Chemistry of Cyclic Tautomers of Tryptophan: Free Radical Reactions at C-2 Occur Preferentially on the Endo-Face of the Diazabicyclooctane Skeleton

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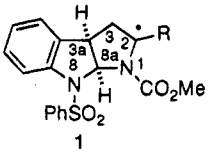
Within the last 10 years a great deal has been learned about the control of diastereoselectivity in free radical reactions such that in certain cases it is now possible to carry out carbon–carbon bond forming radical reactions, at or above room temperature, with the same predictable control[1,2] as is the norm in many kinetic aldol sequences. Recent demonstrations of the compatibility of Lewis acids with certain types of radical reaction suggest that further progress in radical stereoselectivity is to be anticipated; indeed examples of the successful use of designed Lewis acids in the promotion of diastereoselective radical reactions have already been documented.[3] The selective exo-face quenching of bicyclo[3.3.0]octanyl and bicyclo[4.3.0]-nonanyl radicals, whether generated by radical cyclization,[4] by transannular cyclization,[5] or from a preformed fused system,[6] is one of the more established concepts in this area. In extending our study of the reactions of cyclic tautomers of typtophan[7] we had therefore confidently anticipated that any radicals (**1**) generated at the C2 position would be trapped with high selectivity from the exo-face, so that after ring opening and deprotection a useful synthesis of homochiral α-substituted tryptamines would result. Our expectations of high exo-selectivity were further built on the knowledge that all previous alkylations and aldol reactions of the enolate of **2** and all conjugate and cycloadditions of the dehydro analog **3** had taken place with exquisite selectivity from the exo-face.[7] Herein, we report that contrary to all our expectations such was not to be the case and that reactions of the radical **1** could be engineered to give high endo-selectivity by the use of increasingly bulky radical traps.



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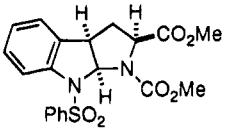

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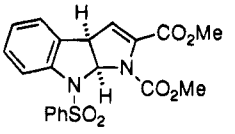

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Saponification of **2** and its derivatives **4**-**6**[7f] gave the acids **7**-**10**. Treatment of the acid **7** with Et_3N and the heterocycle **11**, followed by white light photolysis in the presence of *tert*-butylmercaptan, according to the standard protocol for Barton decarboxylation,[8] gave the reductive decarboxylation product **12** in excellent yield. Application of this protocol to acid **8** gave a mixture of the exo- and endo-2-methylhexahydropyrroloindoles **13** and **16** in the ratio 1.8:1 and 69% isolated yield (Table 1, entry 1). Not only was the diastereoselectivity of this reaction poor, but also the major product arose from quenching of the intermediate C-2 radical on the endo-surface of the diazabicyclooctane nucleus. The stereochemistry of the products was assigned by comparison of the ^{1}H-NMR spectrum of **16** with that of an authentic sample whose stereochemistry had originally been assigned by analysis of the H-2–H-3exo–H-3endo spin system, especially the ^3J = 0 value of H-2–H-3endo which can only be reconciled with endo-substitution at C-2 and the adoption of a conformation in which the C-2endo substituent is oriented so as to minimize ^{1,3} A strain with the partial exocyclic double bond N1$^+$=C-(O$^-$)OMe. This coupling pattern and conformation is found in all C-2endo substituted hexahydropyrrolindoles studied in this laboratory so far,[7] is supported X-ray crystallographic analysis[7m,g] and force field calculations,[7f] and is quite diagnostic. Nevertheless, in view of the unexpected nature of the result further confirmation of stereochemistry was sought. Thus, $LiAlH_4$ reduction of

(1) For reviews see: (a) Smadja, W. *Synlett.* **1994**, 1. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.*, **1991**, *24*, 296.

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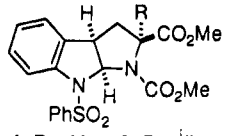
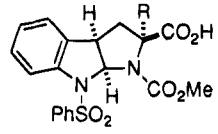
Table 1. Diastereoselective Reactions of Radical 1

entry	substrate	R	trap	products (% yield)	product ratio
1	**8**	Me	^{t}BuSH	**13** + **16** (69)	**13**:**16** = 1.8:1
2	**9**	Et	^{t}BuSH	**14** + **17** (72)	**14**:**17** = 1:1.5
3	**10**	^{i}Pr	^{t}BuSH	**15** + **18** (59)	**15**:**18** = 1:1.9
4	**8**	Me	$Me_3C_6H_2SH$	**13** + **16** (69)	**13**:**16** = 2.96:1
5	**9**	Et	$Me_3C_6H_2SH$	**14** + **17** (65)	**14**:**17** = 1:1.1
6	**10**	^{i}Pr	$Me_3C_6H_2SH$	**15** + **18** (52)	**15**:**18** = 1:2.9
7	**7**	H	CH_2CHCO_2Me	**20** + **21** (84)	**20**:**21** = 13:1
8	**7**	H	PhSSPh	**23** + **24** (83)	**23**:**24** = >1:15

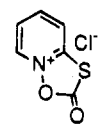
2 gave **19** which was converted to its thiocarbonyl imidazolide and subjected to the Barton deoxygenation protocol[9] in the normal manner to yield a further authentic sample of **16** and so remove any lingering doubt as to stereochemistry.



4: R = Me **6**: R = ^{i}Pr
5: R = Et



7: R = H **9**: R = Et
8: R = Me **10**: R = ^{i}Pr



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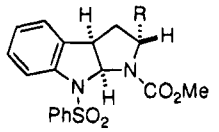
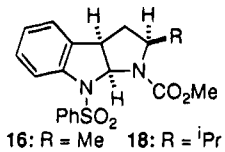
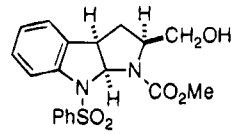


12: R = H **14**: R = Et
13: R = Me **15**: R = ^{i}Pr



16: R = Me **18**: R = ^{i}Pr
17: R = Et



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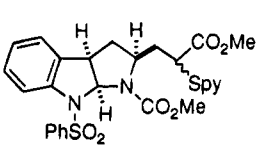
The acids **9** and **10** were also subjected to the Barton decarboxylation reaction in the presence of *tert*-butyl mercaptan yielding, in each case, mixtures of the exo- and endo-products (Table 1, entries 2 and 3). The stereochemistry of the various products was assigned in each case following analysis of the H-2–H-3exo–H-3endo spin system with the endo-diastereomers always having $^3J_{2,3endo} = 0$. Replacement of *tert*-butylmercaptan in the decarboxylation of **8**–**10** by mesitylenethiol[10] gave the results outlined in entries 4–6 of Table 1. Analysis of Table 1, entries 1–6, indicates that for radical **1** (R = Me and Et) the proportion of endo-face quenching, leading to the exo-alkyl products **13** and **14**, respectively, increases in going from *tert*-butylmercaptan to the more hindered mesitylenethiol as radical trap. With R = ^{i}Pr, however, the opposite trend is observed suggesting that diastereoselectivity in the quenching of **1** is a factor of the steric bulk of both the C-2 substituent R and that of the trap.

It seemed apparent from the above results that with a smaller substituent at C-2, ie R = H, and with a more sterically hindered radical trap, good selectivity for quenching of radical **1** on the endo-face should be observed. To test this hypothesis **7** was subjected to decarboxylation in the presence of methyl acrylate,[11] yielding an approximately 13:1 mixture of two adducts. The two adducts were separated by column chromatography and both were found to be almost equimolar mixtures of diastereomers at the side chain stereogenic center. The stereochemistry of the major diasteromer **20** was assigned by conversion to the corresponding sulfoxide and thermal syn-elimination to give **22**, followed by analysis of the H2–H3exo–H3endo spin system in the usual manner. This assignment was further corroborated by oxidative cleavage of **22** with $RuCl_3/NaIO_4$ under Sharpless conditions[12] to give the acid **7**, which was identical with an authentic sample. Decarboxylation of **7** in the presence of diphenyl disulfide[13] resulted in the formation of **23** and **24** in the approximate ratio 1:15 (Table 1, entry 8). Again, stereochemistry was assigned by routine analysis of the H-2–H-3exo–H-3endo spin system. The hypothesis that quenching of radical **1** (R = H) with more bulky traps would lead to greater endo-selectivity was therefore vindicated.



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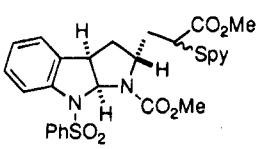

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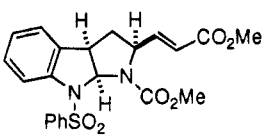

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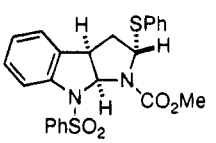

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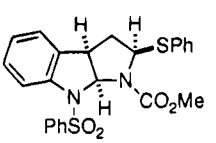

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It seems apparent from consideration of Table 1 that two extreme situations are found for the reactions of radical **1**. In the first (entries 1, 4, 7, and 8) the group R is small and the trap relatively large leading to preferential reaction on the endo-surface and a transition state that may be approximated as shown in Figure 1. In the second (entries 3 and 6) the group R is large and the trap relatively small resulting in preferential reaction on the exo-face through a transition state like that shown in Figure 2. Intermediate cases (entries 2 and 5) showing little selectivity have moderate sized R groups. Evidently, in these kinetically controlled radical reactions there is a competition for the endo-site at C-2 between the C-2 substituent R and the incoming radical trap

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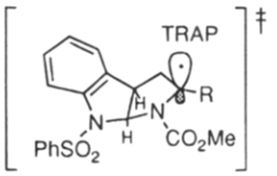

Figure 1. Large trap, small R.

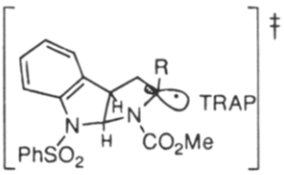

Figure 2. Small trap, large R.

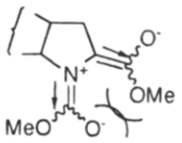

Figure 3. Strain in etholates of **2**.

which is somewhat reminiscent of the established thermodynamic preference of substituents at C-2 for the endo-site.[7f,m]

Why does the diastereoselectivity of radical **1** differ so substantially from that observed in the reactions of the enolate of **2**? If we assume, as is widely recognized,[14] that radical reactions proceed through early transition states then part of the answer must lie in the structure of radical **1**. We assume radical **1** to be extensively delocalized over the π-framework of the carbamate and so to be essentially planar,[15] but at the transition state the radical must assume a degree of σ-character as shown in Figures 1 and 2. If the radical undergoes pyramidalization toward the endo-face (Figure 1) then it maintains maximum stabilizing overlap with the carbamate π-framework. On the other hand pyramidalization toward the exo-face (Figure 2) results in a loss of overlap with the carbamate π-framework and so a higher energy situation. ^{1,3}A-strain also has a role to play. In Figure 1, ^{1,3}A-strain between the C-2 substituent R and the carbamate is maximized[7m] yet that between the carbamate and the incoming radical trap is minimized: this situation is therefore favored when R is small and the trap relatively bulky. In Figure 2, ^{1,3}A-strain between R and the carbamate is minimized but that with the incoming trap maximized: this minimization of ^{1,3}A-strain with R is clearly the predominant factor when R is large and is sufficient to override the preference of the radical to pyramidalize toward the endo-face.[16] Enolates derived from **2** must be subject to considerable steric strain and unfavorable dipolar interactions (Figure 3) which they presumably seek to minimize by torsion of the N-1−C-2 bond and/or pyramidalization of N-1 and C-2. This deformation will inevitably take place so as to place the bulky, possibly aggregated, enolate group on the endo-face so exposing the exo-face to attack (Figure 4).

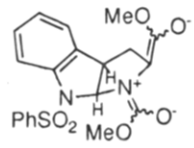

Figure 4. Proposed structure of enolates of **2**.

Experimental Section

General. See reference 7l for the general experimental protocol.

Typical Procedure for Saponification. (+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic Acid (7). Hexahydropyrroloindole **2** (1 g, 2.4 mmol) was dissolved in methanol (55 mL), and 1 N KOH (5 mL) was added followed by solid KOH (1 g). The resulting homogenous reaction mixture was stirred for a total of 12 h when TLC analysis indicated completion of reaction. The reaction mixture was concentrated to a slurry, diluted with water (10 mL), cooled to 0 °C, and acidified with 2 M HCl to a pH of 2. It was then extracted with ethyl acetate (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated to give a white foam (907 mg, 94%) which crystallized from ethyl acetate as colorless needles: mp 105 °C; $[\alpha]_D$ + 91.0 (c = 4.4, CH_2Cl_2); ^{1}H-NMR, δ 2.46 (1H, ddd, J = 13.02, 7.2, 8.3 Hz), 2.55 (1H, d, J = 13.02 Hz), 3.59 (3H, s), 3.65 (1H, dd, J = 7.2, 6.84 Hz), 4.53 (1H, d, J = 8.28 Hz), 6.23 (1H, d, J = 6.36Hz), 7.01−7.71 (9H, m); ^{13}C-NMR, δ 33.2, 45.4, 52.8, 58.8, 80.2, 118.2, 124.2, 125.2, 126.7, 126.5, 128.7, 128.8, 132.7, 132.6, 142.1, 173.5; IR (CH_2Cl_2) 2954, 1713, 1666 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_6N_2S$: C, 56.71; H, 4.50. Found: C, 56.67; H, 4.90.

(+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-methyl-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic Acid (8). Hexahydropyrroloindole **4** was hydrolyzed by the standard protocol to give **8** (93%) which was crystallized from ether: mp 122 °C; $[\alpha]_D$ +75.9 (c = 3.88, CH_2Cl_2); ^{1}H-NMR, δ 1.66 (3H, s), 2.14 (1H, dd, J = 13.25, 6.6 Hz), 2.75 (1H, d, J = 13.35 Hz), 3.32 (1H, dd, J = 6.6 Hz), 3.62 (3H, s), 6.18 (1H, d, J = 6.32 Hz), 6.95−7.58 (9H, m); ^{13}C-NMR, δ 24.5, 42.0, 43.0, 52.6, 66.1, 81.7, 119.1, 124.3, 125.6, 126.0, 128.8, 132.9, 133.3, 138.5, 141.7; IR (CH_2Cl_2) 3013, 1754, 1719, 1654 cm^{-1}. HRMS calcd for $C_{20}H_{20}N_2O_6S$ 416.10421, found 416.10471 ($M^{+\cdot}$). This compound crystallized with the inclusion of ether into the crystal lattice (~1.3 equivalents by NMR and microanalysis), removal of which under vacuum led to sintering and a hygroscopic powder.

(+)-(2*S*,3a*R*,8a*S*)-2-Ethyl-1-(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic Acid (9). Hydrolysis of hexahydropyrroloindole **5** gave the title compound as a foam in 72% yield: mp 136 °C (MeOH); $[\alpha]_D$ +90.5 (c = 0.19, CH_2Cl_2); ^{1}H-NMR, δ 0.84 (3H, t, J = 7.36 Hz), 1.97 (2H, q, J = 7.2 Hz), 2.13 (1H, dd, J = 13.5, 6.7 Hz), 3.00 (1H, d, J = 13.5 Hz), 3.24 (1H, dd, J = 6.7 Hz), 3.88 (3H, s), 6.10 (1H, d, J = 6.1 Hz), 7.05−7.12 (2H, m), 7.22 (1H, m), 7.32 (2H, m), 7.5 (4H, m); ^{13}C-NMR, δ 7.8, 28.0, 36.1, 43.1, 50.7, 53.7, 70.7, 82.0, 119.6, 125.1, 126.3, 126.9, 128.8, 133.1, 133.3, 137.8, 140.6, 171.2; IR (CH_2Cl_2) 3083, 1754, 1648 cm^{-1}; HRMS calcd for $C_{21}H_{22}N_2O_6S$ 430.11985, found 430.11936. Anal. Calcd for $C_{21}H_{22}N_2O_6S$·MeOH: C, 57.13; H, 5.66. Found: 57.15; H, 5.68.

(+)-(2*R*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-(1-methylethyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indole-2-carboxylic Acid (10). Hexahydropyrroloindole **6** was also hydrolyzed to give the title compound as a foam in 70% yield which crystallized from methanol as colorless needles: mp 204 °C; $[\alpha]_D$ +98.4 (c = 1.47, CH_2Cl_2); ^{1}H-NMR, δ 0.82 (6H, d, J = 6.5 Hz), 2.05 (^{1}H, dd, J = 13.6, 7.95 Hz), 2.80 (1H, septet, J = 6.5 Hz), 2.97 (1H, d, J = 13.6 Hz), 3.14 (1H, dd, J = 7.9, 6.10 Hz), 3.97 (3H, s), 6.00 (1H, d, J = 6.06 Hz), 7.1 (2H, m), 7.3 (3H, m), 7.5 (4H, m); ^{13}C-NMR, δ 15.8, 17.1, 29.3, 30.0, 42.9, 54.2, 74.6, 82.1, 119.7, 125.5, 126.6, 127.0, 128.8, 128.8, 133.2, 133.3, 137.4, 139.9, 158.8, 171.2; IR (CH_2Cl_2) 3083, 1754, 1642 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_6N_2S$: C, 59.44; H, 5.44; N, 6.30. Found: C, 59.13; H, 5.34; N, 6.23.

Typical Procedure for Radical Decarboxylation of Hexahydropyrroloindole-2-carboxylic Acids. (+)-(3a*R*,

(14) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 751.

(15) A search of Landolt-Bornstein unfortunately provided no examples of ESR spectra of radicals of this kind with which to verify this assumption.

(16) Beckwith has recently reported a study of diastereoselective radical addition to *N*-carbamoyl methyleneoxazolidinones in which the nature of the carbamate had a dramatic effect on face selectivity: Axon, J. R.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.*, **1995**, 549.

8aS)-1-(Methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (12). The acid **7** (46 mg, 0.14 mmol) was dissolved in dry, freshly distilled dichloromethane (3 mL) and stirred at rt under an argon atmosphere. Triethylamine (48 μL, 0.35 mmol) was added, the reaction flask was enveloped in aluminum foil, the salt **11** (31.8 mg, 0.168 mmol) was added, and the reaction mixture was allowed to stir for 2 h in the dark. *tert*-Butylmercaptan (79 μL, 0.7 mmol) was then added to the clear yellow solution which, after removal of the aluminum foil, was subjected to white light photolysis (250 W tungsten lamp) for approximately 3 h. The reaction mixture was then diluted with dichloromethane (10 mL) and carefully washed with saturated $NaHCO_3$ solution (2 × 10 mL), water (10 mL), and 1 M HCl (2 × 10 mL). The organic phase was dried and evaporated and the residue subjected to silica gel chromatography (eluent: petroleum ether/ethyl acetate 2/1) to yield the title compound (27 mg, 66%) as a white foam: $[\alpha]_D$ +163.5 (c = 1.95, CH_2Cl_2); ^{1}H-NMR, δ 1.96 (1H, dd, J = 5.75, 12.39 Hz), 2.10 (1H, ddd, J = 4.71, 12.38 Hz), 2.63 (1H, dd, J = 6.9 Hz), 3.72 (3H, s), 3.75 (1H, dd, J = 7.6, 10.8 Hz), 6.21 (1H, d, J = 6.6 Hz), 7.07 (2H, m, J = 6.28 Hz), 7.22 (1H, t, J = 6.19 Hz), 7.36 (2H, t, J = 7.9 Hz), 7.46 (2H, m), 7.70 (2H, d, J = 8.35 Hz); ^{13}C-NMR, δ 29.5, 30.7, 44.5, 45.9, 52.4, 79.5, 117.7, 123.9, 125.2, 127.0, 128.4, 139.1, 142.1; IR (CH_2Cl_2) 1703, 1601 cm^{-1}; HRMS calcd for $C_{18}H_{18}N_2O_4S$ 358.09873, found 358.09942.

(+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-methyl-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (13). Eluted from silica gel with petroleum ether/ethyl acetate 2.5/1 before compound **16**: mp 159 °C; $[\alpha]_D$ +93.0 (c = 1.38, CH_2Cl_2); ^{1}H-NMR, δ 1.31 (3H, d, J = 5.94 Hz), 1.78 (1H, ddd, J = 7.05, 10.11, 12.89 Hz), 2.19 (1H, m), 3.22 (1H, dd, J = 6.25 Hz), 3.41 (1H, m), 3.76 (3H, s), 6.07 (1H, d, J = 6.07 Hz), 6.99 (1H, d, J = 7.35 Hz), 7.10 (1H, t, J = 7.49 Hz), 7.24 (2H, t, J = 8.13 Hz), 7.32 (2H, t, J = 7.7 Hz), 7.47 (1H, t, J = 7.44 Hz), 7.55 (2H, d, J = 5.47 Hz); ^{13}C-NMR, δ 20.1, 29.7, 38.3, 43.8, 52.1, 52.7, 81.2, 119.7, 123.6, 126.0, 127.0, 128.4, 128.7, 132.9, 138.3, 141.5; IR (CH_2Cl_2) 1701, 1595 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2SO_4$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.19; H, 5.51; N, 7.50.

(+)-(2*R*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-methyl-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (16).[7f] Eluted from silica gel with petroleum ether/ethyl acetate 2.5/1 after compound **13**: mp 57–59 °C; $[\alpha]_D$ +128.3 (c = 0.72, CH_2Cl_2); ^{1}H-NMR, δ 0.73 (3H, d, J = 6.69 Hz), 1.82 (1H, d, J = 13.03 Hz), 2.35 (1H, ddd, J = 13.03, 8.18, 7 Hz), 3.54 (1H, dd, J = 7.5, 8.18 Hz), 3.71 (3H, s), 4.15 (1H, q, J = 7 Hz), 6.19 (1H, d, J = 7 Hz), 7.07–7.71 (9H, m); ^{13}C-NMR, δ 21.3, 29.7, 36.8, 45.2, 52.4, 53.9, 80.6, 118.5, 123.9, 125.4, 127.0, 128.3, 128.70, 132.8, 141.1, 155.0; IR (CH_2Cl_2) 1701, 1595 cm^{-1}.

(+)-(2*S*,3a*R*,8a*S*)-2-Ethyl-1-(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (14). Eluted as an oil from silica gel with petroleum ether/ethyl acetate 2.5/1 before compound **17**: $[\alpha]_D$ +100.3 (c = 3.6, CH_2Cl_2); ^{1}H-NMR, δ 0.78 (3H, t, J = 7.6 Hz), 1.53 (1H, m), 1.85 (1H, ddd, J = 7.4, 9.7, 12.75 Hz), 2.12 (2H, m), 3.27 (1H, dd, J = 6.6 Hz), 3.34 (1H, m), 3.76 (1H, s), 6.07 (1H, d, J = 6.22 Hz), 6.99–7.8 (9H, m); ^{13}C-NMR, δ 25.5, 34.5, 43.7, 52.0, 57.7, 81.3, 119.6, 123.6, 125.9, 127.0, 128.7, 128.6, 132.8, 136.0, 138.2, 140.9, 152.9; IR (CH_2Cl_2) 1710, 1595 cm^{-1}. HRMS calcd for $C_{20}H_{22}N_2O_4S$ 386.13003, found 386.12978.

(+)-(2*R*,3a*R*,8a*S*)-2-Ethyl-1-(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (17). Eluted from silica gel with petroleum ether/ethyl acetate 2.5/1 after compound **14**: mp 134 °C; $[\alpha]_D$ +134.1 (c = 2.1, CH_2Cl_2); ^{1}H-NMR, δ 0.67 (3H, m, J = 3.5 Hz), 1.26 (2H, m), 1.90 (1H, d, 12.98 Hz), 2.28 (1H, ddd, J = 13, 7.9, 8.17 Hz), 3.56 (1H, dd, J = 8.17 Hz), 3.71 (3H, s), 3.94 (1H, m, J = 7.9 Hz), 6.22 (1H, d, J = 7.38 Hz), 7.06–7.76 (9H, m); ^{13}C-NMR, δ 10.9, 28.0, 34.5, 45.1, 52.5, 60.2, 80.4, 117.6, 123.8, 125.0, 127.0, 128.3, 128.7, 129.1, 132.8, 135.2, 138.6, 141.0, 155.4; IR (CH_2Cl_2): 1701, 1595 cm^{-1}; HRMS calcd for $C_{20}H_{22}N_2O_4S$ 386.13003, found, 386.12928. Anal. Calcd for $C_{20}H_{22}N_2O_4S$: C, 62.16; H, 5.74. Found: C, 62.45; H, 5.75.

(+)-(2*R*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-(1-methylethyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (15). Eluted as an oil from silica gel with petroleum ether/ethyl acetate 2.5/1 before compound **18**: $[\alpha]_D$ +108.4 (c = 5.1, CH_2Cl_2); ^{1}H-NMR, δ 0.72 (3H, d, J = 6.67 Hz), 0.77 (3H, d, J = 7.13 Hz), 1.93 (2H, m), 2.82 (1H, m, J = 6.6 Hz), 3.24 (1H, m), 3.45 (1H, ddd, J = 4.17, 7.97, 8.0 Hz), 3.77 (3H, s), 6.04 (1H, d, J = 5.96 Hz), 7.00–7.56 (9H, m); ^{13}C-NMR, δ 13.8, 18.9, 26.2, 28.0, 29.7, 43.7, 52.1, 61.2, 81.5, 119.7, 123.6, 126.1, 127.0, 128.3, 128.7, 132.8; IR (CH_2Cl_2) 1701, 1601 cm^{-1}; HRMS calcd for $C_{21}H_{24}N_2O_4S$ 400.14569, found 400.14709.

(+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-(1-methylethyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indole (18). Eluted as an oil from silica gel with petroleum ether/ethyl acetate 2.5/1 after compound **15**: $[\alpha]_D$ +142.2 (c = 1.8, CH_2Cl_2); ^{1}H-NMR, δ 0.65 (3H, d, J = 6.46), 0.79 (3H, d, J = 6.59 Hz), 1.06 (1H, septet, J = 8.08 Hz), 1.96 (1H, d, J = 13.1 Hz), 2.23 (1H, m), 3.66 (1H, dd, J = 8.23, 7.65 Hz), 3.74 (3H, s), 3.80 (1H, d, J = 8.4 Hz), 6.29 (1H, d, J = 8.0 Hz), 7.05–7.84 (9H, m). ^{13}C-NMR, δ 19.6, 19.9, 32.3, 34.7, 45.0, 52.7, 65.4, 80.3, 116.1, 123.9, 124.5, 127.1, 128.4, 128.9, 132.9, 141.1, 156.1; IR (CH_2Cl_2): 1697, 1601 cm^{-1}; HRMS calcd for $C_{21}H_{24}N_2O_4S$ 400.14569, found 400.14629.

(+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-[(2*RS*)-2-(methoxycarbonyl)-2-[2-(pyridylthio]ethyl]-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (20) and (+)-(2*R*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-[(2*RS*)-2-(methoxycarbonyl)-2-[2-(pyridylthio)ethyl]-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (21). Acid **7** (1 g, 2.48 mmol) was dissolved in dry, freshly distilled, dichloromethane (5 mL) followed by the addition of triethylamine (0.5 mL, 3.72 mmol) under an argon atmosphere. The flask was enveloped in aluminum foil and stirred at rt and then the salt **10** (564 mg, 2.97 mmol) was added and the reaction mixture stirred in the dark for 2 h. Methyl acrylate (0.89 mL, 9.92 mmol) was then added, the aluminum foil removed, and the reaction mixture subjected to white light photolysis for 3 h. The reaction mixture was concentrated and subjected to silica gel chromatography (eluent: petroleum ether/ethyl acetate 2.5/1). Compound **20**, an oil, was isolated as an unassigned mixture of diasteromers at C-2″ (1.066 g, 78%): ^{1}H-NMR, δ 1.2–2.4 (4H, m), 3.6–3.8 (7H, m), 4.3 (1 H), 4.3–4.5 (1H, m), 6.2 (1H, m), 6.8-7.8 (12H, m), 8.3–8.4 (1H, m); IR (CH_2Cl_2): 1731, 1707 cm^{-1}; HRMS calcd for $C_{27}H_{27}N_3O_6S_2$ 553.13139, found 553.13136. The minor compound **21**, also an unassigned mixture of diastereomers at C-2″, was an oil (82.2 mg, 6%): ^{1}H-NMR, δ 1.80–2.50 (4H, m), 2.75–3.15 (1H, m), 3.30–3.40 (1H, m), 3.50–3.80 (4H, m), 4.62 (1H, m), 6.02 (1H, d, J = 5.98), 6.85–7.60 (12H, m), 8.36 (1H, m); IR (CH_2Cl_2) 1713 cm^{-1}.

(+)-(2*R*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-8-(phenylsulfonyl)-2-(phenylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (24). Acid **7** (58.2 mg, 0.14 mmol) was dissolved under Ar in freshly distilled dichloromethane (1 mL). Triethylamine (0.03 mL, 0.22 mmol) was added and the flask wrapped in aluminum foil. The salt **11** (33 mg, 0.17 mmol) was then added and the reaction mixture stirred at room temperature for 2 h. Diphenyl disulfide (96.2 mg, 0.44 mmol) was then added, the aluminum foil removed, and the reaction mixture irradiated, in a cold water bath, with the tungsten lamp for 3 h. Concentration of the reaction mixture and chromatography on silica gel (eluent: petroleum ether/ethyl acetate 2.5/1) gave the title compound as an oil (56 mg, 83%): $[\alpha]_D$ + 158.9 (c = 2.4, CH_2Cl_2); ^{1}H-NMR, δ 2.33 (1H, d, J = 13.35 Hz), 2.57 (1H, m), 3.52 (3H, s), 3.77 (1H, d, J = 7.66 Hz), 5.51 (1H, d, J = 7.28 Hz), 6.33 (1H, d, J = 7.21 Hz), 7.13 (2H, d, J = 5.31 Hz), 7.21 (3H, m), 7.30 (3H, m), 7.38 (2H, t, J = 7.5, 7.98 Hz), 7.50 (1H, t, J = 7.33), 7.62 (1H, d, J = 8.05 Hz), 7.77 (2H, d, J = 7.47 Hz); ^{13}C-NMR, δ 38.7, 45.1, 52.5, 66.7, 80.1, 118.0, 124.3, 125.1, 127.0, 127.6, 128.5, 128.7, 132.6, 133.7, 134.0, 139.4; IR (CH_2Cl_2) 1713, 1595 cm^{-1}; HRMS calcd for $C_{24}H_{22}N_2O_4S_2$ 466.10210, found 466.10219. The minor isomer, not isolated pure, was characterized by signals at δ 6.20 (1H, d), 5.2 (1H, m) in the ^{1}H-NMR spectrum.

(+)-(2*S*,3a*R*,8a*S*)-1-(Methoxycarbonyl)-2-[2-(methoxycarbonyl)vinyl]-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (22). The major diastereomer **20** (30 mg, 0.054 mmol) was dissolved in dry THF (0.5 mL), followed by the addition of magnesium monoperphthalate (13.3 mg, 0.027 mmol). The reaction mixture was allowed to stir at rt and monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate (5 mL) and washed successively with $NaHCO_3$ (2 × 5 mL) and brine (1 × 5 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a colorless oil which was directly dissolved in xylenes (2 mL) and refluxed for 1 h.

The solvent was then evaporated under high vacuum to give **22**, an oil (30 mg), as a single isomer which was used for oxidation directly: $[\alpha]_D$ +132.1 (c = 2.4, CH_2Cl_2); ^{1}H-NMR, δ 2.07 (1H, d, J = 13.35 Hz), 2.69 (1H, m), 3.45 (1H, dd, J = 7.27 Hz), 3.66 (3H, s), 3.73 (3H, s), 5.38 (1H, d, J = 9.99 Hz), 5.49 (2H, m), 6.20 (1H, d, J = 6.54 Hz), 6.97 (1H, d, J = 7.55 Hz), 7.06 (1H, t, J = 7.5 Hz), 7.25 (1H, t, J = 8.8 Hz), 7.36 (2H, t, J = 7.9 Hz), 7.50 (1H, t, J = 7.49 Hz), 7.62 (1H, d, J = 8.00 Hz), 7.69 (2H, d, J = 13 Hz); ^{13}C-NMR, δ 38.7, 45.2, 51.1, 52.7, 56.9, 81.1, 118.2, 118.8, 124.4, 125.6, 127.2, 128.7, 128.8, 132.9, 141.3, 152.5, 166.0; IR (CH_2Cl_2) 1713 cm^{-1}; HRMS calcd for $C_{22}H_{23}N_2O_6S$ 443.1276, found 443.1286 [MH$^{\bullet+}$].

Oxidative Degradation of 22 to 7. Crude **22** (30 mg) was dissolved in acetonitrile (1 mL) and added to a solution of sodium metaperiodate (115 mg, 0.54 mmol) in a (2:1: v/v) water/CCl_4 (3 mL) mixture. $RuCl_3 \cdot 3H_20$ (10 mol%) was then added, and the reaction mixture was allowed to stir for 10 h at rt. The reaction mixture was then acidified by addition of 2 M HCl and extracted with ethyl acetate (3 × 5 mL). The organic phase was then extracted with saturated sodium bicarbonate (3 × 5 mL). The extracts were acidified with 2 M HCl and reextracted with ethyl acetate (3 × 5 mL) to give an organic phase which was dried ($MgSO_4$) and concentrated to give **7** (8 mg, 37% overall yield from **21**) which was identical with the sample of **7** obtained by saponification of **2**.

Reduction of 2: (+)-(2*S*,3a*R*,8a*S*)-2-(Hydroxymethyl)-1-(methoxycarbonyl)-8-(phenylsulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (19). Hexahydropyrroloindole **2** (1g, 2.4 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C in an ice bath under an argon atmosphere and treated with LAH (250 mg, 6.5 mmol). After completion, the reaction mixture was quenched by carefully pouring into cold 2 M HCl (10 mL). The acidic solution was then extracted with ethyl acetate (3 × 10 mL) and washed with brine. The organic phase was then dried ($MgSO_4$) and concentrated to give **19** as a white foam (612 mg, 66%) which crystallized as colorless needles from methanol. mp 167 °C; $[\alpha]_D$ +129.3 (c = 4.0, CH_2Cl_2); ^{1}H-NMR, δ 1.97 (1H, d, J = 10 Hz), 2.38 (1H, dt, J = 13.44, 8.9 Hz), 3.03 (1H, bs), 3.49 (1H, dd, J = 5.48, 6.08 Hz), 3.75 (3H, s), 4.21 (1H, m, J = 5.25 Hz), 6.16 (1H, d, J = 5.17 Hz), 7.07 (3H, m), 7.25 (2H, m), 7.39 (1H, t, J = 5.87 Hz), 7.52 (1H, t, 5.61 Hz), 7.61 (1H, d, J = 6.05 Hz), 7.07 (1H, bs); ^{13}C-NMR, δ 32.7, 44.9, 53.0, 60.5, 80.9, 123.8, 125.6, 127.0, 128.7, 128.9, 133.1, 140.7; IR (CH_2Cl_2) 3436, 1707, 1684, 1601 cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_5N_2S$: C, 58.75; H, 5.19; N, 7.21. Found: C, 58.41; H, 5.18; N, 7.16.

Deoxygenation of 19 to 16. The alcohol **19** (30 mgs, 0.077 mmol) was dissolved in dry dichloromethane (3 mL) under an argon atmosphere. Thiocarbonyl diimidazole (20.5 mg) was then added, and the reaction mixture was refluxed for 3 h at the end of which TLC analysis indicated complete conversion. The dichloromethane was evaporated, and the crude thiocarbonyl imidazolide (39 mg) was dissolved in chlorobenzene (2 mL) and refluxed under argon for 1 h prior to the addition of a solution of tributyltin hydride (22.7 μL, 0.084 mmol) and AIBN (0.6 mg 0.0038 mmol) in chlorobenzene (1 mL). After 30 min TLC analysis indicated complete consumption of the thiocarbonylimidazolide. The chlorobenzene was removed under high vacuum and the residue washed with petroleum ether, followed by silica gel chromatography (eluent: petroleum ether/ethyl acetate 2/1) to yield **16** (19.8 mg, 68%) identical with the sample of **16** isolated above.

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Supporting Information Available: ^{1}H-NMR (300-MHz) and ^{13}C (75 MHz) spectra of **8**, **12**, **14**, **15**, **18**, **20**, **21**, **22**, and **24** (18 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.

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