On the Reaction of Tryptophan Derivatives with *N*-Phenylselenyl Phthalimide: The Nature of the Kinetic and Thermodynamic Hexahydropyrrolo[2,3-*b*]indole Products. Alkylation of Tryptophan with Inversion of Configuration

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The cyclization of a range of tryptophan derivatives with *N*-phenylselenyl phthalimide leading to 3a-phenylselenyl-1,2,3,3a,8,8a-hexahydro[2,3-*b*]pyrroloindoles has been studied. It is established that in each case the kinetic diastereomer has the C-2 substituent on the exo face of the diazabicyclo-[3.3.0]octane skeleton, whereas the thermodynamic isomers have the C-2 substituent endo. A simple protocol for the alkylation of tryptophan, leading to α-substituted tryptophans with clean inversion of configuration, is presented.

Over a period of approximately 10 years, this laboratory has exploited the closure of the tryptophan derivative **1** to a thermodynamic 9:1 mixture of the two diastereomeric hexahydropyrroloindole tautomers **2** and **3** on dissolution in 85% phosphoric acid, as first reported by Taniguchi and Hino.[1] Both **2** and **3** are somewhat unstable with respect to reversion to **1** in the absence of strong acid, but sulfonylation of the crude mixture greatly enhances stability and permits the ready isolation of crystalline **4** in excellent overall yield and as a single diastereoisomer.[2,3] Alkylations and kinetic aldol condensations of the lithium enolate of **4**, and related derivatives, take place exclusively on the exo surface of the diazabicyclo[3.3.0]octane nucleus so permitting, after cycloreversion to the tryptophan skeleton, the overall conversion of L-tryptophan to optically pure α-substituted derivatives without recourse to the use of an external chiral auxiliary or catalyst.[2−5] The overall concept is related, but not identical to, Seebach's self-reproduction of chirality method:[6] the essential difference being that the key ring formation arises from a simple tautomerization rather than formation of a derivative such as a cyclic acetal. Dehydrogenation of **4**, by the usual sequence of selenenation and selenoxide syn elimination, provides **5**, which is amenable to conjugate additions and cycloadditions, again on the exo face, ultimately providing *β*- and α,*β*-substituted tryptophan derivatives in enantiomerically pure form.[7,8] Radical bromination of **4** with NBS in CCl_4 provided **6**,[9] which, on treatment with allyltributylstannane and AIBN, afforded **7** and so a convenient entry into the synthesis of related indole alkaloids.[10] The success of this chemistry is underpinned by the initial highly diastereoselective ring closure, which enables preparation of **2** and so **4** on a significant scale without recourse to chromatographic purification.[1−3] Perhaps, the most striking observation in all of the above is the thermodynamically more stable nature of the 2-*endo*-carbomethoxy isomer **2**,[1−3] which prompted us to carry out a series of computational[11] and crystallographic studies aimed at understanding this phenomenon.[12,13] Ultimately, we determined that the thermodynamic preference for the endo site is a subtle function of torsional interactions around the bicyclo[3.3.0]octane nucleus, rather than a minimization of ^{1,3}A-strain due to the N=C double implicit in the N1-carbamate or a consequence of π-stacking between the endo ester and the surface of the fused benzene ring.[13] This is not to say that these factors do not contribute to the overall stability of the system but simply that they are not the decisive factors. This notion is reinforced by the fact that under equilibrating conditions the 2-CO_2Me substituent in the aflatoxin model **8** also prefers the endo position: seemingly the same torsional interactions are at work here.[14] Similar observations have also been reported for systems related to **8** in which the 2-substituent was OMe or OH.[15,16] This thermodynamic preference for the endo-position in 2-substituted bicyclo[3.3.0]octane nuclei is not limited to heterocyclic systems. As noted previously,[13] under equilibrating conditions, 2-alkylbicyclo[3.3.0]octan-1-ones are 1:1 mixtures of exo and endo isomers, which

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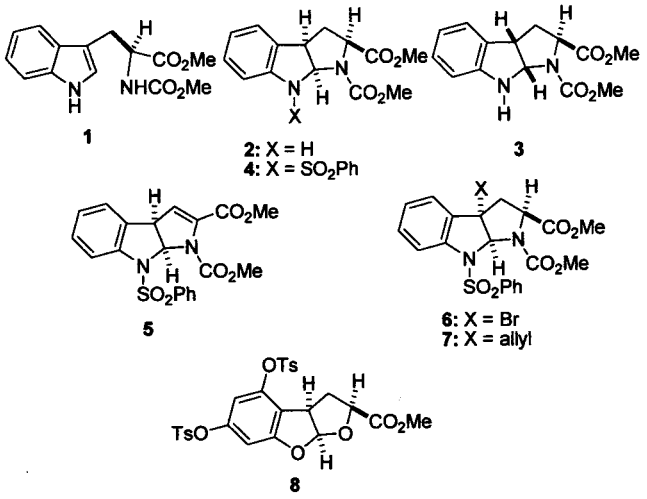
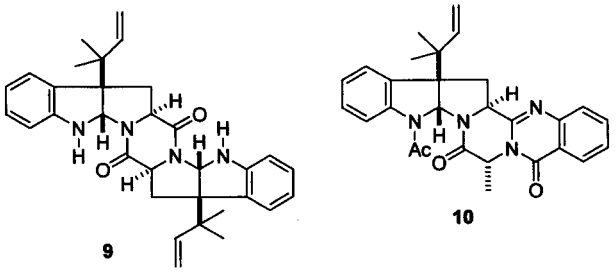
suggests that similar factors exist in this carbocyclic system,[17,18] albeit to a lesser extent. Finally, it is necessary to draw attention to two characteristics of the ^{1}H NMR spectrum of **4** and all of its 2-endo congenors. These are the unusual upfield shift of the Me group in the C2 ester and the approximately 90° torsion angle and so minimal scalar coupling, between the 2-exo-H and the 3-endo-H that is reflected in the simple doublet nature of the H2 resonance.[3,11,13] Together, these phenomena indicate that in solution the terminal heterocyclic ring of **4** is in an envelope conformation with the flap (C2) folded under the endo surface of the fused nucleus, as found in the crystal. We stress that the same features are found in the 3a-ramified systems **6** and **7**, which indicates that substitution at this position does not change the basic conformational preference.[10] We also point out that the same coupling pattern, and so conformation, is found in the dioxabicyclooctane system, which serves again to illustrate the generality of the phenomenon.[14,17,18]



With this background, we were considerably surprised to read a 1994 paper by Danishefsky and co-workers on the synthesis of the indole alkaloids amauromine (**9**) and 5-*N*-acetylardeemin (**10**).[19] In this paper, it was reported



that cyclization of **11** with *N*-phenylselenophthalimide led to an initial 1:1 mixture of the *endo*- and *exo*-hexahydropyrroloindoles **12** and **13** and that equilibration, under unspecified conditions, resulted in conversion to an inseparable 1:9 mixture favoring the exo isomer **13**. Perplexed by this apparent exception to the above body of work, we have reinvestigated the cyclization of

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(19) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143−11144.

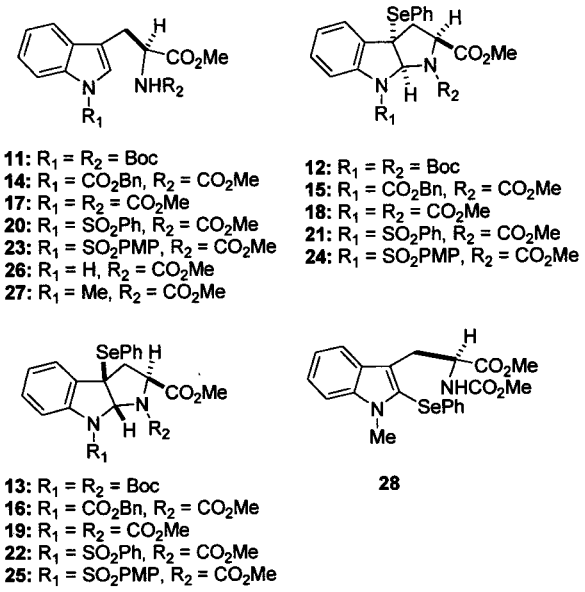
Table 1. Cyclization Reactions

substrate	total cyclized yield (%)	endo product	exo product ($[\alpha]_D$)	endo/exo ratio	other products (%)
11	65	**12**	**13** (−78.4°)[a]	1:9[b]	
14	76	**15**	**16** (−74.5°)	1:12[c]	
17	83	**18**	**19** (−100.6°)	1:11[c]	
20	40	**21**	**22** (−62.0°)	<2:98	
23	31	**24**	**25** (−35.6°)	<2:98	
26[d]	0				
27	0				**28** (85)

[a] Taken on the 9:1 inseparable mixture. [b] Inseparable by chromatography. [c] Separable by chromatography. [d] No reaction.

11 and related tryptophan derivatives with *N*-phenylselenophthalimide and report here on our findings.

A number of *N*,*N*′-diprotected L-tryptophan derivatives were prepared and treated with *N*-phenylselenophthalimide in dichloromethane with catalysis by *p*-toluenesulfonic acid. The reactions were clean with no significant byproducts; in each case, the mass balance consisted of recovered starting material. Examination of the crude reaction mixtures by ^{1}H NMR spectroscopy revealed the presence of exo- and endo-cyclized products in almost every case. As we have discussed numerous times previously, the spectra taken at room temperature were ill-resolved owing to a dynamic NMR phenomenon.[3,13] However, at 50 °C much sharper spectra were obtained. Chromatography on silica gel then permitted separation of the cyclic products from minor, unidentified byproducts. The various cyclizations, together with their isolated yields and endo/exo ratios, are presented in Table 1.

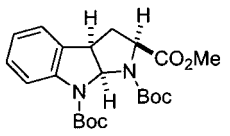


With **11** a 9:1 ratio of cyclized products was obtained, which, as reported by Danishefsky, we were unable to separate chromatographically. With the closely analogous dicarbamates **14** and **17** the ratio was 12:1 and 11:1, respectively, and the isomers could now be separated chromatographically without difficulty. When the indole nitrogen was protected with a sulfonyl group, as in **20** and **23**, the yield of cyclized products was lower but the ratios much higher giving essentially a single isomer. In the case of **26**, with the free indole NH, no cyclized product was obtained. This result can probably be attributed to the instability of any such cyclic product in

the absence of an electron-withdrawing group on both nitrogen atoms (cf. **2** and **3** above). Finally, with the *N*-methyl derivative **27** the only product formed arose from substitution at the indole C2 position, in accord with previous work from this laboratory on the reaction of tryptophan derivatives not bearing an electron-withdrawing group on the indole N with selenium-based electrophiles.[20]

With a range of cyclic tautomers in hand, we turned to the assignment of configuration. In the mixture of **12** and **13**, the minor isomer exhibited a singlet at δ 3.07 reminiscent of the ester methyl group in **4**. Similar observations were made for the minor isomers arising from the cyclizations of **14** and **17**. The products derived from the cyclizations of **20** and **23** had no such upfield singlets. These observations suggested that the major isomer, in each case, was the exo isomer in agreement with the conclusion of Danishefsky and co-workers. Nevertheless, there remained the possibility, however small given the fact that **6** fit well the established pattern, that the 3a-phenylseleno moiety was having an unexpected effect on the chemical shifts of the methyl esters. Thus, the mixture of **12** and **13** was reduced with tributyltin hydride and AIBN in benzene at reflux to give a 1:9 mixture of **29** and **30**. Still, the characteristic upfield shift of the methyl ester was found only in the minor isomer. A similar experiment was conducted with both **19** and **25**, leading to **31** and **32**, respectively, with the same result. Thus, it was established that the major isomer arising from each of the cyclizations had the C-2 CO_2Me group on the exo surface of the bicyclo[3.3.0]-octane nucleus. This assignment is borne out by an X-ray crystallographic study from the Joullié group that appeared recently.[21]

In principle, equilibration between the exo and endo isomers in any given case can occur through a reversal of the ring closing and selenation steps or by epimerization at C-2. The two processes will give enantiomeric products. Thus, the cycloreversion/selenation mode of equilibration will give the products in the configurations depicted all having the *S* configuration at C-2. On the other hand, epimerization at C-2 would lead to the enantiomers of the products drawn. For example, the cycloreversion/selenation mode of equilibration of **12** would provide **13**, whereas base-catalyzed epimerization at C-2 would lead to *ent*-**13**. As Danishefsky had not specified the equilibration conditions, it was necessary to ascertain which, if any, of the two processes was occurring. This was readily determined from the specific rotations of the various products. Our extensive experience with dozens of cyclic tautomers of tryptophan, both 2-exo- and 2-endo-substituted, taught us that the sign of the specific rotation at the sodium D lines is determined by the absolute configurations at the two ring junction stereogenic centers. Other substituents, exo or endo, make only small contributions to the numerical value of the specific rotation. Thus, all of the 2-endo products **4**−**7**, derived from L-tryptophan have strongly dextrorotatory specific rotations, whereas that of the 2-exo product **32**, also derived from L-tryptophan, was levorotatory. The major products from each of the cyclizations conducted here were levorotatory (Table 1), indicating that they had the absolute configurations indicated.



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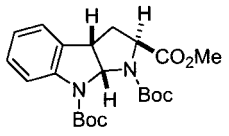

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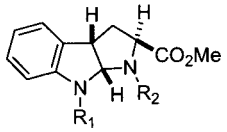
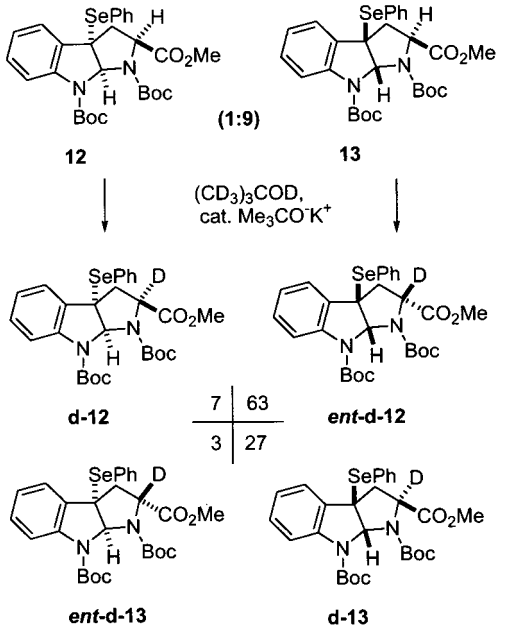


31: $R_1 = R_2 = CO_2Me$
32: $R_1 = SO_2PMP$, $R_2 = CO_2Me$

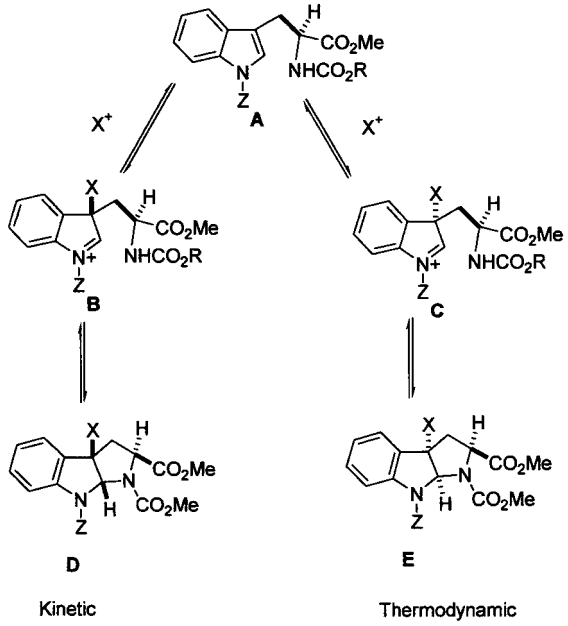
Next, we turned to the question of the thermodynamic or kinetic nature of the product mixtures isolated. Danishefsky had indicated that his initial reaction mixtures had a **12**:**13** ratio of 1:1 and that this was improved to 1:9 upon the unspecified equilibration. In our hands, we never observed the 1:1 mixture in any instance. Neither did the product ratios change significantly with time when left exposed to the cyclization reaction conditions. This suggested that either the equilibration was very rapid or, alternatively, that the ratios observed were kinetic and that no equilibration was taking place. To clarify the situation, the 1:9 mixture of **12** and **13** was dissolved in perdeuterio-*tert*-butyl alcohol and treated with a catalytic quantity potassium *tert*-butoxide. Within the space of a few minutes all the C-2 hydrogens were exchanged for deuterium atoms and the nature of the minor and major product spectra were reversed. The new ratio was 7:3 in favor of the endo isomer with its strikingly upfield methyl ester chemical shift at δ 3.07 (Scheme 1). The fact that this conversion is taking place under equilibrating conditions, and does not arise from a kinetic exo protonation of the enolate, is incontrovertibly established by the complete exchange of the C-2 hydrogens in both epimers. Finally, the *tert*-butyl alcohol was removed and the reaction mixture taken up in $CDCl_3$ when the same spectral features were noted: the observed changes in the spectra in *t*-BuOH-d_{10} therefore did not arise from the unusual solvent. The specific rotation of the final equilibrium mixture was strongly negative (−34°). This indicates that this equilibration has taken place simply through epimerization at C-2 rather than via a coupled process including deprotonation at C-2 and cycloreversion, which would have led to complete racemization. Analogous experiments were conducted with pure *exo*-**19** and pure *exo*-**25**, which were both converted to fully C-2-deuterated mixtures (80:20 and 86:14, respectively) in favor of the endo isomers. It is therefore unambiguously established that, in the pair of diastereoisomers **12** and **13**, the former is the thermodynamically favored isomer. This is fully consistent with the general picture established previously in this laboratory and briefly reviewed in the Introduction. It is also clear that the exo isomers are the kinetically preferred products and may be isolated in high yield under the selenation conditions. Again, this is consistent with previous work from this laboratory wherein it was demonstrated that even under the phosphoric acid cyclization conditions **1** is converted kinetically to **3**, which very rapidly equilibrates to **2**.[13] We conclude that the 1:9 ratio of **12** and **13** originally reported by Danishefsky was a kinetic and not a thermodynamic ratio. Subsequent

(20) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1989**, *30*, 4307−4308.
(21) Chen, W.-C.; Joullie, M. M. *Tetrahedron Lett.* **1998**, *39*, 8401−8404.

Scheme 1



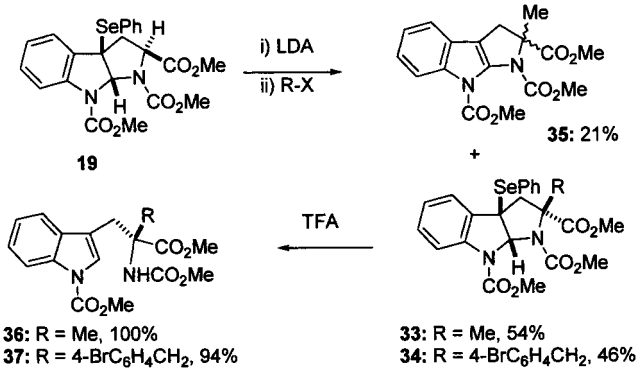
Scheme 2



work from the Danishefsky group concurs with this assessment.[22]

It is of some interest to ask why the 2-CO_2Me exo isomers are kinetically favored in these ring-closure reactions. In principle, this kinetic preference might arise at either of two steps. In the first scenario it is the initial attack of the electrophile ($X^+ = H^+$ or PhSePhth) on the indole that shows face selectivity leading preferentially to indolenium ion **B** rather than **C** (Scheme 2). Subsequent ring closure then gives the products **D** and **E**, respectively. This seems unlikely simply because the only stereogenic center in the substrate (**A**) is two freely rotating bonds removed from the reaction center and so is unlikely to confer the type of induction seen. In the second, more plausible, scenario, the stereodiscriminating step is the ring closure with **B** → **D** being easier than **C** → **E**. This requires the equilibration of **B** and **C**, via **A**, to be rapid on the time scale of the ring closure. It follows from this scenario that the transition state for the ring-closure step is early, as a late, product-like transition state would result in a kinetic preference for **E**. In an early transition state, the attacking carbamate ought still to be protonated and the nucleophilic lone pair to have considerable p-character, whereas, after ring closure and deprotonation, it ends up as a σ bond. Thus, the conformation of the forming ring at the transition state for ring closure will be rather different from that of the final ring in the product. There is therefore no reason to expect the same set of torsional strains in the transition state as in the product and, consequently, no reason for the kinetic and thermodynamic stereoselectivity to have the same bias.

Scheme 3



Finally, we returned briefly to an old theme in this laboratory, namely, the alkylation of tryptophan with inversion of configuration. Our original interest in the chemistry of cyclic tautomers of tryptophan was in alkylation at the stereogenic center with clean retention or inversion without recourse to the use of a chiral auxiliary. We were very successful with retention using **4** and related products. Here, the enolate is quenched under kinetic conditions exclusively on the exo face, i.e., with clean retention of configuration. Moreover, this chemistry was very practical as **4** could be obtained stereochemically pure in excellent yield from L-tryptophan.[3,20] We were much less successful with inversion, which would allow passage from the cheap L-tryptophan series to the more expensive D series. We were able to demonstrate that the kinetic product **32** did indeed undergo alkylation with clean inversion of configuration.[13] However, the rapid equilibration of **2** and **3** under the H_3PO_4 cyclization conditions meant that **32** could only be obtained in very low yield, which rendered the process inefficient and unattractive. We have now taken advantage of the formation of **19** as the major isomer from closure of **17** under kinetic conditions (Table 1) to briefly demonstrate this alkylation with inversion. Thus, **19** was deprotonated with LDA at −78 °C in THF and the resulting enolate treated with methyl iodide and *p*-bromobenzyl bromide (Scheme 3). In each case, alkylation occurred in moderate yield with clean inversion of configuration as signaled by the now familiar change in chemical shift of the ester Me group in the ^1H NMR spectra. A byproduct from the reaction with methyl iodide was the tetrahydropyrroloindole **35**. Treatment of both **33** and **34** with neat TFA at room temperature brought

(22) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, in press.

about the ring opening and provided the respective α-alkylated D-tryptophans **36** and **37** in excellent yield.

Experimental Section

General Methods. All solvents were dried and distilled by standard means. All experiments were conducted under an atmosphere of dry N_2 or Ar. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz in $CDCl_3$ solution unless otherwise stated. Chemical shifts (δ) are in ppm downfield from tetramethylsilane. Microanalyses were conducted by Midwest Microlabs, Indianapolis, IN.

Hexahydropyrrolindoles 12 and 13. General Protocol for Cyclization with *N*-Benzeneselenyl Phthalimide. To a solution of **11** (0.403 g, 0.964 mmol) in dry dichloromethane (6 mL) were added Na_2SO_4 (1.5 g), and *p*-TsOH·H_2O (19 mg, 0.10 mmol, 10 mol %) successively. The resulting mixture was stirred for 5 min before *N*-phenylselenyl phthalimide (1.5 equiv, 0.438 g, 1.45 mmol) was added. The system was stirred at room temperature under Ar for 24−48 h. The reaction was worked up by addition of EtOAc (30 mL) and H_2O (15 mL). The water layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue taken up in chloroform and hexane and filtered. The filtrate was concentrated to dryness and the residue purified with flash chromatography on silica gel (hexane/EtOAc 1:1) and afforded the pure title compound as an amorphous white solid (0.333 g, 65%; 100% conversion based on recovered **11**) as an exo/endo inseparable mixture (exo/endo ca. 9:1): $[\alpha]^{20}_D = -78.4°$ (c = 1.9, $CHCl_3$); ^{1}H NMR δ endo (**12** taken from mixture) 7.36−6.94 (m, 9 H), 6.31 (s, 1 H), 4.42 (br d, J = 7.2 Hz, 1 H), 3.07 (s, 3 H), 2.91 (d, J = 12.4 Hz, 1 H), 2.60 (dd, J = 12.4, 9.6 Hz, 1 H), 1.54 (s, 9 H), 1.40 (br s, 9 H); ^{1}H NMR δ exo (**13** taken from mixture) 7.36−6.94 (m, 9 H), 6.26 (s, 1 H), 3.89 (dd, J = 9.8, 6.6 Hz, 1 H), 3.63 (s, 3 H), 2.88 (dd, J = 12.4, 6.6 Hz, 1 H), 2.36 (dd, J = 12.4, 6.6 Hz, 1 H), 1.54 (s, 9 H), 1.33 (br s, 9 H); ^{13}C NMR exo/endo mixture δ 172.4 (br), 152.2, 142.0, 137.6, 132.6, 129.5, 129.3, 129.0, 126.2, 123.5, 117.3 (br), 82.6 (br), 81.7, 80.8 (br), 60.5, 59.2, 54.7 (br), 52.3, 52.0, 38.7, 28.4 (br). Anal. Calcd for $C_{28}H_{34}N_2O_6Se·^3/_2H_2O$: C, 56.00; H, 6.21. Found: C, 56.34; H, 5.94.

Hexahydropyrrolindoles 15 and 16 were obtained in 76% yield as a 12/1 exo/endo mixture from which the pure exo isomer (**16**), a glass, was obtained by column chromatography. **16**: $[\alpha]^{20}_D = -74.5°$ (c = 1.73, $CHCl_3$); ^{1}H NMR δ 7.03−7.45 (m, 9 H), 6.32 (s, 1 H), 5.24 (br s, 1 H), 5.14 (br s, 1 H), 3.99 (dd, J = 9.7, 6.7 Hz, 1 H), 3.69 (s, 3 H), 3.46 (br s, 3 H), 2.98 (dd, J = 12.6, 6.7 Hz, 1 H), 2.44 (dd, J = 12.6, 9.7 Hz, 1 H); ^{13}C NMR δ 171.9, 152.9, 141.3, 137.5, 136.0, 132.6, 129.5, 128.9, 128.8, 128.5, 125.6, 124.4, 123.6, 117.6, 83.1, 67.9, 59.2, 52.8, 52.6, 38.2. Anal. Calcd for $C_{28}H_{26}N_2O_6Se·H_2O$: C, 57.64; H, 4.84. Found: C, 57.88; H, 4.74. **15** was not isolated pure, but key data were taken from a mixture: ^{1}H NMR δ 7.60−6.96 (m, 14 H), 6.37 (s, 1 H), 5.26 (br s, 1 H), 5.17 (br s, 1 H), 4.53 (br d, 1 H), 3.58 (br s, 3 H), 3.09 (s, 3 H), 3.01 (d, J = 12.4 Hz, 1 H), 2.69 (dd, J = 12.4, 6.6 Hz, 1 H).

Hexahydropyrrolindoles 18 and 19 were obtained in 83% yield as an 11/1 exo/endo mixture from which both isomers were obtained pure by column chromatography. **19**: mp 57−59 °C; $[\alpha]^{20}_D = -100.6°$ (c = 2.76, $CHCl_3$); ^{1}H NMR δ 7.07−7.23 (m, 9H), 6.30 (s, 1 H), 4.00 (dd, J = 9.6, 6.8 Hz, 1 H), 3.78 (br s, 3 H), 3.69 (s, 3 H), 3.61 (br s, 3 H), 2.98 (dd, J = 12.7, 6.8 Hz, 1 H), 2.44 (dd, J = 12.7, 9.6 Hz, 1 H); ^{13}C NMR δ 171.7, 153.2, 141.1, 137.2, 132.2, 129.3, 128.7, 125.4, 124.1, 123.4, 117.3, 83.1, 58.9, 52.8, 52.4, 38.0. Anal. Calcd for $C_{22}H_{22}N_2O_6Se·^1/_2H_2O$: C, 53.02; H, 4.65. Found: C, 52.66; H, 4.76. **18**: $[\alpha]^{20}_D = +12.1°$ (c = 1.17, $CHCl_3$); ^{1}H NMR δ 7.13−7.33 (m, 8 H), 7.03 (t, J = 7.5 Hz, 1 H), 6.32 (s, 1 H), 4.51 (br d, 1 H), 3.76 (s, 3 H), 3.69 (br s, 3 H), 3.07 (s, 3H), 3.01 (d, J = 12.9 Hz, 1 H), 2.67 (dd, J = 12.9, 9.1 Hz, 1 H); ^{13}C NMR δ 170.9, 153.3, 137.3, 129.4, 129.3, 128.8, 125.7, 123.9, 123.7, 117.1, 83.6, 59.3, 52.8, 52.0, 39.0. Anal. Calcd for $C_{22}H_{22}N_2O_6Se·^1/_2H_2O$: C, 53.02; H, 4.65. Found: C, 53.43; H, 4.66.

Hexahydropyrrolindole 22, a viscous yellow oil, was obtained in 40% yield as the pure exo isomer: $[\alpha]^{20}_D = -62.0°$ (c = 0.83, $CHCl_3$); ^{1}H NMR δ 7.91 (m, 2 H), 7.21−7.52 (m, 10 H), 7.03 (t, J = 7.3 Hz, 1 H), 6.92 (d, J = 6.9 Hz, 1 H), 6.17 (br s, 1 H), 3.86 (dd, J = 10.0, 6.2 Hz, 1 H), 3.61 (s, 3 H), 3.59 (s, 3 H), 2.74 (dd, J = 12.7, 6.2 Hz, 1 H), 2.37 (dd, J = 12.7, 10.0 Hz, 1 H); ^{13}C NMR δ 171.2, 154.3, 140.6, 139.5, 137.6, 133.4, 129.9, 129.6, 129.4, 128.9, 128.6, 127.9, 126.48, 125.4, 124.1, 118.0, 84.9, 59.2, 52.8, 52.5, 39.9. Anal. Calcd for $C_{26}H_{24}N_2O_6SSe$: C, 54.64; H, 4.23. Found: C, 54.59; H, 4.32.

Hexahydropyrrolindole 25, a pale yellow solid, was obtained in 31% yield as the pure exo isomer: mp 75−77 °C; $[\alpha]^{20}_D = -35.6°$ (c = 1.45, $CHCl_3$); ^{1}H NMR δ 7.86 (br d, 2 H), 7.49 (d, J = 7.3 Hz, 2 H), 7.31−7.41 (m, 4 H), 7.23 (t, J = 7.8 Hz, 1 H), 7.02 (t, J = 7.4 Hz, 1 H), 6.93 (m, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.16 (s, 1 H), 3.86 (dd, J = 10.2, 6.2 Hz, 1 H), 3.78 (s, 3 H), 3.71 (br s, 3 H), 3.60 (br s, 3 H), 2.73 (dd, J = 12.6, 6.2 Hz, 1 H), 2.36 (dd, J = 12.6, 10.2 Hz, 1 H); ^{13}C NMR δ 171.1, 163.3, 140.5, 137.4, 133.2, 130.7, 130.3, 129.7, 129.5, 126.5, 125.1, 123.8, 117.68, 113.8, 84.7, 58.9, 55.5, 55.2, 52.7, 52.3, 52.1, 39.6. Anal. Calcd for $C_{27}H_{26}N_2O_7SSe$: C, 53.91; H, 4.36. Found: C, 54.02; H, 4.53.

***N*$_{ind}$-Methyl-2-phenylselenyl-*N*$_\alpha$-methoxycarbonyl-L-tryptophan Methyl Ester (28).** Application of the general protocol for cyclization to **27** yielded only the title compound, as a white solid, in 85% yield: $[\alpha]^{20}_D = +25.3°$ (c = 0.38, $CHCl_3$); ^{1}H NMR δ 7.65 (d, J = 7.8 Hz, 1 H), 7.04−7.35 (m, 8 H), 5.20 (d, J = 7.7 Hz, 1 H), 4.66 (br dd, J = 13.9, 6.6 Hz, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H), 3.59 (s, 3 H), 3.44 (ABX system, J = 29.4, 14.5, 6.6 Hz, 2 H); ^{13}C NMR δ 172.7, 156.5, 138.7, 132.2, 129.7, 128.8, 127.3, 126.6, 124.7, 123.4, 120.0, 119.4, 117.9, 110.2, 54.9, 52.6, 52.4, 31.8, 29.4. Anal. Calcd for $C_{21}H_{22}N_2O_4Se$: C, 56.63; H, 4.98. Found: C, 56.72; H, 5.01.

Hexahydropyrrolindole 31. General Protocol for Reduction with Tributyltin Hydride. *n*-Bu_3SnH (0.568 mL, 2.04 mmol) was added to a solution of diphenyl diselenide[23] (47.7 mg, 0.15 mmol, 15 mol %) in degassed toluene (5.0 mL) at room temperature under Ar. The yellow solution was stirred at room temperature for 30 min until the system became almost colorless. Then a solution of **19** (0.481 g, 1.02 mmol) and AIBN (25.6 mg, 0.153 mmol, 15 mol %) in degassed toluene (2.0 mL) was added dropwise. The resulting solution was refluxed for 12 h before it was cooled to room temperature, diluted with EtOAc (30 mL) and H_2O (15 mL), and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, the residue dissolved in methanol (3.0 mL), and $NaBH_4$[24] (77.5 mg, 2.04 mmol) added. After the mixture was stirred for 5−10 min at room temperature, the methanol was removed in vacuo and the residue subjected to flash chromatography on silica gel (hexane/EtOAc 1:2) to afford the title compound as a white solid (0.31 g, 90%): $[\alpha]^{20}_D = -111.2°$ (c = 0.17, $CHCl_3$); ^{1}H NMR δ 7.64 (d, J = 8.0 Hz, 1 H), 7.24 (t, J = 7.7 Hz, 1 H), 7.17 (d, J = 7.4 Hz, 1 H), 7.05 (dt, J = 7.4, 0.9 Hz, 1 H), 6.35 (d, J = 5.8 Hz, 1 H), 4.00 (m, 1 H), 3.86 (s, 3 H), 3.72 (s, 3 H), 3.64 (s, 3 H), 2.59 (dd, J = 12.8, 7.1 Hz, 1 H), 2.31 (ddd, J = 12.8, 9.6, 7.1 Hz, 1 H); ^{13}C NMR δ 172.8, 154.0, 141.7, 131.5, 128.8, 124.1, 123.6, 117.3, 77.1, 59.1, 53.1, 52.9, 52.5, 45.4, 32.6. Anal. Calcd for $C_{16}H_{18}N_2O_6·^1/_2H_2O$: C, 55.98; H, 5.58. Found: C, 56.08; H, 5.66.

Hexahydropyrrolindoles 29 and 30. Reduction of a 1:9 mixture of **12** and **13** according to the general protocol gave 94% of a 1:9 mixture of **29** and **30**, in the form of a white foam: mp 53−55 °C; $[\alpha]^{20}_D = -58.8°$ (exo/endo c = 3.0, $CHCl_3$); ^{1}H NMR δ endo (**29** taken from mixture) 6.41 (d, J = 6.7 Hz, 1 H), 4.56 (d, J = 8.8 Hz, 1 H), 3.13 (s, 3 H), 1.54 (s, 9 H), 1.46 (s, 9 H); exo (**30** taken from mixture) 6.37 (d, J = 5.9 Hz, 1 H), 3.95 (dd, J = 9.9, 7.1 Hz, 1 H), 3.72 (s, 3 H), 2.54 (dd, J = 12.7, 7.1 Hz, 1 H), 2.28 (ddd, J = 12.9, 9.9, 7.1 Hz, 1 H), 1.57 (s, 9 H), 1.40 (s, 9 H); exo/endo (overlapping data) 7.53 (br s,

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1 H), 7.26−6.96 (m, 3 H), 3.96 (m, 1 H); ^{13}C NMR (exo/endo) δ 173.1, 152.3, 142.3, 132.0, 128.2, 123.4, 117.6, 81.5, 80.7, 76.7, 58.9, 52.1, 44.7, 32.8, 28.3, 28.1. Anal. Calcd for $C_{22}H_{30}N_2O_6 \cdot 0.5H_2O$: C, 61.80; H, 7.31. Found: C, 61.77; H, 7.36.

Hexahydropyrrolindole 32. Reduction of **25** according to the general protocol gave 74% of **32**:[13] $[\alpha]^{20}_D = -167.2°$ (c = 0.75, $CHCl_3$); ^{1}H NMR δ 7.60 (d, J = 8.0 Hz, 2 H), 7.58 (br s, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.12 (t, J = 7.2 Hz, 1 H), 7.03 (d, J = 7.2 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 2 H), 6.12 (d, J = 4.8 Hz, 1 H), 3.97 (br t, 1 H), 3.79 (s, 6 H), 3.72 (s, 3 H), 3.40 (br m, 1 H), 2.37 (ddd, J = 12.8, 6.9, 2.2 Hz, 1 H), 2.22 (dt, J = 12.8, 7.9 Hz, 1 H).

Equilibration of a 1:9 Mixture of 12 and 13 in *tert*-Butyl Alcohol-d_{10} with Catalytic Potassium *tert*-Butoxide. Equilibration of a 1:9 mixture of **12** and **13**, as described below for **19**, led to a 70/30 endo/exo mixture of **12**:**13** and their enantiomers with complete exchange of the enolizable protons in all products. The specfic rotation of the final mixture was $[\alpha]_D = -34°$ (c 3.0, $CHCl_3$): ^{1}H NMR δ endo (±**12**-d_1 taken from mixture) 7.36−6.93 (m, 9 H), 6.31 (s, 1 H), 3.08 (s, 3 H), 2.92 (d, J = 12.9 Hz, 1 H), 2.61 (d, J = 12.9 Hz, 1 H), 1.55 (s, 9 H), 1.41 (br s, 9 H); δ exo (±**13**-d_1 taken from mixture) 7.36−6.93 (m, 9 H), 6.27 (s, 1 H), 3.65 (s, 3 H), 2.89 (d, J = 12.4 Hz, 1 H), 2.37 (d, J = 12.4 Hz, 1H), 1.55 (s, 9 H), 1.34 (s, 1 H).

Equilibration of 19 in *tert*-Butyl Alcohol-d_{10} with Catalytic Potassium *tert*-Butoxide. 19 (11.2 mg, 0.023 mmol) in *t*-BuOH-d_{10} (0.55 mL) in an NMR tube was treated with *t*-BuOK powder (ca. 20 mol %) under Ar at 40 °C. An ^{1}H NMR spectrum taken after 15 min showed isomerization. A further spectrum recorded after 45 min, 22, 60, and 70 h showed no difference to the one taken after 15 min. The reaction mixture was filtered through a short silica gel column (0.5 × 0.5 cm), eluting with $CHCl_3$. The solvent was removed under vacuum and the mixture reexamined by ^{1}H NMR spectroscopy in $CDCl_3$ when it was determined that 100% d substitution had occurred at the enolizable carbon of both products and that the endo/exo ratio was 80:20: $[\alpha]^{20}_D = -37.5°$ (c = 0.73, $CHCl_3$); ^{1}H NMR δ endo (**18**-d_1 taken from mixture) 7.44−6.98 (m, 9 H), 6.35 (s, 1 H), 3.78 (s, 3 H), 3.70 s, 3 H), 3.10 (s, 3 H), 3.00 (d, J = 13.0 Hz, 1 H), 2.67 (d, J = 13.0 Hz, 1 H); δ exo (**19**-d_1 taken from mixture) 7.44−6.98 (m, 9 H), 6.31 (s, 1 H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.61 (s, 3 H), 2.97 (d, J = 12.9 Hz, 1 H), 2.45 (d, J = 12.9 Hz, 1 H).

Equilibration of 25 in *tert*-Butyl Alcohol-d_{10} with Catalytic Potassium *tert*-Butoxide. Equilibration of **25**, as described above for **19**, led to an 86/14 endo/exo mixture with complete exchange of the enolizable protons in both products: $[\alpha]^{20}_D = +6.7°$ (c = 0.46, $CHCl_3$); ^{1}H NMR δ endo (**24**-d_1 taken from mixture) 7.89 (d, J = 8.9 Hz, 2 H), 7.50 (d, J = 6.9 Hz, 2 H), 7.38−6.90 (m, 9 H), 6.31 (s, 1 H), 3.82 (s, 3 H), 3.52 (s, 3 H), 3.16 (s, 3 H), 2.89 (d, J = 12.9 Hz, 1 H), 2.59 (d, J = 12.9 Hz) δ exo (**25**-d_1 taken from mixture) 7.89 (d, J = 8.9 Hz, 2 H), 7.50 (d, J = 6.9 Hz, 2 H), 7.38−6.90 (m, 9 H), 6.17 (s, 1 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.61 (s, 3 H), 2.72 (d, J = 12.9 Hz, 1 H), 2.40 (d, J = 12.9 Hz, 1 H).

General Procedure for Alkylation with Inversion of Configuration. Hexahydropyrrolindole 33 and Tetrahydropyrrolindole 35. To a solution of **19** (0.115 g, 0.24 mmol) in THF (4 mL) LDA (0.96 mL, 0.48 mmol, 0.5 M in THF) was added dropwise at −78 °C. After the solution was stirred at −78 °C for 0.5 h, MeI (0.075 mL, 1.2 mmol, 5 equiv) was added dropwise. After 3 h, the reaction was quenched with saturated NH_4Cl solution (15 mL) and EtOAc (30 mL) and then extracted with EtOAc (3 × 15 mL). The combined EtOAc phases were washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford **33** (65 mg, 54%) and **35** (17 mg, 21%) both as colorless oils. **33**: $[\alpha]^{20}_D = -40.0°$ (c = 2.73, $CHCl_3$); ^{1}H NMR δ 7.11−7.48 (m, 8 H), 7.02 (t, J = 7.3 Hz, 1 H), 6.35 (s, 1 H), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.18 (d, J = 13.3 Hz, 1 H), 2.97 (s, 3 H), 2.43 (d, J = 13.3 Hz, 1 H), 1.62 (s, 3 H); ^{13}C NMR δ 173.4, 154.0, 153.8, 142.7, 137.5, 129.6, 129.4, 129.3, 128.9, 125.9, 123.9, 123.8, 123.6, 117.5, 85.1, 66.6, 53.1, 52.5, 52.3, 48.3, 25.7. Anal. Calcd for $C_{23}H_{24}N_2O_6Se$: C, 54.88; H, 4.80. Found: C, 54.55; H, 4.95. **35:** $[\alpha]^{20}_D = -2.7°$ (c = 1.07, $CHCl_3$); ^{1}H NMR δ 7.94 (m, 1 H), 7.18−7.26 (m, 3 H), 3.95 (s, 3 H), 3.76 (s, 6 H), 3.43 (d, J = 14.8 Hz, 1 H), 2.92 (d, J = 14.8 Hz, 1 H), 1.85 (s, 3 H); ^{13}C NMR δ 172.6, 153.3, 151.6, 140.3, 138.8, 125.3, 123.7, 122.7, 117.7, 114.9, 104.7, 75.9, 54.3, 53.3, 53.0, 38.4, 24.5. Anal. Calcd for $C_{17}H_{18}N_2O_6 \cdot {}^1/_2H_2O$: C, 57.46; H, 5.39. Found: C, 57.95; H, 5.36.

Hexahydropyrroloindole 34. Alkylation of **19** with *p*-bromobenzyl bromide according to the general protocol gave 46% yield of **34**, as a colorless oil: $[\alpha]^{20}_D = -31.0°$ (c = 1.16, $CHCl_3$); ^{1}H NMR δ 7.01−7.59 (m, 11 H), 6.83 (d, J = 7.9 Hz, 2 H), 5.89 (s, 1 H), 3.82 (s, 3 H), 3,72 (s, 3 H), 3.04 (d, J = 13.4 Hz, 1 H), 3.02 (s, 3 H), 2.93 (d, J = 14.9 Hz, 2 H), 2.48 (d, J = 13.4 Hz, 1 H); ^{13}C NMR δ 173.3, 154.2, 138.1, 137.5, 134.2, 132.5, 131.8, 129.7, 129.5, 129.3, 125.9, 124.1, 123.6, 121.4, 117.7, 84.1, 70.0, 53.2, 52.6, 52.4, 42.2, 38.3. Anal. Calcd for $C_{29}H_{27}BrN_2O_6Se \cdot {}^3/_2H_2O$: C, 50.82; H, 4.41. Found: C, 50.76; H, 4.33.

D-Tryptophan 36. 33 (0.047 g, 0.1 mmol) was stirred in TFA (2.0 mL) at room temperature for 4 h followed by removal of the solvent in vacuo. The ^{1}H NMR spectrum showed complete conversion to **36**, which could subsequently be isolated by filtration on silica gel, as a colorless oil: $[\alpha]^{20}_D = -42.9°$ (c = 0.68, $CHCl_3$); ^{1}H NMR δ 8.12 (br d, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.21−7.33 (m, 3 H), 5.48 (s, 1 H), 4.02 (s, 3 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.54 (d, J = 14.4 Hz, 1 H), 3,31 (d, J = 14.4 Hz, 1 H), 1.68 (s, 3 H); ^{13}C NMR δ 174.1, 155.3, 135.0, 130.9, 124.6, 124.0, 122.7, 119.0, 115.9, 115.1, 77.1, 60.3, 53.7, 52.7, 51.8, 31.4, 23.7. Anal. Calcd. for $C_{17}H_{20}N_2O_6 \cdot {}^1/_2H_2O$: C, 57.14; H, 5.92. Found: C, 56.86; H, 5.86.

D-Tryptophan 37. Treatment of **34** with TFA, as described above for **36**, gave 94% of **37** in the form of an amorphous white solid: mp 115−117 °C; $[\alpha]^{20}_D = -15.3°$ (c = 0.51, $CHCl_3$); ^{1}H NMR δ 8.11 (br d, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 2 H), 7.20−7.33 (m, 3 H), 6.93 (d, J = 8.3 Hz, 2 H), 5.58 (s, 1 H), 4.02 (s, 3 H), 3.95 (d, J = 13.6 Hz, 1 H), 3.89 (d, J = 13.6 Hz, 1 H), 3.73 (s, 3 H), 3.65 (s, 3 H), 3.30 (d, J = 31.0 Hz, 1 H), 3.26 (d, J = 31.0 Hz, 1 H); ^{13}C NMR δ 172.2, 155.2, 135.0, 131.2, 130.7, 124.6, 124.0, 122.6, 121.0, 119.0, 115.7, 115.1, 65.9, 53.7, 52.6, 51.9, 40.4, 30.9. Anal. Calcd for $C_{23}H_{23}BrN_2O_6$: C, 54.88; H, 4.60; Found: C, 54.60; H, 4.80.

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Supporting Information Available: Procedures for the preparation of **11**, **14**, **17**, **20**, **23**, and **27** together with full characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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