 7.00–7.05 (m, 2H), 7.14–7.23 (m, 1H), 7.36–7.44 (m, 3H), 7.50 (tt, 1H, J = 7.4, 1.3 Hz, H-4′), 7.75–7.81 (m, 2H, 2 × H-2′); δ_C 13.81 ($MeCH_2$), 22.37 (CH_2), 29.54 (CH_2), 34.28 (CH_2), 47.39 (C3a), 51.30, 51.84, 52.62, 64.40 (C2), 79.43 (C8a), 118.04, 124.38, 124.89, 126.65, 128.82, 128.96, 132.63, 132.78, 140.46, 142.51, 155.07, 171.09; ν 1711, 1603, 1448, 1388, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97, N, 5.93; S, 6.78. Found: C, 60.85; H, 5.89, N, 5.93; S, 6.66.

Dimethyl 3-Methyl-8-(phenylsulfonyl)-1,2(*S*),3(*S*),3a-(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (18). This substance was prepared in 79% yield according to the general procedure using methyllithium in place of butyllithium. It was a white crystalline solid: mp 160–161 °C (EtOH); $[\alpha]_D$ +68° (*c* 1); δ_H 1.21 (d, 3H, J = 7.2 Hz, 3-Me), 2.91 (q, 1H, J = 7.2 Hz, H-3), 3.14 (s, 1H, CO_2Me), 3.32 (d, 1H, J = 6.7 Hz, H-3a), 3.57 (s, 3H, CO_2Me), 4.22 (s, 1H, H-2), 6.33 (d, 1H, J = 6.4 Hz, H-8a), 6.99–7.03 (m, 2H), 7.16–7.21 (m, 1H), 7.35–7.43 (m, 3H), 7.48 (tt, 1H, J = 9.5, 2.1 Hz, H-4′), 7.75–7.78 (m, 2H, 2 × H-2′); δ_C 20.65 (3-Me),

41.64 (C3a), 51.80 (CO_2Me), 52.62 (CO_2Me), 52.78 (C3), 66.02 (C2), 79.34 (C8a), 118.06, 124.40, 124.91, 126.55, 128.82, 128.85, 132.47, 132.66, 140.00, 142.35, 155.07 (NCO_2Me), 170.77 (CO_2Me); ν 1710, 1448, 1387, 1168 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_6S$: C, 58.59; H, 5.15, N, 6.51; S, 7.45. Found: C, 58.71; H, 5.12, N, 6.51; S, 7.32.

Dimethyl 3-*tert*-Butyl-8-(phenylsulfonyl)-1,2(*S*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (20). This substance was prepared in 65% yield according to the general procedure using *tert*-butyllithium in place of butyllithium. It was a white crystalline solid: mp 125–126 °C (EtOH); $[\alpha]_D$ +58° (*c* 1); δ_H 0.98 (s, 9H, $(CH_3)_3C$), 2.45 (s, 1H, H-3), 3.22 (s, 3H, CO_2Me), 3.55 (s, 3H, CO_2Me), 3.59 (d, 1H, J = 6.8 Hz, H-3a), 4.51 (s, 1H, H-2), 6.23 (d, 1H, J = 6.8 Hz, H-8a), 6.96–7.07 (m, 2H), 7.15–7.23 (m, 1H), 7.38–7.45 (m, 3H), 7.51 (tt, 1H, J = 7.4, 1.3 Hz, H-4′), 7.77–7.83 (m, 2H, 2 × H-2′); δ_C 27.44 (CMe_3), 32.91, 47.48, 51.97 (CO_2Me), 52.68 (CO_2Me), 59.76 (C3), 61.40 (C2), 80.35 (C8a), 117.80, 124.09, 124.92, 126.64, 128.63, 128.89, 132.64, 133.94, 142.15, 144.60, 151.20 (NCO_2Me), 171.87 (CO_2Me); ν 1709, 1448, 1387, 1169 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97, N, 5.93; S, 6.78. Found: C, 60.72; H, 5.99, N, 5.80; S, 6.72.

Dimethyl 3-Phenyl-8-(phenylsulfonyl)-1,2(*S*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (21). This substance was prepared in 70% yield according to the general procedure using phenyllithium in place of butyllithium. It was a white crystalline solid: mp 89–90 °C (EtOH); $[\alpha]_D$ +24° (*c* 1); δ_H 3.24 (s, 3H, CO_2Me), 3.66 (s, 3H, CO_2Me), 3.80 (d, 1H, J = 6.5 Hz, H-3a), 4.00 (s, 1H, H-3), 4.64 (s, 1H, H-2), 6.51 (d, 1H, J = 6.4 Hz, H-8a), 7.05–7.21 (m, 4H), 7.21–7.44 (m, 6H), 7.45–7.53 (m, 2H), 7.76–7.82 (m, 2H, 2 × H-2′); δ_C 52.07 (CO_2Me), 52.59, 52.79 (CO_2Me), 53.02, 66.01 (C2), 80.11 (C8), 118.09, 124.45, 125.08, 126.29, 126.64, 127.63, 128.88, 129.09, 129.29, 132.31, 132.74, 139.91, 141.65, 142.32, 154.57 (NCO_2Me), 170.42 (CO_2Me); ν 1714, 1448, 1385, 1168 cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O_6S$: C, 63.40; H, 4.91, N, 5.69; S, 6.51. Found: C, 63.15; H, 5.12, N, 5.47; S, 6.60.

Dimethyl 2,3-Dimethyl-8-[(4-methoxyphenyl)sulfonyl)]-1,2(*S*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (22). Into a suspension of CuCN (41.1 mg, 0.459 mmol) in THF (1 mL) was added dropwise methyllithium in Et_2O (1.4 M, 0.65 mL, 0.91 mmol) under Ar at −70 °C. The solution was allowed to come to −10 °C over 1 h then recooled to −70 °C before **12** (68 mg, 0.153 mmol) in THF (0.5 mL) and TMSCl (25 μL, 0.2 mmol) were added simultaneously. The reaction mixture was allowed to come to room temperature and then cooled to −70 °C again before methyl iodide (0.297 mL, 0.918 mmol) was added. After warming to 0 °C over 1 h the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). After separation of the organic layer the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave **22** as a white crystalline solid (56.3 mg, 78%): mp 153–154 °C (MeOH); $[\alpha]_D$ +58.8° (*c* 0.95); δ_H 1.10 (d, 3H, J = 7.2 Hz, 3-Me), 1.53 (s, 3H, 2-Me), 2.56–2.65 (m, 1H, H-3), 3.10 (dd, 1H, $J_{3,3a}$ = 4, $J_{3a,8a}$ = 6.5 Hz, H-3a), 3.25 (s, 3H, CO_2Me), 3.71 (s, 3H, ArOMe), 3.81 (s, 3H, NCO_2Me), 6.24 (d, 1H, J = 6.5 Hz, H-8a), 6.86 (dd, 2H, J = 2.1, 9.0 Hz, 2 × H-3′), 6.97–7.04 (m, 2H, H-4,5), 7.17–7.24 (m, 1H, H-6), 7.50 (d, 1H, J = 8.1 Hz, H-7), 7.72 (dd, 2H, J = 2.1, 9.0 Hz, 2 × H-2′); δ_c 14.91 (Me), 19.76 (Me), 45.83, 50.88, 52.02 (OMe), 52.12 (OMe), 55.45 (OMe), 69.80 (C2), 81.22 (C8a), 114.01, 117.76, 124.22, 124.42, 128.63, 129.16, 130.98, 132.13, 142.44, 154,69 (NCO_2Me), 163.13 (C4′), 173.83 (CO_2Me); ν 1715, 1597, 1369, 1265, 1163 cm^{-1}; MS 474 ($M^{+\cdot}$, 15%), 415 (48%), 244 (100%), 303 (60%). Anal. Calcd for $C_{22}H_{26}N_2O_7S$: C, 58.21; H, 5.52; N, 5.90. Found: C, 58.26; H, 5.50; N, 5.80.

Dimethyl 3-Methyl-2-(phenylselenyl)-8-(phenylsulfonyl)-1,2(*R*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (23) and Dimethyl 3-Methyl-2-(phenylselenyl)-8-(phenylsulfonyl)-1,2(*S*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (24). The 3-methyl derivative **18** (2.900 g, 6.74 mmol) was dissolved in THF (50 mL) under Ar and chilled to −70 °C. To this solution was added LDA (1 M in THF, 7.7 mL, 7.7 mmol) and after stirring for 50 min, phenylselenyl chloride (1.677 g, 8.76 mmol) in THF (5 mL) was added. After stirring for a further 5 min at −70 °C the reaction was quenched by addition of a saturated solution of NH_4Cl (50 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography on silica gel (eluent: hexane/ethyl acetate 4/1) gave first the *exo*-phenyl selenide **23** (1.736 g, 44%) followed by the *endo*-isomer **24** (0.907 g, 23%). Compound **23** was a white foam with $[\alpha]_D$ +90.6° (*c* 1.7); δ_H 1.37 (d, 3H, J = 7.2 Hz, 3-Me), 2.62 (t, 1H, J = 7.3 Hz, H-3a), 2.81 (quint., 1H, J = 7.1 Hz, H-3), 3.49 (s, 3H, CO_2Me), 3.81 (s, 3H, NCO_2Me), 5.95 (d, 1H, J = 6.7 Hz, H-8a), 6.90–6.95 (m, 2H), 7.12–7.21 (m, 1H), 7.24–7.36 (m, 3H), 7.38–7.46 (m, 2H), 7.48–7.54 (m, 2H), 7.72–7.77 (m, 2H), 7.83–7.88 (m, 2H); δ_C 15.64 (3-Me), 48.84, 50.30, 53.01 (CO_2Me), 53.03 (CO_2Me), 79.63 (C2), 81.75 (C8a), 116.21, 123.93, 124.01, 127.11, 127.76, 128.75, 128.89, 128.95, 129.27, 130.26, 133.01, 137.87, 138.30, 141.07, 154.58 (NCO_2Me), 170.22 (CO_2Me); ν 1730, 1368 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_6SSe$: C, 55.38; H, 4.48; N, 4.78. Found: C, 55.19; H, 4.40; N, 4.60. The *endo*-isomer **24** had $[\alpha]_D$ −7.5°; δ_H 1.02 (d, 3H, J = 7.0 Hz, 3-Me), 2.25 (m, 1H, H-3), 3.12 (dd, 1H, $J_{3a,3}$ = 10.6, $J_{3a,8a}$ = 7.4 Hz, H-3a), 3.79 (s, 3H, CO_2Me), 3.87 (s, 3H, NCO_2Me), 6.05 (d, 1H, J = 7.4 Hz, H-8a), 6.83–6.92 (m, 2H), 7.10–7.17 (m, 1H), 7.25–7.45 (m, 5H), 7.46–7.55 (m, 2H), 7.65–7.70 (m, 2H), 7.96–8.02 (m, 2H); δ_C 11.40 (3Me), 49.54, 50.88, 52.87 (OMe), 53.05 (OMe), 79.41 (C2), 82.87 (C8a), 115.25, 122.95, 123.30, 126.45, 127.97, 128.73, 128.81, 129.13, 129.30, 130.03, 133.09, 137.25, 138.71, 140.55, 155.78 (NCO_2Me), 170.47 (CO_2Me); ν 1737, 1370, 1177 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_6SSe$: C, 55.38; H, 4.48; N, 4.78. Found: C, 55.59; H, 4.52; N, 4.65.

Dimethyl 3-Methyl-8-(phenylsulfonyl)-1,3a(*R*),8,8a(*S*)-tetrahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (25). The selenide **24** (0.253 g, 0.432 mmol) was dissolved in THF (7 mL) and treated at 10 °C with MMPP (0.320 g, 0.648 mmol). The reaction was stirred at room temperature for 4 h and then poured into $CHCl_3$ (30 mL) and washed with $NaHCO_3$ (3 × 30 mL) and water (3 × 30 mL). The organic layer was dried ($MgSO_4$) and the solvents removed under vacuum to provide a residue which after silica gel chromatography (eluent: hexane/ethyl acetate 3/1) yielded **25** as a white foam (0.1443 g, 78%) which could be crystallized from MeOH and which had mp 162–163 °C; $[\alpha]_D$ +208.7° (*c* 1.21); δ_H 1.87 (d, 3H, J = 7.3 Hz, 3-Me), 3.79 (s, 3H, CO_2Me), 3.82 (s, 3H, CO_2Me), 4.30 (d, 1H, J = 7.3 Hz, H-3a), 6.45 (d, 1H, J = 7.3 Hz, H-8a), 6.99 (td, 1H, J = 7.5, 0.8 Hz, H-5), 7.16 (d, 1H, J = 8.0 Hz, H-4), 7.21–7.28 (m, 1H, H-6), 7.45–7.52 (m, 2H, 2 × H-3′), 7.57 (tt, 1H, J = 1.3, 7.2 Hz, H-4′), 7.67 (d, 1H, J = 8.2 Hz, H-7), 8.02–8.08 (m, 2H, 2 × H-2′); δ_C 11.26 (3-Me), 51.94 (C3a), 53.55 (OMe), 53.59 (OMe), 81.04 (C8a), 114.11, 123.47, 125.05, 126.58, 127.78, 128.70, 129.04, 129.07, 132.51, 133.30, 141.15, 154.79 (NCO_2Me), 162.80 (CO_2Me). HRMS calcd for $C_{21}H_{20}N_2O_6S$: 428.1036, found 428.1042 ($M^{+\cdot}$).

Dimethyl 3-Methyl-8-(phenylsulfonyl)-1,2(*S*),3(*R*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (26). The α,β-unsaturated ester **25** (80 mg, 0.187 mmol) was dissolved in MeOH (1.5 mL), and $Pd(OH)_2$ on charcoal (15 mg) was added. The reaction flask was flushed with H_2 and the reaction mixture stirred vigorously for 2.5 days at room temperature and under pressure H_2 before the reaction mixture was diluted with MeOH (5 mL), filtered on Celite, and the solvent stripped off. Chromatography on silica gel (eluent: hexane/ethyl acetate 3/10 gave **26** as a white solid (56 mg, 70%): mp 163–164 °C; $[\alpha]_D$ +74.4° (*c* 2.1); δ_H 1.30 (d, 3H, J = 7.4 Hz, 3-Me), 2.80 (sextet, 1H, J = 7.4 Hz, H-3), 3.18 (s, 3H, CO_2Me), 3.62 (s, 3H, NCO_2Me), 3.61–3.65 (m, 1H, H-3a), 4.42 (d, 1H, J = 8.6 Hz, H-2), 6.31 (d, 1H, J = 7.7 Hz, H-8a), 6.98 (t, 1H, J = 7.5 Hz, H-5), 7.07 (d, 1H, J = 7.5 Hz, H-4), 7.23 (t, 1H, J = 7.9 Hz, H-6), 7.32–7.39 (m, 2H, 2 × H-3′), 7.45–7.55 (m, 2H, H-4′, H-7), 7.67–7.72 (m, 2H, 2 × H-2′); δ_C 12.32 (3Me), 38.59 (C3), 49.57 (C3a), 51.37 (OMe), 52.60 (OMe), 62.56 (C2), 79.59 (C8a), 118.44, 124.18, 125.56, 128.48, 128.77, 128.84, 130.57, 132.64, 145.63, 154.42 (NCO_2Me), 169.80 (CO_2-

Me); ν 1728, 1707, 1390, 1372, 1170 cm^{-1}. HRMS calcd for $C_{21}H_{22}N_2O_6S$: 430.1198, found 430.1209 ($M^{+\cdot}$).

Dimethyl 2,3-Methano-8-(phenylsulfonyl)-1,2(*S*),3(*S*),3a(*R*),8,8a(*S*)-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate (27). To a mixture of 80% NaH in mineral oil (45 mg, 1.5 mmol) and trimethylsulfoxonium iodide (0.330 g, 1.5 mmol) under Ar at room temperature was added dry DMSO (3 mL). After stirring for 2.5 h a solution of **3** (0.240 g, 0.58 mmol) was added dropwise and stirring continued for a further 5 h at room temperature. The reaction mixture was then poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine and dried on $MgSO_4$. Chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave **27** as a colorless foam (138 mg, 56%): $[\alpha]_D$ +122° (*c* 1); δ_H 1.08 (t, 1H, *J* = 4.2 Hz, 1 × cyclopropyl C*H*$_2$), 2.02–2.15 (m, 2H, 1 × cyclopropyl C*H*$_2$, H-3), 3.67 (d, 1H, *J* = 7.1 Hz, H-3a), 3.70 (s, 3H, CO_2*Me*), 3.80 (CO_2*Me*), 6.15 (d, 1H, *J* = 7.1 Hz, H-8a), 7.04 (dt, 1H, *J* = 1.0, 7.5 Hz), 7.15 (d, 1H, *J* = 7.5 Hz), 7.28 (dt, 1H, *J* = 1.4, 7.4 Hz, H-6), 7.42–7.49 (m, 2H, 2 × H-3′), 7.54 (tt, 1H, *J* = 1.4, 7.4 Hz, H-4′), 7.66 (d, 1H, *J* = 8.2 Hz, H-7), 7.93–7.99 (m, 2H, 2 × H-2′); δ_C 27.60 (*C*H$_2$), 37.26 (C3), 48.02 (C2), 48.35 (C3a), 52.57 (CO_2*Me*), 53.28 (CO_2*Me*), 86.07 (C8a), 115.48, 124.25, 124.31, 127.53, 128.91, 129.10, 130.14, 133.13, 137.76, 141.30, 156.29 (N*C*O$_2$Me), 170.49 (*C*O$_2$Me); ν 1718, 1602, 1447 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_6S$: C, 58.87; H, 4.71, N, 6.54; S, 7.48. Found: C, 58.78; H, 4.76, N, 6.48; S, 7.38.

Diels–Alder Adduct 29. The substrate **3** (0.122 g, 0.295 mmol) and cyclopentadiene (0.195 g, 2.95 mmol) were dissolved in CH_2Cl_2 (3 mL) and heated to reflux for 24 h, after which the volatiles were then removed under vacuum. The residue was washed with methanol–ether (1:1, 2 × 1 mL) to leave **29** as a white crystalline solid (0.100 g, 71%) with mp 225–6 °C (2-propanol); $[\alpha]_D$ = +118° (*c* 2.26, $CHCl_3$); δ_H 1.71 (td, 1H, *J* = 1.6, 9.3 Hz, 1 × C*H*$_2$), 1.89 (d, 1H, J_{gem} = 9.3 Hz, 1 × C*H*$_2$), 2.87 (d, 1H, *J* = 3 Hz), 3.02 (m, 1H), 3.06 (d, 1H, *J* = 6.5 Hz, H-3a), 3.24 (s, 3H, CO_2Me), 3.67 (s, 3H, CO_2Me), 3.69 (m, 1H), 5.82 (d, 1H, *J* = 6.5 Hz, H-8a), 6.18 (dd, 1H, *J* = 3.2, 5.7 Hz, =CH), 6.28 (dd, 1H, *J* = 2.8, 5.6 Hz, =CH), 7.00 (d, 1H, *J* = 7.5 Hz, H-4), 7.08 (dt, 1H, *J* = 1.0, 7.3 Hz, H-5), 7.17–7.24 (m, 1H, H-6), 7.30–7.37 (m, 2H, 2 × H-3′), 7.44–7.52 (m, 2H, H-4′, H-7), 7.54–7.60 (m, 2H, 2 × H2′); δ_C 46.61, 47.58, 50.07 (*C*H$_2$), 50.64, 51.86 (CO_2*Me*), 52.36 (CO_2*Me*), 58.81, 77.14, 83.20 (C8a), 119.28, 123.74, 125.65, 126.95, 127.97, 128.62, 132.67, 135.30, 136.30, 138.46, 139.00, 141.12, 154.34 (N*C*O$_2$Me), 173.27 (*C*O$_2$Me); ν 1734, 1700, 1448, 1363, 1048 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03, N, 5.83; S, 6.67. Found: C, 62.12; H, 5.14; N, 5.81; S, 6.90.

***erythro*-β-Phenyl-*N*-(methoxycarbonyl)-1-(phenylsulfonyl)-L-tryptophan Methyl Ester 33. General Protocol for Ring Opening with TFA.** The pyrroloindole **21** (0.940 g, 1.19 mmol) was dissolved in TFA (13 mL) and stirred for 14 days at room temperature with monitoring by ^{1}H-NMR spectroscopy. The TFA was then removed *in vacuo* and the residue taken up in $CHCl_3$ (10 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). After drying ($MgSO_4$), purification by chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave an inseparable 15:1 mixture of **33** and **21** (0.865 g, 92%) as an oil: δ_H 3.40 (s, 3H, CO_2Me), 3.64 (s, 3H, CO_2Me), 4.60 (d, 1H, *J* = 7.8 Hz, H-β), 5.10 (t, 1H, *J* = 8.3 Hz, H-α), 5.43 (d, 1H, *J* = 8.7 Hz, NH), 7.09 (t, 1H, *J* = 7.6 Hz), 7.18–7.30 (m, 6H), 7.41 (d, 2H, *J* = 7.5 Hz, 2 × H-3′), 7.50 (t, 1H, *J* = 7.4 Hz, H-4′), 7.73 (s, 1H, H-2), 7.87 (d, 2H, *J* = 7.5 Hz, 2 × H-2′), 7.98 (d, 1H, *J* = 8.2 Hz, H-7); δ_C 45.65 (Cβ), 52.03 (CO_2*Me*), 52.39 (CO_2*Me*), 57.59 (Cα), 113.66, 119.78, 121.16, 123.30, 123.74, 124.94, 126.62, 127.49, 128.17, 128.52, 129.18, 130.21, 132.77, 133.70, 135.24, 137.91, 156.33 (*C*O$_2$Me), 171.61 (*C*O$_2$Me); ν 3435, 1725, 1507, 1449, 1371 cm^{-1}.

***erythro*-*N*-(Methoxycarbonyl)-β-methyl-1-(phenylsulfonyl)-L-tryptophan Methyl Ester 30.** The tryptophan derivative **30** was prepared from **18** in 93% yield by the standard protocol for ring opening with TFA. The reaction time was 4 days and the product was isolated as an inseparable 14:1 mixture with **18**. It had δ_H 1.37 (d, 3H, *J* = 7.2 Hz, 3-Me), 3.46 (s, 3H, CO_2Me), 3.64 (m, 1H, H-β), 3.69 (s, 3H, CO_2Me), 4.69 (dd, 1H, *J* = 4.0, 8.6 Hz, H-α), 5.25 (d, 1H, *J* = 8.6 Hz, NH), 7.20–7.34 (m, 2H, H-5, H-6), 7.38 (s, 1H, H-2), 7.42 (d, 2H, *J* = 7.8 Hz, 2 × H-3′), 7.52 (tt, 1H, *J* = 1.3, 7.5 Hz, H-4′), 7.61 (d, 1H, *J* = 7.7 Hz, H-4), 7.81–7.86 (m, 2H, 2 × H-2′), 7.97 (d, 1H, *J* = 8.0 Hz, H-7); δ_C 16.50 (β-Me), 33.70 (C-β), 52.02 (CO_2Me), 52.41 (CO_2Me), 57.57 (C-α), 113.74, 119.76, 123.07, 123.34, 125.02, 126.56, 129.21, 129.93, 133.75, 135.19, 138.02, 156.66 (N*C*O$_2$Me), 171.21 (*C*O$_2$Me); ν 3432, 1725, 1512, 1449, 1367 cm^{-1}.

***erythro*-β-*n*-Butyl-*N*-(methoxycarbonyl)-1-(phenylsulfonyl)-L-tryptophan Methyl Ester 31.** The tryptophan derivative **31** was prepared from **19** by the standard protocol for ring opening with TFA. The reaction time was 4 days and the product was isolated in 92% yield as an inseparable 13:1 mixture with **19**. It had δ_H 0.84 (t, 3H, *J* = 7.2 Hz, *Me*(CH$_2$)$_3$), 1.20–1.37 (m, 4H, 2 × CH$_2$), 1.68–1.91 (m, 2H, CH$_2$), 3.48 (s, 3H, CO_2Me), 3.52 (m, 1H, H-β), 3.64 (s, 3H, CO_2Me), 4.73 (dd, 1H, *J* = 3.6, 9.1 Hz, H-α), 5.07 (d, 1H, *J* = 9.1 Hz, NH), 7.20–7.34 (m, 2H, H-5, H-6), 7.36 (s, 1H, H-2), 7.38–7.56 (m, 4H, 2 × H-3′, H-4′, H-4), 7.78–7.84 (m, 2H, 2 × H-2′), 7.98 (d, 1H, *J* = 8.1 Hz, H-7); δ_C 13.94 (*Me*(CH$_2$)$_3$), 22.46 (CH$_2$), 29.52 (CH$_2$), 31.16 (CH$_2$), 39.27 (Cβ), 52.16 (CO_2Me), 52.50 (CO_2Me), 56.78 (Cα), 113.96, 119.70, 123.43, 123.91, 125.12, 126.54, 129.24, 130.53, 132.73, 133.80, 135.38, 137.95, 156.78 (N*C*O$_2$Me), 171.54 (*C*O$_2$Me); ν 3425, 1726, 1511, 1371, 1177 cm^{-1}.

***threo*-*N*-(Methoxycarbonyl)-β-methyl-1-(phenylsulfonyl)-L-tryptophan Methyl Ester 36.** Compound **36** was prepared from **26** by the standard protocol for ring opening with TFA. The reaction time was 1 h and the product isolated by evaporation of the TFA, followed by stirring in $CHCl_3$ with solid $NaHCO_3$ for 5 min and filtration on Celite and basic alumina. It was isolated as a white foam (93%) with $[\alpha]_D$ +31.7° (*c* 1.09); δ_H (50 °C) 1.39 (d, 3H, *J* = 7.1 Hz, β-Me), 3.45–3.67 (m, 7H, 2 × OMe, H-β), 4.64 (dd, 1H, *J* = 5.3, 9.1 Hz, H-α), 5.15 (broad, 1H, NH), 7.20–7.34 (m, 2H, H-5, H-6), 7.40 (s, 1H, H-2), 7.39–7.46 (m, 2H, 2 × H-3′), 7.48–7.56 (m, 2H, H-4′, H-4), 7.80–7.86 (m, 2H, 2 × H-2′), 7.96–7.99 (d, 1H, *J* = 7.6 Hz, H-7); δ_C 15.81 (β-Me), 33.62 (Cβ), 52.18 (OMe), 52.38 (OMe), 58.10 (Cα), 113.72, 119.45, 123.29, 123.33, 123.46, 124.95, 126.66, 129.21, 130.00, 133.87, 135.11, 138.24, 171.74 (*C*O$_2$Me); ν 3428, 1728, 1513, 1369, 1177 cm^{-1}. HRMS calcd for $C_{21}H_{22}N_2O_6S$: 430.1198, found 430.1202 ($M^{+\cdot}$).

***erythro*-α,β-Methano-*N*-(methoxycarbonyl)-1-(phenylsulfonyl)-L-tryptophan Methyl Ester 37.** The cyclopropane **27** (0.530 g, 1.24 mmol) was dissolved in a 3:1 mixture of $CHCl_3$ and TFA (6 mL) and stirred at room temperature for 30 min before workup according to the general protocol for ring opening with TFA. Chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave **37** as a white solid (0.428 g, 81%): mp 136–7 °C (EtOH); $[\alpha]_D$ −16° (*c* 1); δ_H 1.68 (bt, 1H, *J* = 6.0 Hz, 1 × C*H*$_2$), 2.20 (m, 1H), 2.91 (t, 1H, *J* = 8.7 Hz), 3.50 (bs, 3H, CO_2Me), 3.76 (s, 3H, CO_2Me), 4.74 (bs, 1H, NH), 7.22–7.39 (m, 2H, H-5, H-6), 7.40–7.57 (m, 4H), 7.82 (d, 2H, *J* = 7.7 Hz, 2 × H-2′), 7.97 (d, 1H, *J* = 8.0 Hz, H-7); δ_C 22.14 (*C*H$_2$), 23.84 (Cβ), 39.58 (Cα), 52.15 (CO_2Me), 52.66 (CO_2Me), 113.93, 117.58, 119.13, 123.59, 124.27, 125.24, 126.64, 129.25, 130.99, 133.71, 135.35, 138.24, 156.93 (N*C*O$_2$Me), 172.34 (*C*O$_2$Me); ν 3427, 2956, 1730, 1501, 1449, 1374 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_6S$: C, 58.87; H, 4.71, N, 6.54. Found: C, 58.78; H, 4.61, N, 6.41.

***erythro*-*N*-(Methoxycarbonyl)-α,β-dimethyl-1-[(4-methoxyphenyl)sulfonyl]-L-tryptophan Methyl Ester 35.** In an experiment designed to estimate the rate of ring opening of the [(4-methoxyphenyl)sulfonyl]hexahydropyrroloindole **22** in TFA/$CDCl_3$, **22** (15 mg) was dissolved in TFA/$CDCl_3$ (3/1, 0.5 mL) and the progress of the reaction monitored periodically by ^{1}H-NMR. Conversion to **35** was complete after 24 h at room temperature with no trace of **22** remaining. The solvents were removed *in vacuo* and **35** was characterized by δ_H 1.33 (d, 3H, *J* = 7.3 Hz, 3-Me), 1.57 (s, 3H, 2-Me), 3.62 (s, 3H, CO_2Me), 3.71 (q, 1H, *J* = 7.3 Hz, H-3), 3.79 (s, 3H, CO_2Me), 5.36 (bs, 1H, NH), 6.88 (d, 2H, *J* = 9 Hz, H-3′), 7.22–7.34 (m, 2H, H-5,6), 7.42 (s, 1H, H-2), 7.63 (d, 1H, *J* = 7.0 Hz), 7.79 (d, 2H, *J* = 9.0 Hz, 2 × H-2′), 7.96 (d, 1H, *J* = 7.6 Hz); ν 3427, 1726, 1596, 1498 cm^{-1}. No attempt was made to further characterize this compound.

Attempted Closure of 30 to 18 in TFA. A pure sample of the 1-(phenylsulfonyl)tryptophan **30** (10 mg), free of **18** as judged by ^{1}H-NMR at 300 MHz, was obtained by repeated

preparative TLC on silica gel. In $CDCl_3$ solution this sample showed no tendency to revert to **18**. It was dissolved in TFA (0.5 mL) and allowed to stand at room temperature for 3 days, with periodic monitoring by ^{1}H-NMR, after which no further change was observed. The TFA was removed under vacuum. ^{1}H-NMR spectroscopy of the residue in $CDCl_3$ demonstrated the reaction mixture to consist of a 13/1 mixture of **30/18**.

***erythro*-*N*-(Methoxycarbonyl)-β-methyl-L-tryptophan Methyl Ester 38 and the 5-Phenylsulfonyl Derivative 40.** The substrate **30** (0.390 g, 0.91 mmol), ascorbic acid (0.797 g, 4.55 mmol), and anisole (0.986 mL, 9.1 mmol) were dissolved in 80% EtOH (150 mL). The solution was purged with N_2 and then irradiated (Pyrex, 100 W, medium pressure Hg) for 16 h at room temperature. The solvent was then removed under reduced pressure and the residue taken up in CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (2 × 15 mL), dried, and concentrated. Chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) yielded **38** (0.197 g, 75%) as a white crystalline solid: 145–6 °C (hexane/$CHCl_3$); $[\alpha]_D$ = +73° (*c*, 1.03, $CHCl_3$); δ_H (50 °C) 1.47 (d, 3H, β-Me), 3.61 (s, 3H, CO_2-Me), 3.67 (s, 3H, CO_2 Me), 3.77 (m, 1H, H-β), 4.64 (dd, 1H, *J* = 4.4, 8.5 Hz, H-α), 5.13 (bs, 1H, NH), 6.99 (s, 1H, H-2), 7.07–7.20 (m, 2H, H-5, H-6), 7.31 (d, 1H, *J* = 8.0 Hz, H-4), 7.59 (d, 1H, *J* = 7.8 Hz, H-7), 8.22, (bs, 1H, NH); δ_C (50 °C) 18.26 (β-Me), 33.95 (Cβ), 51.96 (CO_2Me), 52.24 (CO_2Me), 58.91 (Cα), 111.31 (C2), 115.72, 119.02, 119.59, 121.63, 122.30, 126.72, 136.46, 156.92 (NCO_2Me), 172.22 (*C*O_2Me); ν 3478, 3429, 1724, 1508, 1457, 1347 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25, N, 9.65. Found: C, 62.16; H, 6.18, N, 9.59. Further elution gave the 5-phenylsulfonyl derivative **40** (35 mg, 9%): δ_H 1.41 (d, 3H, *J* = 7.2 Hz, 3-Me), 3.57 (s, 3H, CO_2Me), 3.66 (s, 3H, CO_2Me), 3.73 (m, 1H, H-β), 4.65 (dd, 1H, *J* = 4.1, 9 Hz, H-α), 5.14 (d, 1H, *J* = 9 Hz, NH), 7.25 (s, 1H, H-2), 7.44–7.53 (m, 3H, H-3′,4′), 7.61 (dd, 1H, *J* = 1.5, 8.5 Hz, H-6), 7.71 (d, 1H, *J* = 8.5 Hz, H-7), 7.92–7.98 (m, 2H, H-2′), 8.09 (d, 1H, *J* = 1.5 Hz, H-4), 8.81 (bs, 1H, NH).

***erythro*-*N*-(Methoxycarbonyl)-β-phenyl-L-tryptophan Methyl Ester 39 and Its 5-Phenylsulfonyl Derivative 41.** Photolytic deprotection of **33** (0.67 g, 1.36 mmol) with ascorbic acid (1.195 g, 6.8 mmol) and anisole (1.48 mL) in 80% EtOH (300 mL) followed by purification by chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave **39** as a white crystalline solid (0.339 g, 71%): mp 160–2 °C (hexanes/$CHCl_3$); $[\alpha]_D$ = +83° (*c* 0.98); δ_H 3.45 (s, 3H, CO_2Me), 3.57 (s, 3H, CO_2-Me), 4.77 (d, 1H, *J* = 7.4 Hz, H-β), 5.08 (t, 1H, *J* = 7.9 Hz, H-α), 5.41 (d, 1H, *J* = 8.4 Hz, NH), 6.95–7.02 (m, 1H), 7.07–7.33 (m, 9H), 8.48 (bs, 1H, NH); δ_C 45.18 (Cβ), 52.05 (CO_2Me), 52.30 (CO_2Me), 58.09 (Cα), 111.27, 113.66, 118.92, 119.49, 122.15, 122.31, 126.82, 126.90, 128.31, 136.26, 140.19, 156.68 (NCO_2Me), 172.37 (*C*O_2Me); ν 3478, 3436, 1722, 1509, 1457 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72, N, 7.95. Found: C, 67.96; H, 5.73, N, 7.82. Further elution gave the 5-phenylsulfonyl derivative **41** (130 mg, 19%) with δ_H 3.46 (s, 3H, CO_2Me), 3.58 (s, 3H, CO_2Me), 4.74 (d, 1H, *J* = 8.0 Hz, H-β), 5.09 (dd, 1H, *J* = 8.0, 9.0 Hz, H-α), 5.31 (d, 1H, *J* = 9.0 Hz, NH), 7.15–7.28 (m, 5H), 7.36–7.49 (m, 6H), 7.87–7.92 (m, 2H, 2 × H-2′), 8.11 (d, 1H, *J* = 1.4 Hz, H-4), 9.26 (bs, 1H, NH); δ_C 45.40 (C-3), 52.18 (CO_2Me), 52.43 (CO_2Me), 58.04 (C-α), 112.12, 114.57, 118.12, 119.78, 126.71, 127.24, 128.09, 128.48, 129.08, 130.34, 132.72, 134.04, 135.19, 139.49, 142.26, 156.64, 172.06.

***erythro*-*N*-(Methoxycarbonyl)-α,β-dimethyl-L-tryptophan Methyl Ester 42.** The [(4-methoxyphenyl)sulfonyl]-hexahydropyrroloindole **22** (220 mg, 0.464 mmol) was dissolved in methanesulfonic acid (3 mL). The reaction mixture was stirred for 6 h at room temperature under Ar before it was poured into water (5 mL) followed by addition of CH_2Cl_2 (5 mL). The aqueous phase was adjusted to pH 8 with 15% $NaHCO_3$, the organic layer separated, and the water layer further extracted with CH_2Cl_2 (2 × 3 mL). The combined organic layers were dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue purified by chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) to give **35** as a white foam (107.8 mg, 76%): $[\alpha]_D$ −6.0°; δ_H (50 °C) 1.39 (d, 3H, *J* = 7.3 Hz, β-Me), 1.66 (s, 3H, α-Me), 3.58 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.71 (q, 1H, *J* = 7.3 Hz, H-3), 5.36 (bs, 1H, NH), 7.06 (d, 1H, *J* = 2.5 Hz, H-2), 7.11–7.23 (m, 2H, H-5, H-6), 7.34–7.39 (m, 1H, H-4), 7.69 (d, 1H, *J* = 7.8 Hz, H-7), 8.50 (bs, 1H, indole NH); δ_C 16.39 (Me), 18.19 (Me), 37.93 (Cβ), 51.85 (OMe), 52.44 (OMe), 63.10 (Cα), 111.55 (C2), 114.55 (C3), 118.80, 119.84, 122.22, 122.98, 127.21 (C3a), 136.05 (C7a), 155.78 (NCO_2Me), 174.53 (*C*O_2Me), ν 3465, 3422, 1726, 1500, 1458 cm^{-1}. HRMS calcd for $C_{16}H_{20}N_2O_4$: 304.1423, found 304.1430 ($M^{+\bullet}$).

***erythro*-β-Methyl-L-tryptophan Hydrochloride (43).** The β-Me derivative **38** (45 mg, 0.155 mmol) was heated to reflux with stirring in 6 M HCl (5 mL) under an Ar atmosphere for 24 h. After it was cooled, the reaction mixture was washed successively with CH_2Cl_2 (2 × 5 mL) and ether (2 × 5 mL) before concentration to dryness under vacuum yielded **43** in the form of its hydrochloride salt as an amorphous powder (36.7 mg, 93%): $[\alpha]_D$ = +36° (*c* 1.55, MeOH); δ_H (D_2O) 1.50 (d, 3H, *J* = 7.3 Hz, β-Me), 3.84 (m, 1H, H-β), 4.23 (d, 1H, *J* = 5.5 Hz, H-α), 7.12 (t, 1H, *J* = 8 Hz), 7.22 (t, 1H, *J* = 7.0 Hz), 7.30 (s, 1H, H-2), 7.48 (d, 1H, *J* = 8.1 Hz), 7.63 (d, 1H, *J* = 7.0 Hz); δ_C (D_2O) 19.69 (β-Me), 34.65 (Cβ), 60.23 (Cα), 114.52, 121.08, 121.92, 124.71, 126.66, 128.04, 138.80, 174.08 (*C*O_2H); ν (Nujol) 3387, 2925, 1734, 1457, 1377 cm^{-1}; FAB-HRMS calcd for $C_{12}H_{14}N_2O_2$·HCl − Cl 219.11335, found 219.11366 ($M^{+\bullet}$ − Cl).

***erythro*-β-Phenyl-L-tryptophan Hydrochloride (44).** The β-Ph derivative **39** (53 mg, 0.15 mmol) was heated to reflux with stirring in 6 M HCl (5 mL) under an Ar atmosphere for 24 h. After it was cooled, the reaction mixture was washed successively with CH_2Cl_2 (2 × 5 mL) and ether (2 × 5 mL) before concentration to dryness under vacuum yielded **44** in the form of its hydrochloride salt as an amorphous powder (43.9 mg, 92%): $[\alpha]_D$ = +43° (*c* 4.29, MeOH); δ_H (CD_3OD) 4.75 (d, 1H, *J* = 9.2 Hz), 4.83 (d, 1H, *J* = 9.2 Hz), 6.99 (t, 1H, *J* = 7.4 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), 7.16–7.32 (m, 3H), 7.36–7.45 (m, 3H), 7.49 (d, 1H, *J* = 7.8 Hz), 7.54 (s, 1H, H-2); δ_C (CD_3OD) 46.10 (Cβ), 58.20 (Cα), 112.58 (C2), 112.84, 119.36, 120.23, 123.01, 123.91, 128.13, 128.44, 129.52, 129.60, 138.20, 140.40, 171.16 (*C*O_2H); ν (Nujol) 3354, 2953, 2930, 2853, 1733, 1456, 1377 cm^{-1}; FAB-HRMS calcd for $C_{17}H_{16}N_2O_2$·HCl − Cl 281.12939, found 281.12900 ($M^{+\bullet}$ − Cl).

***erythro*-α,β-Dimethyl-L-tryptophan Hydrochloride (45).** The α,β-dimethyltryptophan derivative **42** (52 mg, 0.171 mmol) was heated to reflux with stirring in 6 M HCl (5 mL) under an Ar atmosphere for 24 h. After it was cooled, the reaction mixture was washed successively with CH_2Cl_2 (2 × 5 mL) and ether (2 × 5 mL) before concentration to dryness under vacuum yielded **45** in the form of its hydrochloride salt as an amorphous powder (42.8 mg, 93%): $[\alpha]_D$ = +6.6° (*c*, 0.5, MeOH); δ_H (CD_3OD) 1.52 (d, 3H, *J* = 7.4 Hz, β-H), 1.60 (s, 3H, α-Me), 3.72 (q, 1H, *J* = 7.4 Hz, H-β), 7.08 (m, 2H), 7.24 (s, 1H, H-2), 7.37 (d, 1H, *J* = 8.0 Hz), and 7.64 (d, 1H, *J* = 7.9 Hz); δ_C (CD_3-OD) 16.30, 19.99, 38.35, 64.71, 112.53, 113.44, 119.97, 120.22, 122.70, 125.17, 128.20, 137.98, 173.58; ν (Nujol) 3300, 2930, 1719 cm^{-1}; FAB-HRMS calcd for $C_{13}H_{16}N_2O_2$·HCl − Cl 233.12900, found 233.12948 ($M^{+\bullet}$ − Cl).

Acknowledgment. We thank the University of Illinois at Chicago for the award of University Fellowships to MB and for support of this work and Dr. David Horwell, Parke-Davis Neuroscience Research Centre, Cambridge, UK for stimulating discussion in the planning stages of this project.

Supplementary Material Available: Copies of ^{1}H- and ^{13}C-NMR spectra of **3**, **5**, **25**, **26**, (**30** + **18**), (**31** + **19**), (**33** + **21**), **35**, **36**, and **40**–**45** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.