Enantiospecific Formation of *Trans* 1,3-Disubstituted Tetrahydro-β-carbolines by the Pictet−Spengler Reaction and Conversion of *Cis* Diastereomers into Their *Trans* Counterparts by Scission of the C-1/N-2 Bond

Eric D. Cox, Linda K. Hamaker, Jin Li, Peng Yu, Kevin M. Czerwinski, Li Deng, Dennis W. Bennett, and James M. Cook*

Department of Chemistry, University of Wisconsin−Milwaukee, Milwaukee, Wisconsin 53201

William H. Watson and Mariusz Krawiec

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

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The factors which effect the stereoselective formation of *trans*-1-alkyl-2-benzyl-3-(alkoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines and *trans*-3-(alkoxycarbonyl)-1-alkyl-2-(diphenylmethyl)-1,2,3,4-tetrahydro-β-carbolines by the Pictet−Spengler cyclization were examined by heating tryptophan derivatives with aldehydes of varied steric bulk under aprotic and acidic conditions, followed by determination of the ratio of *cis* to *trans* diastereomers so formed. The presence of a benzyl group at the N_b-nitrogen atom alters the diastereochemical outcome of this condensation to provide 100% *trans* stereoselectivity when the cyclization is carried out with cyclohexanecarboxaldehyde. Furthermore, when N_b-(diphenylmethyl)tryptophan isopropyl ester was condensed with aldehydes of any size, *trans* diastereomers are formed with 100% stereoselectively. The *trans* N_b-substituted diastereomers are thermodynamically more stable than their *cis* congeners as shown by equilibration experiments in TFA. Conversion of the *cis* diastereomers into the more stable *trans* diastereomers is believed to occur under acidic conditions by cleavage of the carbon (C-1)−nitrogen (N-2) bond with complete retention of configuration at the C-3 stereocenter. Evidence from deuterium exchange experiments as well as optical rotations support this model for epimerization. In addition, when *cis* diastereomer **66a** was allowed to stir in CF_3COOD, the *trans* isomer **66b** was isolated in 90% yield, while treatment of *cis* **66a** with $CF_3COOH/NaBH_4$ provided a mixture of the ring cleaved [scission across C(1)−N(2) bond] product **67** and the *trans* isomer **66b**. Treatment of **66b** (control experiment) with $NaBH_4/CF_3COOH$ under the same conditions returned only starting *trans* **66b** in excellent yield. The Pictet−Spengler reaction of substrates with sufficiently large substituents, followed by treatment with acid, permits the 100% enantiospecific formation of *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines for alkaloid total synthesis.

Introduction

The Pictet−Spengler reaction has long been an important reaction for the syntheses of both indole and isoquinoline alkaloids.[1] Discovered in 1911 by Amé Pictet and Theodor Spengler, the reaction was first utilized to prepare simple tetrahydroisoquinolines by heating phenethylamine, phenylalanine, and tyrosine with methylal, individually, in the presence of hydrochloric acid.[2] It was Tatsui, apparently, who first utilized this method with indole bases, specifically for the synthesis of 1-methyl-1,2,3,4-tetrahydro-β-carboline (tetrahydroharmane).[3] The condensation by Ungemach et al. of N_b-benzyltryptophan methyl ester with aldehydes of large steric size was significant for it led to the 100% stereoselective formation of *trans*-1,3-disubstituted diastereomers (Scheme 1) in the methyl ester series.[4] Furthermore, development of this enantiospecific Pictet−Spengler reaction has since facilitated the total synthesis of a number of indole alkaloid natural products including (−)-sauveoline,[5,6] (−)-raumacline,[5,6] (−)-N_b-methylraumacline,[5,6] (−)-alstonerine,[7] and (+)-macroline.[8] The central intermediate in the syntheses of all of these monomeric indole alkaloids is the tetracyclic ketone **3**; the enantiospecific Pictet−Spengler reaction is the key step in its formation.[9,10]

Underlying interest in the enantiospecific Pictet−Spengler reaction dates back to the work of Ungemach et al.[4,11] He was able to show that introduction of a benzyl function at the N_b-nitrogen moiety permitted control of the stereochemical outcome of this cyclization. Condensation of (±)-N_b-benzyltryptophan methyl ester with cyclohexanecarboxaldehyde under nonacidic aprotic

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(9) Zhang, L. H.; Bi, Y.; Yu, F.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, *34*, 517. Previously a typographical error led to the report of the rotation of the *trans* isomer in the 3(*R*)[10] series as −36° rather than the correct −56 ± 2°. The optical rotation of **64b** [3(*S*) series] was +54.8°; moreover, the tetracyclic ketone prepared from the *trans* isomer in both the 3(*R*) and 3(*S*)[10] series had the same optical rotation as reported, although the sign was opposite.

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Scheme 1. Enantiospecific Synthesis of the Tetracyclic Ketone 3 by the Pictet−Spengler Condensation

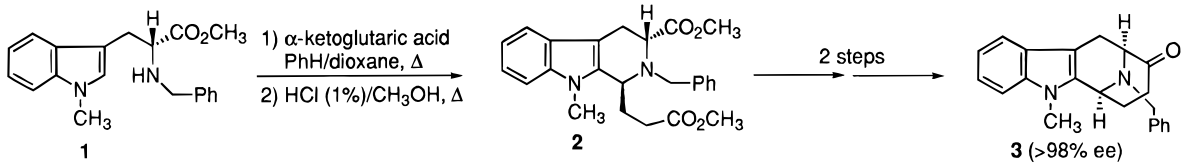
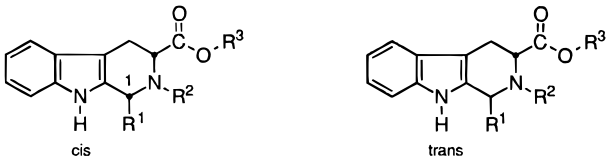


Table 1. *Cis*:*Trans* Ratios[a] of 1,2-Disubstituted and 1,2,3-Trisubstituted Tetrahydro-β-carbolines



compd no.	R^1	R^2	R^3	nonacidic aprotic *cis*:*trans*	acidic *cis*:*trans*
4a,4b	CH_3	H	CH_3	NA	75:25
5a,5b	CH_2CH_3	H	CH_3	NA	43:57[b]
6a,6b	C_6H_{11}	H	CH_3	40:60	41:59[b]
7a,7b	CH_3	Bn	CH_3	26:74	12:88
8a,8b[c]	$CH_2CH_2CH_3$	Bn	CH_3	23:77	11:89[c,e]
9	C_6H_{11}	Bn	CH_3	0:100	0:100
10a,10b	CH_3	Bn	$CH(CH_3)_2$	23:77	13:87
11a,11b	$CH_2CH_2CH_3$	Bn	$CH(CH_3)_2$	13:87	12:88
12	C_6H_{11}	Bn	$CH(CH_3)_2$	0:100	0:100
13a,13b	CH_3	$CH(Ph)_2$	CH_3	10:90	0:100
14	$CH_2CH_2CH_3$	$CH(Ph)_2$	CH_3	0:100	0:100
15	C_6H_{11}	$CH(Ph)_2$	CH_3	0:0[d]	0:100
16	CH_3	$CH(Ph)_2$	$CH(CH_3)_2$	0:100	0:100
17	$CH_2CH_2CH_3$	$CH(Ph)_2$	$CH(CH_3)_2$	0:0[d]	0:100
18	C_6H_{11}	$CH(Ph)_2$	$CH(CH_3)_2$	0:0[d]	0:100

[a] ±3% as determined by integration of the ^1H NMR spectrum (compounds labeled "a" are the *cis* diastereomer and "b" the *trans*). [b] See ref 11. [c] Carried out in the optically active series. [d] These transformations yielded only starting materials under nonacidic aprotic conditions but were converted to tetrahydro-β-carbolines upon addition of TFA to the reaction medium. [e] When the equilibration was effected directly on the reaction mixture in benzene in the presence of aldehyde the ratio was determined as reported here. Pure **8a** in CF_3COOH was completely converted into **8b** in CH_2Cl_2.

conditions resulted in the 100% stereoselective formation of (±)-*trans*-2-benzyl-3-carbomethoxy-1-cyclohexyl-1,2,3,4-tetrahydro-β-carboline as noted above.[12,13] The advantage of this method centered on exclusive formation of the *trans* isomer after which the benzyl group could be easily removed by hydrogenolysis. The stereochemical configuration at C-1 could then be determined by ^{13}C NMR spectroscopy.[11] This afforded one diastereomeric tetrahydro-β-carboline in high yield as opposed to the mixture of diastereomers traditionally formed in Pictet−Spengler condensations.[1] The use of a benzyl group as a substituent at the N_b-nitrogen atom inverted the diastereochemical outcome of the Pictet−Spengler reaction from preferential formation of the *cis* isomer[1] to the *trans* isomer stereoselectively. Although diastereochemical product ratios had previously been reported[11,14,15] for the Pictet−Spengler reaction of N_a-H, N_b-H derivatives, systematic variation of the steric bulk of the substituents in the Pictet−Spengler condensation of N_b-benzyltryptophan derivatives was undertaken to determine the stereochemical scope of the process.[16,17] Examination of the results of these studies, presented here, permit the 100% stereospecific formation of any 3-(alkoxycarbonyl)-1-alkyltetrahydro-β-carboline regardless of the size of the desired alkyl substituent at position-1. This is especially important since both D-(+)-tryptophan and L-(−)-tryptophan are readily available resulting in the enantiospecific synthesis of either antipode via this process. Furthermore, evidence is presented here to suggest that conversion of the thermodynamically less stable *cis* diastereomers into their *trans* isomers occurs by cleavage of the carbon (position-1)−nitrogen (position-2) bond followed by recyclization to the *trans* isomer.

Results and Discussion

Previous reports highlighted the variance in the diastereochemical product ratios obtained when employing the Pictet−Spengler reaction.[11,14,15] Three such examples are shown in Table 1 (**4**−**6**). The ratios of diastereomers when acetaldehyde, propionaldehyde, and cyclohexanecarboxaldehyde were reacted with tryptophan methyl ester under acidic conditions reportedly varied from 75:25-*cis*:*trans* (**4a**:**4b**), to a more equal ratio of 43:57-*cis*-*trans* (**5a**:**5b**), to 41:59-*cis*-*trans* (**6a**:**6b**). (The terms *cis* and *trans* here refer to the stereocenters at C-1 and C-3 according to the β-carboline numbering convention; two representative structures are shown at the top of Table 1.) The only significant difference between these reactions is the size of the substituent at position C-1 of the tetrahydro-β-carboline.

To examine the effect the steric bulk of the incoming aldehyde had upon the diastereomeric ratio realized in the Pictet−Spengler condensation in the presence of a

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(13) De Silva, K. T. D.; King, D.; Smith, G. N. *J. Chem. Soc., Chem. Commun.* **1971**, 908.
(14) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.
(15) Brossi, A.; Focella, A.; Teitel, S. *J. Med. Chem.* **1973**, *16*, 418.
(16) Deng, L.; Czerwinski, K. M.; Cook, J. M. *Tetrahedron Lett.* **1991**, *32*, 175.
(17) Czerwinski, K. M.; Deng, L.; Cook, J. M. *Tetrahedron Lett.* **1992**, *33*, 4721−4724.

benzyl group at the amino nitrogen function, N_b-benzyltryptophan methyl ester was prepared[18] and reacted with acetaldehyde, butyraldehyde, and cyclohexanecarboxaldehyde individually under the conditions of Soerens et al.[4] This afforded a series of 1-alkyl-2-benzyl-3-(methoxycarbonyl)tetrahydro-β-carbolines in which the substituent at position-1 varied in steric bulk from the relatively small methyl group, to propyl, to the larger cyclohexyl moiety.

The reactants were heated in benzene at reflux under nonacidic aprotic conditions for 36 h. All the condensations were stopped after 36 h to provide uniform experimental conditions, thus enabling an unbiased comparison of the stereochemical effects of the various substituents. Chemical yields are thus unoptimized. The reactions utilizing acetaldehyde were carried out in a sealed glass tube to avoid loss of the aldehyde. Each aldehyde was purified by vacuum distillation and the IR spectrum measured to verify that the reactants were indeed free of acid. In all cases, after 36 h a small aliquot was removed and the proton NMR spectrum recorded. It was sometimes difficult to accurately measure the diastereomeric ratio due to impurities which masked the signals. In these cases the reaction mixture was passed through a short wash column of silica gel to remove the impurities, and the NMR spectrum was recorded once again. Comparison of the spectra before and after chromatography assured that the diastereochemical ratio had not been altered. Flash chromatography on silica gel permitted separation of the *cis* and *trans* diastereomers, and close examination of the NMR spectra of the individual diastereomers clearly illustrated which proton signals differed significantly between diastereomers. These signals were then used to determine the diastereomeric ratio of *cis* to *trans* isomers in the spectra of the mixtures. Although $CDCl_3$ was initially employed as the solvent for NMR spectroscopy, it was found that acidic impurities were in high enough concentration to effect epimerization of the *cis* diastereomers into their *trans* congeners. The cause of this epimerization will be expanded upon later. These impurities could be removed but it was found easier to employ C_6D_6 as the solvent for spectroscopy. Not only was it free of acidic impurities but its use generally provided a greater anisotropy between the critical signals in the proton NMR spectra of the *cis* and *trans* diastereomers. Catalytic transfer hydrogenation of the 1,2,3-trisubstituted species afforded 1,3-disubstituted-tetrahydro-β-carbolines that are generally well known compounds, consequently, the stereochemistry of the individual diastereomers could be unequivocally established by comparison of their ^{13}C NMR spectra.[11] Determination of the stereochemistry of these individual diastereomers had been carried out previously according to the method of Ungemach et al., a method which has been validated by independent sources.[11,19]

The condensation of N_b-benzyltryptophan methyl ester with acetaldehyde and butyraldehyde (individually) resulted in the formation of mixtures of *cis* and *trans* diastereomers. This condensation using cyclohexanecarboxaldehyde furnished only the *trans* diastereomer as was expected.[4] Examination of the product ratios for the condensations of N_b-benzyltryptophan methyl ester with acetaldehyde (26:74-*cis* **7a**:*trans* **7b**) and with butyraldehyde (23:77-*cis* **8a**:*trans* **8b**) revealed that the ratio of *cis* to *trans* for both was essentially the same. As the steric bulk of the substituents increased to cyclohexyl, however, the *cis* isomer was excluded from formation. Ungemach proposed this phenomenon was the result of a steric interaction between the ester function at C-3 and the alkyl group at C-1 in the *syn* spiroindolenine intermediate, as well as A-strain in the six-membered rearranged ring.[4]

Since aldehydes similar in size to an *n*-butyl group provided a mixture of diastereomers the synthetic potential of the process was limited. If Ungemach's hypothesis were correct, however, any increase in steric interactions between the ester and alkyl groups should shift the diastereomeric ratios toward increased *trans* stereoselectivity. To this end, replacement of the methyl ester function at C-3 with the larger isopropyl group was undertaken. The N_b-benzyltryptophan isopropyl ester was synthesized in a fashion analogous to the methyl ester,[14] after which the previously mentioned series of condensations was repeated, and the diastereomeric ratios were examined by proton NMR spectroscopy. Comparison of the diastereochemical ratios obtained in both series (**7**−**9** and **10**−**12**) showed that the condensation of N_b-benzyltryptophan isopropyl ester with butyraldehyde yielded an increased amount of the *trans* isomer. In the methyl ester series **8**, the ratio of *cis* **8a** to *trans* **8b** was 23:77 while in the isopropyl ester series **11** the quantity of *trans* isomer **11b** was increased to 13:87-*cis*:*trans*. The stereochemical configuration of the 1-cyclohexyl-3-isopropyl ester **12** was confirmed as *trans* by single crystal X-ray crystallography.

The previous work in this area clearly demonstrated that introduction of a benzyl group at the N_b-nitrogen function favored formation of the *trans* diastereomer. Substituents at the N_b-nitrogen atom have come under scrutiny previously, and it has been shown by Sandrin[20] et al. that electronic effects[21] play a significant role in the stereochemical outcome of the reaction. The effect the steric bulk of the N_b-alkyl function had upon the diastereochemical ratio had not been studied in detail. In order to increase the size of the substituent at the N_b-nitrogen atom without altering the electronic character of the group a diphenylmethyl moiety was employed. Introduction of this group was accomplished by transimination of the appropriate ester hydrobromide or hydrochloride salt with benzophenone imine according to the procedure of Polt and O'Donnell.[22] Reduction (Scheme 2) of the resultant imine with sodium cyanoborohydride in methanol under acidic conditions provided the desired N_b-diphenylmethyl-substituted tryptophan derivative. This protocol provided excellent yields, could easily be scaled up to the 10 g level, and was not subject to disubstitution or to the formation of quaternary ammonium salts. With the methyl and isopropyl esters of N_b-(diphenylmethyl)tryptophan (**27**, **28**) in hand, the series of condensations was repeated (benzene at reflux), and the diastereomeric ratios were measured by NMR spectroscopy. In the methyl ester series, the condensation with acetaldehyde furnished the desired products (**13a**, **13b**) as evidenced by ^1H and ^{13}C

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(19) Tóth, G.; Szántay, C.; Kalaus, G.; Thaler, G.; Snatzke, G. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1849.

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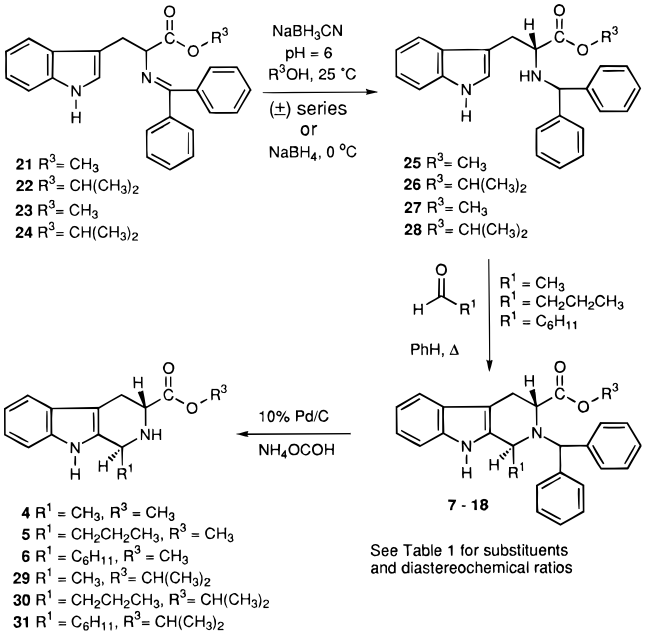
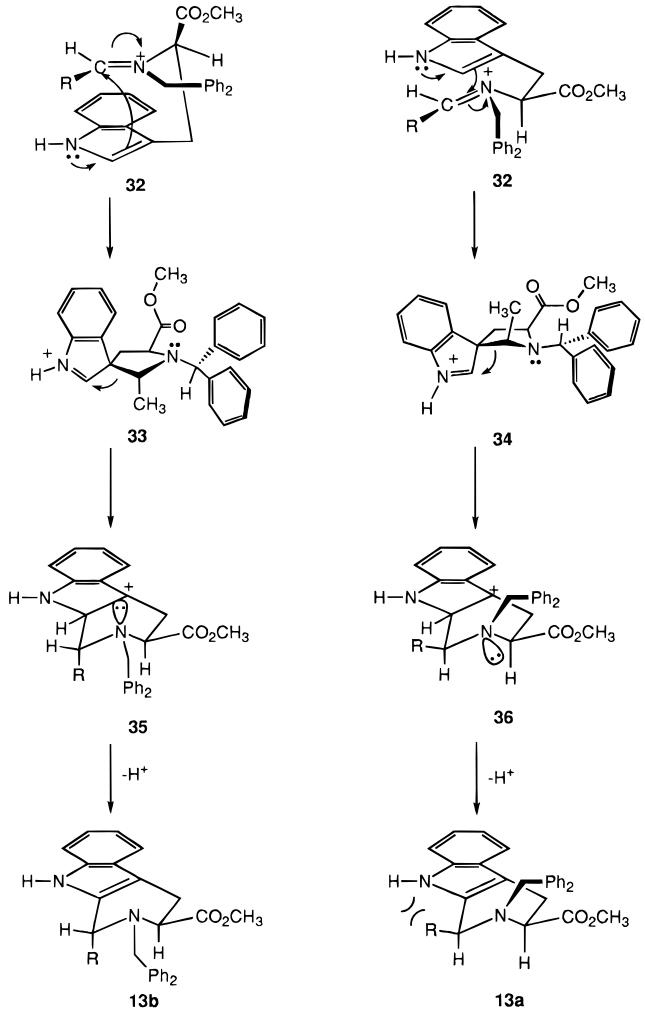
(22) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

Scheme 2. Synthesis of 1,2,3-Trisubstituted Tetrahydro-β-carbolines



See Table 1 for substituents and diastereochemical ratios

Scheme 3



NMR spectroscopy after initial removal of the non-indolic byproducts. However, attempts to isolate the *cis* diastereomer **13a** were unsuccessful. Only the *trans* diastereomer **13b** was found upon examination of the chromatography fractions. Moreover, the reaction of N_b-(diphenylmethyl)tryptophan isopropyl ester with acetaldehyde provided only the *trans* diastereomer **16**. In the methyl ester series the reaction of butyraldehyde also provided only the *trans* diastereomer **14**. In three of the cases (**15**, **17**, and **18**) no reaction was observed under nonacidic aprotic conditions after 36 h. Prolonged heating only increased the amount of byproducts which were formed. In order to effect cyclization it was necessary to add TFA to the reaction medium. The addition of TFA to catalyze the formation of **15**, **17**, and **18** resulted in the formation of only the *trans* diastereomer for each. Although TFA is known to cleave some diphenylmethyl groups,[23−25] at low concentrations it failed to do so here as evidenced by control reactions executed in the absence of aldehyde. For example, compounds **15**, **17**, **18**, **27**, and **28** were individually stirred under conditions identical to those employed in their formation in the absence of aldehyde and were monitored daily by TLC for a period of five days with no changes observed in retention factor or proton NMR spectrum. In all of the reactions which employed the diphenylmethyl group, the chemical yields are somewhat lower than the corresponding reactions in the benzyl cases. This is not unreasonable since the presence of such bulky moieties should retard the rate of the Pictet−Spengler condensation.[23−25] Under these conditions it was also observed that the amount of polymeric material increased due to self condensation of the aldehydes. This made chromatographic separations more difficult and further contributed to the decreased chemical yields.

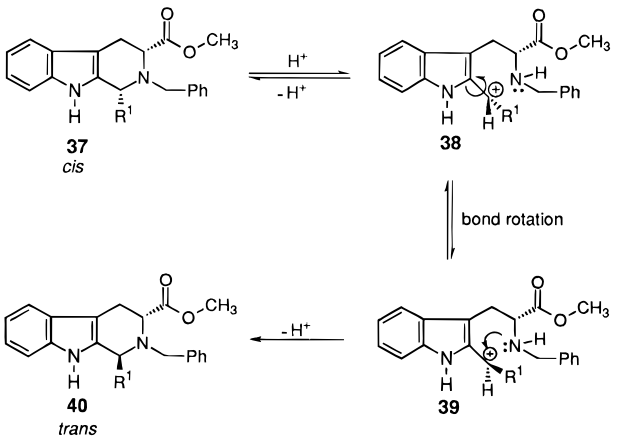
A comparison of the cyclizations which employed acetaldehyde show a marked trend. In the N_b-H case (**4**--75:25--*cis*:*trans*), the Pictet−Spengler reaction yielded the *cis* isomer as the major product. Introduction of a benzyl function at the N_b-nitrogen atom inverted the stereochemical outcome to provide the *trans* diastereomer under nonacidic aprotic conditions (**7**--26:74--*cis*:*trans*) as the major product. Furthermore, when the N_b-substituent was increased to the large diphenylmethyl group under similar conditions, a 100% stereoselective formation of the *trans* diastereomer **16** was observed in the isopropyl ester case.

This high *trans* diastereoselectivity under nonacidic aprotic conditions presumably results from the increased energy of the transition states involving the *cis* spiroindolenine intermediates (Scheme 3). Two distinct spiroindolenine intermediates may result from attack on the iminium ion double bond. In the N_b-(diphenylmethyl)-tryptophan methyl ester case, attack of the iminium ion **32** from the face opposite the ester function would provide the anti spiroindolenine **33**. Attack from the same face as that occupied by the ester would result in a spiroindolinine of *syn* configuration such as **34**. Molecular mechanics calculations combined with conformational searching (MacroModel 2.5 - MM2 force field) revealed that the anti configuration is 2.1 kcal/mol lower in energy than the syn configuration.[17] It is the anti isomer which rearranges to provide the *trans* diastereomer.

The data from the experiments under nonacidic aprotic conditions reflect ratios which are the result of kinetic trapping experiments. As noted earlier, however, if the mixtures of diastereomers realized in the nonacidic

(23) Pless, J. *Helv. Chim. Acta* **1976**, 59, 499.
(24) Hanson, R. W.; Law, H. D. *J. Chem. Soc.* **1965**, 7285.
(25) Zervas, L.; Photaki, I. *J. Am. Chem. Soc.* **1962**, *84*, 3887.

Scheme 4. Epimerization of the Stereocenter at C-1 by Cleavage of the C-1/N-2 Bond under Acidic Conditions

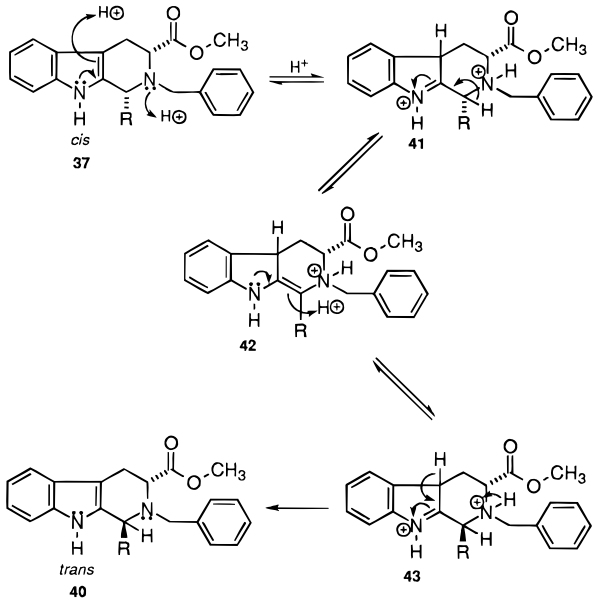


aprotic Pictet−Spengler reaction were exposed to a proton source, the diastereomeric ratios shifted to further increase the amount of *trans* isomer. This generality was confirmed by either the addition of TFA to a small aliquot of the reaction mixture or as in cases **15**, **17**, and **18**, by reaction in the presence of TFA to catalyze the cyclization. Examination of the ratios of **7a** to **7b**, **8a** to **8b**, **10a** to **10b**, and **13a** to **13b** clearly indicated that the ratio of *cis* diastereomer to *trans* diastereomer formed under nonacidic aprotic conditions was higher than that realized under acidic conditions. The method by which the conversion of the *cis* diastereomers into the more thermodynamically stable *trans* diastereomers takes place can now be rationalized.

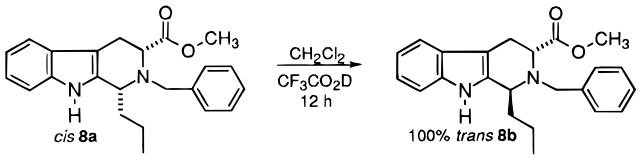
The work of Zhang[10] suggested that scission of the C-1/N-2 bond was involved in the *cis* to *trans* isomerization. He isolated a mixture of two byproducts formed in the Pictet−Spengler condensation of (D)(+)-N_a-methyl-N_b-benzyltryptophan methyl ester with methyl 3-formylpropionate. These byproducts, an olefin and a methyl ether, were heated as a mixture in 1% anhydrous methanolic hydrogen chloride after which the *trans* diastereomer was isolated as the sole product in 70% yield. The most probable intermediate from which all four of the isolated species could arise is one that is carbocationic in nature. Zhang proposed[10] (Scheme 4) that the mechanism by which these byproducts were formed was preceeded by protonation of the N_b-nitrogen atom with concomitant cleavage of the carbon (position-1)−nitrogen (position-2) bond. The carbocation so generated could undergo elimination to yield an olefin, attack by the solvent to form the ether, or after rotation of the C-1/C-10 carbon−carbon bond, recyclize to provide the *trans* diastereomer now epimeric at C-1. In addition, this appears to be the same mechanism of isomerism whereby reserpine is converted into isoreserpine as well as the epimerization of the C-1 stereocenter of (−)-1,2,3,4-tetrahydroroeharmine enroute to racemic material.[10,26,27]

Another possible mechanism for this *cis*−*trans* epimerization involves the initial protonation of the indole 3-position and subsequent formation of an olefinic species (Scheme 5). This olefin could then be attacked preferentially from one face to yield the thermodynamically more stable *trans* diastereomer. Although this model

Scheme 5. Olefin Protonation Mechanism for Epimerization of the Stereocenter at C-1



Scheme 6



$[\alpha]_D$ = - 13.3 ° (*c* = 1, C_6H_6) $[\alpha]_D$ = - 50.4 ° (*c* = 1.6, C_6H_6)

does not account for the formation of the two byproducts which Zhang observed, it could not be discounted without further examination.

In order to test the model for carbon−nitrogen bond cleavage versus the olefinic protonation model, two experiments were carried out. In the first, optically active N_b-benzyltryptophan methyl ester was synthesized from D-(+)-tryptophan according to the method employed by Zhang for the analogous N_a-methyl compound.[18] This material was heated under the nonacidic aprotic conditions of benzene at reflux under an atmosphere of nitrogen gas with freshly distilled butyraldehyde to provide the kinetic ratio of optically active diastereomers as a 23:77-*cis*:*trans* mixture. Separation of the diastereomers on silica gel with CH_2Cl_2 by gravity chromatography provided the pure *cis* **8a** and *trans* **8b** isomers. The specific rotation $[\alpha]^{25}_D$ of the (−)-*trans* diastereomer **8b** was measured as −50.4° (*c* = 1, benzene) and the *cis* **8a** as $[\alpha]^{25}_D$ = −13.3° (*c* = 1, benzene). The (−)-*cis* diastereomer **8a** was then taken up in CH_2Cl_2 and stirred with 2 equiv of TFA (Scheme 6). Examination of the mixture by TLC after 12 h revealed that **8a** had been completely converted into the *trans* compound **8b**. Workup with mild base ($NaHCO_3$) and chromatography on a short wash column of silica gel (CH_2Cl_2) yielded the pure (−)-*trans* diastereomer. The specific rotation $[\alpha]^{25}_D$ of this sample was −50.4° (*c* = 1.6, benzene). The specific rotations of the two (−)-*trans* compounds were identical (as well as the NMR and mass spectra) and presumably the epimerization that Zhang observed[10] across the C(1)−N(2) had occurred here as well. Epimerization of the stereocenter at C-3 had not occurred; had epimerization occurred at C-3 then the enantiomer of **8b** should have

(26) Searle, P. A.; Molinski, T. F. *J. Org. Chem.* **1994**, *59*, 6600−6605.
(27) Reddy, M. S.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413.

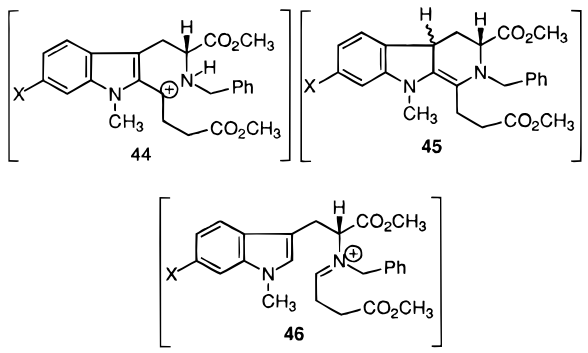


Figure 1. Potential intermediates.

been formed and the rotation would then have been opposite in sign, namely $[\alpha]^{25}_{D} = +50.4°$.

To test the olefinic mechanism of *cis*−*trans* epimerization, the same experiment was repeated with 2 molar equiv of pure CF_3COOD. If the olefin protonation mechanism was in operation, then deuterium would be incorporated into the tetrahydro-β-carboline at C-1 upon reprotonation (D^+) of the olefin to reform the tetrahydro-β-carboline. Repke et al. have shown that incorporation of deuterium at position-1 is found to occur when an olefinic mechanism of isomerization is found to be in operation.[28] We found no evidence for deuterium incorporation at C-1 by integration of the ^1H NMR spectrum nor by mass spectrometry.

It is clear that the isomerization of the *cis* diastereomers to the more thermodynamically stable *trans* diastereomers does not take place by the olefinic intermediate **45** (Figure 1). In the experiments which involve N_a-H derivatives **8a** and **8b**, it was observed that upon treatment of the *cis* isomer **8a** with acid, *cis* **8a** was completely converted into the *trans* diastereomer **8b**. However, treatment of the *trans* diastereomer **8b** under similar conditions provided only *trans* **8b**. Furthermore, when optically active *trans* isomer **8b** was heated in TFA for 12 h and the reaction monitored hourly by TLC, *cis* isomer **8a** was not observed. After prolonged heating no *cis* isomer **8a** was observed in the mixture. Moreover, there was no evidence of the original starting material (N_a-H-N_b-benzyltryptophan methyl ester) which would be indicative of a retro-Pictet−Spengler process.[29] From these experiments and the epimerizations illustrated in Table 1, it was concluded that the *trans* diastereomers are thermodynamically more stable than their *cis* counterparts in the N_a-H, N_b-alkyl series. When optically pure N_b-benzyl-D-(+)-tryptophan methyl ester and butyraldehyde were again heated to reflux in benzene until TLC indicated the consumption of all the indolic starting material, it was found that the *trans* diastereomer **8b** could be formed exclusively upon addition of an excess of TFA to the reaction mixture at room temperature. The epimerization of the *cis* diastereomer **8a** to the *trans* diastereomer **8b** was monitored by TLC (74% isolated yield).

With the advent of asymmetric control,[1,30] the importance of the Pictet−Spengler condensation, as pointed out, for the stereospecific synthesis of indole alkaloids has rapidly increased.[30] In 1988 Zhang proposed that an intermediate such as **44** (X = H) was involved in the epimerization of *cis* N_b-benzyl-1,3-disubstituted tetrahydro-β-carbolines into their *trans* diastereomers when heated in methanolic hydrogen chloride.[10] Although three potential mechanisms would account for this isomerization, Zhang trapped byproducts related to **44** (X = H) in poor yield and converted this material under analogous conditions (CH_3OH, 1% HCl, Δ) into the *trans* diastereomer exclusively.[10]

The three potential intermediates depicted in Figure 1 are related to three different mechanistic pathways earlier investigated by Joule with regard to the isomerization of reserpine into isoreserpine.[31] In 1989 evidence from our laboratory was provided to indicate the isomerization of reserpine into isoreserpine took place via C(1)−N(2) bond session related to **44** rather than an iminium ion related to **46**.[32] Experiments with reserpine in CF_3-COOD pioneered by Joule[31] unequivocally ruled out the intermediacy of an olefinic intermediate related to **45** during the isomerization of reserpine to isoreserpine. Deuterium would have been incorporated at C(1) of the tetrahydro-β-carboline nucleus during regeneration of the 2,3-indole double bond. In fact, in all of the epimerization reactions described here (see below), stirring a *cis*-N_b-benzyl-1,3-disubstituted tetrahydro-β-carboline in CF_3-COOD provided the *trans* isomer exclusively with no incorporation of deuterium at C(1). These results rule out an intermediate such as **45** during the process of epimerization.

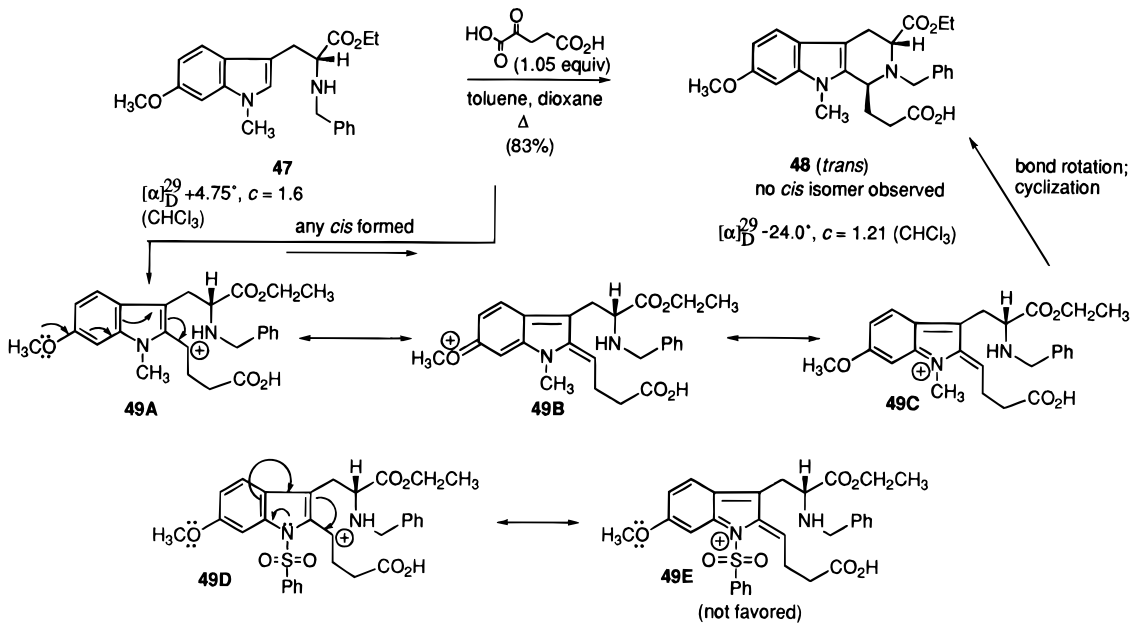
More recently, the optically active 6-methoxy-N_a-methyl-N_b-benzyltryptophan ethyl ester **47** was heated with a slight excess of α-ketoglutaric acid to provide the *trans* diastereomer **48** stereospecifically and in excellent yield (Scheme 7).[29] It is believed the electrons on the 6-methoxy moiety of the indole contributed to the stabilization of intermediate **49A** via oxonium ion contributor **49B** as well as iminium ion form **49C**. If the *cis* diastereomer did form during the Pictet−Spengler reaction, it was felt the methoxy moiety would help to stabilize intermediate **49A** via **49B** and **49C** to facilitate C(1)−N(2) cleavage and epimerization to the thermodynamically more stable *trans* diastereomer **48**.[29]

Since the carbocationic intermediate **49A** was stabilized by **49B** and **49C**, attention turned toward the synthesis of a 6-methoxytryptophan analog which might retard electronic stabilization of these resonance forms. The N_a-sulfonamido-protected 6-methoxy-N_b-benzyl-(D)-tryptophan ethyl ester **50**[33] was chosen for this purpose. The sulfonamide moiety on the indole N_a-nitrogen function should withdraw electron density from the indole N_a-nitrogen atom and decrease the stability of carbocationic intermediates **49D** and **49E**. The N_a-sulfonamidotryptophan ethyl ester **50** prepared earlier[33] was stirred with benzaldehyde at room temperature followed by reduction of the resulting imine with sodium borohydride at −5 °C (low temperature to ensure against racemization[10]) to provide the N_b-benzyl-6-methoxytryptophan analog **51** (Scheme 8).

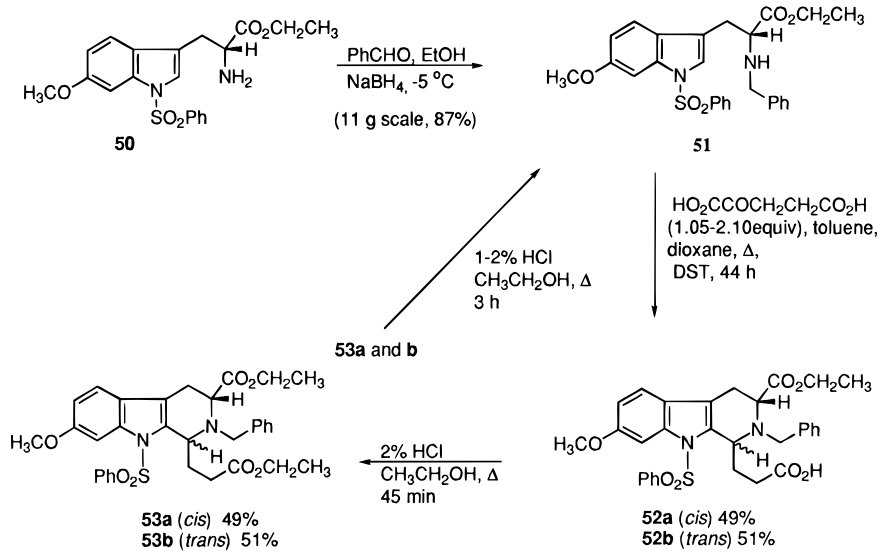
The Pictet−Spengler reaction of sulfonamide **51** and α-ketoglutaric acid (1.05−2.10 equiv) in toluene/dioxane was allowed to reflux for 44 h to provide a mixture of *cis*

(28) Repke, D. B.; Artis, D. R.; Nelson, J. T.; Wong, E. H. F. *J. Org. Chem.* **1994**, *59*, 2164.
(29) Hamaker, L. H.; Cook, J. M. 208th American Chemical Society National Meeting, Washington D.C., 1994, Abstract No. 269. Hamaker, L. K. Ph.D. Thesis, University of Wisconsin−Milwaukee, 1995.
(30) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(31) Gaskell, A.; Joule, J. *Tetrahedron* **1967**, *23*, 4053.
(32) Zhang, L.-H.; Gupta, A.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 4708.
(33) Allen, M. S.; Hamaker, L. K.; Laloggia, A.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077.

Scheme 7



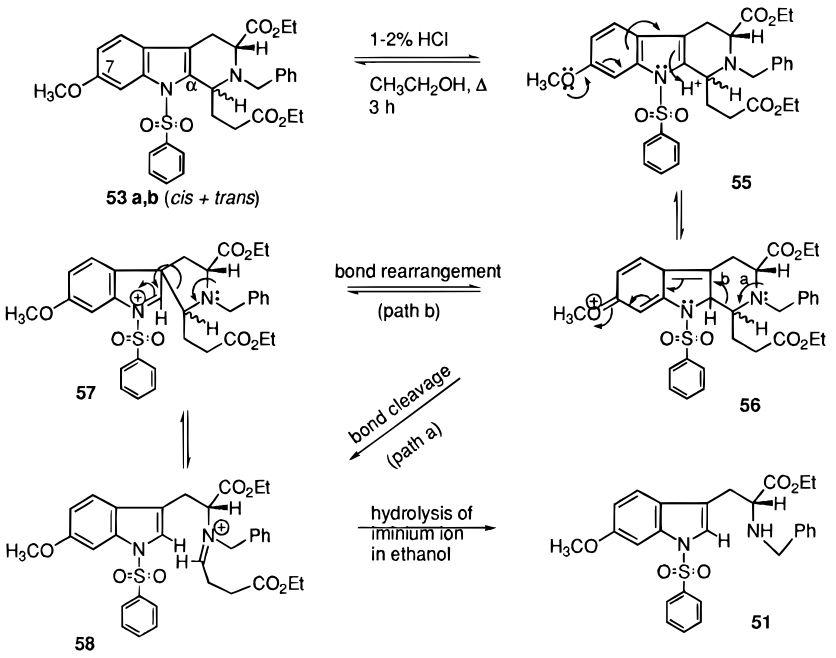
Scheme 8



(**52a**) and *trans* (**52b**) acids in a ratio of 49:51 (Scheme 2), respectively. When the reaction mixture was heated for a longer period of time (91 h), the ratio of *trans* acid **52b** to *cis* acid **52a** increased slightly; however, the *cis* isomer **52a** diminished until it was no longer detected (TLC). It should be noted that the actual yield of the *trans* acid **52b** did not increase as the reaction solution was heated at length presumably due to the decomposition of the *cis* isomer **52a** rather than epimerization of *cis* **52a** into *trans* **52b**. In contrast to the results in the N_a-methyl-6-methoxytryptophan case **47**,[29] in the N_a-sulfonamido series the addition of excess α-ketoglutaric acid did not promote the acid-catalyzed epimerization of the *cis* isomer **52a** into the *trans* diastereomer **52b**. The sulfonamide group had effectively retarded the acid-catalyzed epimerization of the *cis* isomer **52a** into *trans* compound **52b** in the Pictet−Spengler reaction itself in stark contrast to the 100% stereoselective formation[29] of the *trans* isomer in the N_a-methyl-N_b-benzyl-6-methoxytryptophan **48** series.

The mixture of *cis* **52a** and *trans* **52b** acids was esterified upon heating in refluxing 2% ethanolic hydrogen chloride in the presence of triethyl orthoformate for 45 min to furnish the mixture of esters **53a** (*cis*) and **53b** (*trans*) still in an approximately 1:1 ratio. Attempts were again made to effect the epimerization [at C(1)] of the *cis* diester **53a** into the N_a-sulfonamido *trans* diester **53b**. When the mixture of *cis* and *trans* diesters (**53a**,**b**) was heated in refluxing 2% ethanolic hydrogen chloride for 3 h to effect epimerization, analysis of the reaction mixture (TLC) did not indicate the presence of increased amounts of the *trans* diester **53b** but rather 6-methoxy-N_a-sulfonamido-N_b-benzyltryptophan ethyl ester **51** was formed in 76% yield. This material was identical to the ethyl ester **51** prepared by an independent method.[33] The sulfonamido group on the N_a-nitrogen function of the *cis* isomer **11a** had clearly prevented epimerization presumably by destabilization of a carbocationic intermediate related to **49D**. The *cis* **53a** and *trans* **53b** diesters were then heated separately in ethanolic hydrogen chloride for 3 h, and workup of each reaction provided the same N_b-benzyltryptophan derivative **51**. Since the sulfonamido group withdrew electron density from the indole nitrogen function and destabilized the carbocationic intermediate

Scheme 9



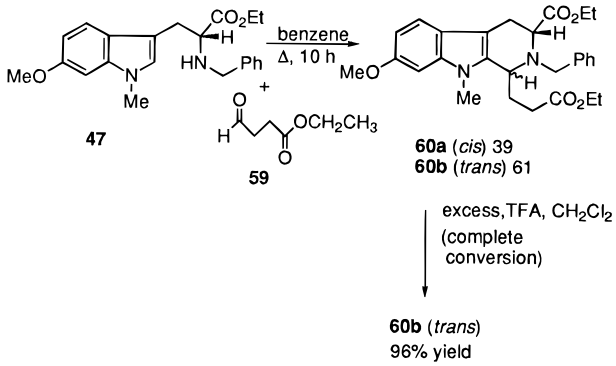
which would result from C(1)−N(2) cleavage, a retro Pictet−Spengler (type) process (see **56** → **57** → **58**) has instead occurred under these conditions, as illustrated in Scheme 9. Donation of the electron density from the 7-methoxy group presumably facilitated protonation at the α-carbon atom of the indole double bond to provide **56**. This protonated indole could then undergo C−C bond cleavage to furnish iminium ion **58** (path a) or bond migration (path b, see **57**) followed by rearrangement into the same iminium ion **58**. Hydrolysis of the C=N bond of iminium ion **58** in ethanol would furnish the N_b-benzyl-6-methoxytryptophan ethyl ester analog **51** (Scheme 9).

Even upon heating in excess acid (at length) at no time did any of the *cis* N_a-H (see **37**) or *cis* N_a-CH_3 diastereomers described herein provide the related N_a-H or N_a-CH_3-N_b-benzyltryptophan derivatives which would arise from the retro-Mannich (Pictet−Spengler) process. This provides evidence (although indirect) that the iminium ion pathway **56** to **58** is not operating in any of these epimerizations with the exception of the N_a-sulfonamido-substituted (deactivated) series of Scheme 9.

For comparison purposes, the Pictet−Spengler reaction of N_a-methyl-N_b-benzyl-6-methoxy-(D)tryptophan ethyl ester[29] with an aldehyde under conditions of kinetic trapping in nonacidic aprotic media was investigated. Analogous to the method of Zhang,[9,10] ethyl 3-formyl propionate **59** was prepared for the Pictet−Spengler reaction and dissolved with the N_a-methyl-N_b-benzyl-6-methoxytryptophan derivative **47** in benzene (Scheme 10). The solution was heated at reflux for 10 h, and this resulted in a mixture of *trans* **60b** to *cis* **60a** diesters in a ratio of 61:39 (Scheme 10). More importantly, when the *cis* and *trans* diesters **60a**,**b** were dissolved in a mixture of methylene chloride/trifluoroacetic acid and stirred at room temperature (90 minutes), a 96% yield of the *trans* diester **60b** was realized (TLC, silica gel, R_f *cis* = 0.28, R_f *trans* = 0.32, EtOAc/hexane, 30:70).

When the above results in nonacidic aprotic media were compared to the results from reaction of 6-methoxytryptophan analog **47** with an excess (1.00−1.05 equiv) of α-ketoglutaric acid, it was felt that protonation of the N_b-benzyl nitrogen group was essential for the

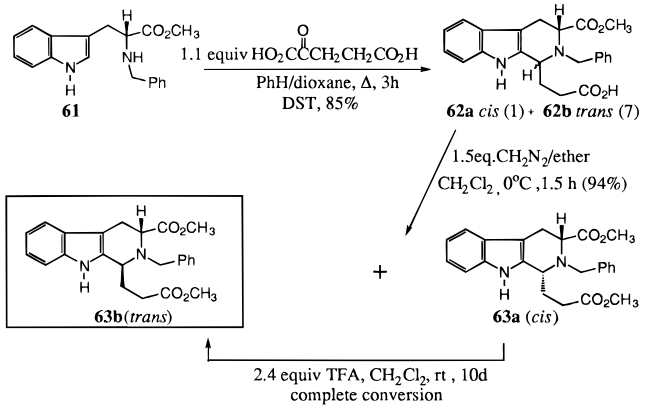
Scheme 10



realization of 100% *trans* diastereoselectivity in this Pictet−Spengler condensation. Analysis of this data further supported the proposed mechanism of epimerization [C(1)−N(2) cleavage] at C(1) of *cis* into *trans*-1,2,3-trisubstituted tetrahydro-β-carbolines (see Schemes 4 and 7) and prompted additional investigation of the mechanism of this isomerization in tetrahydro-β-carbolines derived from nonactivated (desmethoxy) N_b-benzyltryptophan derivatives.

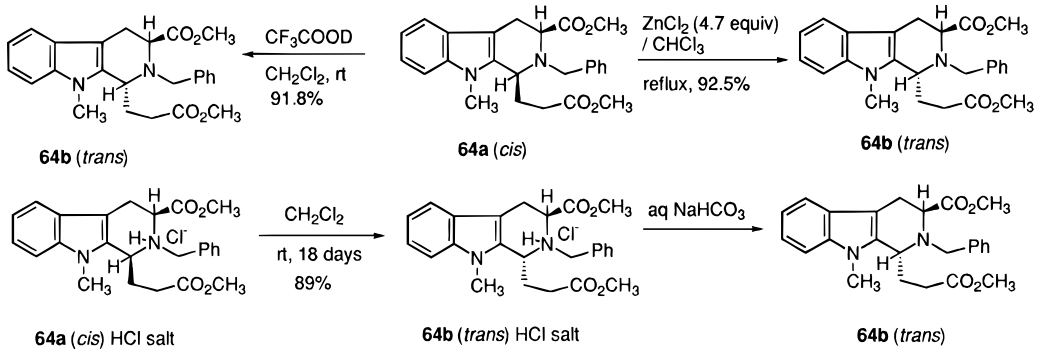
As outlined at the top of Table 2, heating N_b-benzyl-(D)tryptophan methyl ester **61** with α-ketoglutaric acid gave a mixture of *cis* **62a** and *trans* **62b** diastereomers in a ratio of 1:7. Conversion of the mixture of acids into the corresponding esters was accomplished under neutral conditions to provide the *cis* **63a** and *trans* **63b** diesters in the N_a-H, N_b-benzyl series. When the *cis* isomer **63a** was stirred at room temperature with 2.4 equiv of CF_3-COOH in CH_2Cl_2 for 10 days, the stereospecific formation of the *trans* diastereomer **63b** was realized (90% yield). The optical rotation of *trans* **63b** was identical to that of pure **63b** obtained earlier; epimerization had occurred only at C(1). When the mixture of *cis* **63a** and *trans* **63b** isomers was treated under the same conditions, again a 90% yield of the desired *trans* isomer **63b** was realized. The rate of the epimerization could be drastically increased by heating the solution (see Experimental Section for details). As illustrated in Table 2, the percent

Table 2. Conversion of *Cis* Isomer 63a into *Trans* Isomer 63b



start. mater., mg	temp/time, d	catalyst	solvent (mL)	product (%)
63a (*cis*), 20	rt/10	TFA	CH_2Cl_2 (1.0)	**63b** (90)
63a (*cis*), 20	rt/10	TFA	$CHCl_3$ (1.0)	**63b** (85)
63a (*cis*), 20	rt/10	TFA	PhH (1.0)	**63b** (60), **63a** (20)
63a (*cis*), 20	rt/10	TFA	THF (1.0)	**63b** (0), **63a** (85)
63b (*trans*), 20	rt/10	TFA	CH_2Cl_2 (1.0)	**63b** (80)
63a+**63b** (1:1), 20	rt/10	TFA	CH_2Cl_2 (1.0)	**63b** (90)

Scheme 11



conversion of **62a** into **62b** in the presence of TFA took place more readily in the polar aprotic solvent CH_2Cl_2 than in benzene. Moreover, when this same transformation was attempted in THF, no epimerization was observed.

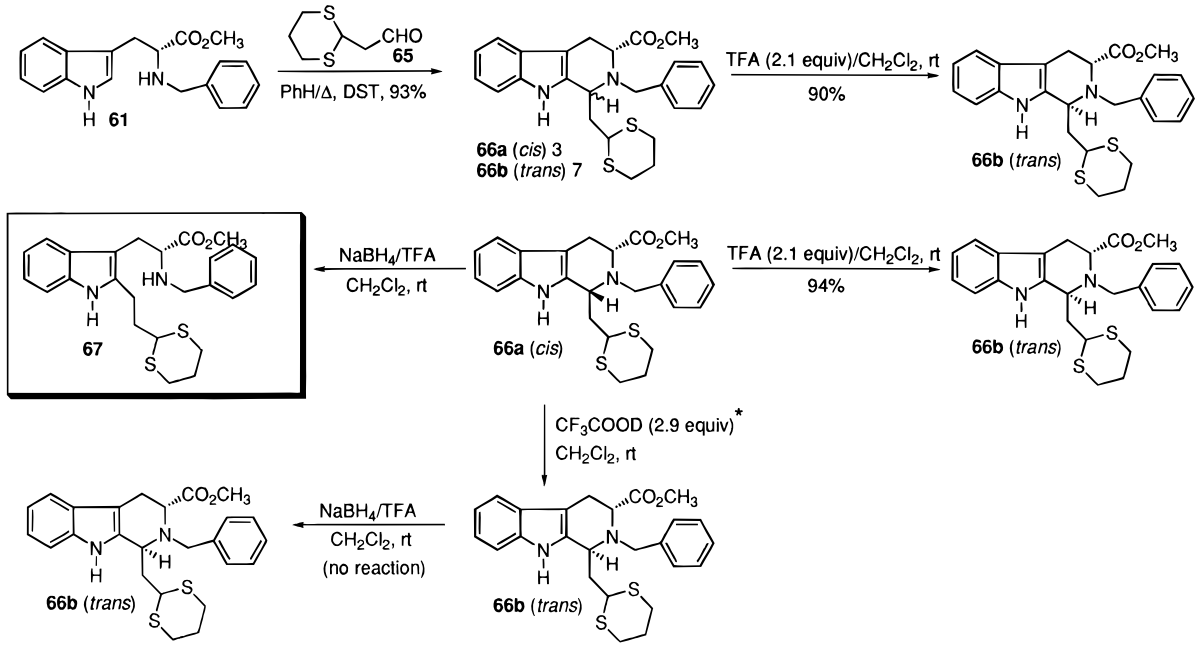
Similar results were observed in CF_3COOH/CH_2Cl_2 in the N_a-methyl, N_b-benzyl series. Pictet−Spengler reaction of N_a-methyl-N_b-benzyl-(L)tryptophan methyl ester with methyl 3-formylpropionate in refluxing benzene furnished a mixture of *cis* **64a** and *trans* **64b** diastereomers in a ratio of 28:72 in 90% yield as expected.[9,10] When the *cis* isomer **64a** was stirred in CH_2Cl_2/CF_3COOD for several days at room temperature, the *trans* isomer **64b** was obtained in optically pure form (92% yield) with no deuterium incorporation at C(1) or C(3). Again, intermediate **45** was unequivocally ruled out; moreover, the mixture [*cis* (**64a**) 28: *trans* (**64b**) 72] was converted into optically active *trans* **64b** on heating for 5 h in CF_3COOD/CH_2Cl_2.

In order to form intermediate **46** (Figure 1) in this process, protonation of the indole double bond (at the α-carbon atom) must precede iminium ion formation,[31,32] consequently the *cis* isomer **64a** was heated in dry distilled chloroform (EtOH, HCl free) with anhydrous $ZnCl_2$ (4.7 equiv). This process provided the *trans* isomer **64b** in 92% yield. It was felt the Lewis acid promoted the formation of carbocationic intermediate **44** and not iminium ion **46** since the solution was devoid of protons. The control reaction with **64a** in refluxing $CHCl_3$ in the absence of anhydrous $ZnCl_2$ returned only *cis* isomer **64a** in quantitative yield. A similar experiment with the dry pure hydrochloride salt of *cis* isomer **64a** gave the salt of the *trans* analog **64b** again in support of intermediate **44** over **45** or **46** (Scheme 11).

Evidence above supported the C(1)−N(2) scission mechanism (see **44**) illustrated in Figure 1 for this isomerization prompting a similar set of experiments in a different series (Scheme 12). When optically active N_b-benzyl-(D)-tryptophan methyl ester **61** was heated with aldehyde **65** in refluxing benzene, a mixture of *cis* **66a** and *trans* **66b** isomers was formed in 90% yield in a ratio of 3:7, as expected.[9,10] When the mixture was stirred in CF_3COOD, the *trans* isomer **66b** was formed in high yield; moreover, no deuterium incorporation was observed. Epimerization of **66a** had taken place at C(1) presumably via intermediate **44** or **46**. The *cis* isomer **66a** was allowed to stir in CF_3COOH in the presence of $NaBH_4$[34] which furnished a mixture of the reduced ring-cleaved intermediate **67** [C(1)−N(2) cleavage] and the *trans* isomer **66b** in approximately equal amounts. The structure of 2-substituted indole **67** was deduced based on HR NMR including 2D COSY and TOCSY experiments. No *cis* diastereomer **66a** was observed in this mixture nor was any product isolated which would correspond to either reduction of/or hydrolysis of an iminium ion related to that in intermediate **46**. Moreover, when the thermo-

(34) Gribble, G.; Nutaitis, C. *Org. Prep. Proced. Int.* **1985**, *17*, 317.

Scheme 12



*No deuterium incorporation observed in **66b** by mass spectrometry or by ^{1}H NMR.

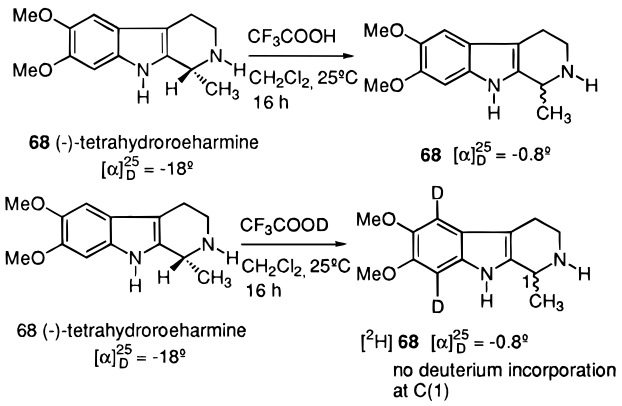
dynamically more stable *trans* isomer **66b** was allowed to stir with $CF_3COOH/NaBH_4$[34] under exactly the same conditions no product **67** of ring opening was observed. The *trans* isomer **66b** was recovered from this process in greater than 90% yield. The failure of *trans* isomer **66b** to provide **67** under these (control) conditions suggests that the origin of **67** (from *cis* isomer **66a**) arises from reduction of a carbocation "like" intermediate related to **44** (or the corresponding iminium ion resonance form similar to **49C** in the desmethoxy series) and not borane-mediated cleavage of the C(1)−N(2) bond. If the latter event had occurred, then the isolation of **67** from *trans* isomer **66b** would have also been expected. The isolation of thioacetal **67** from treatment of *cis* **66a** with $CF_3COOH/NaBH_4$ as well as conversion of **66a** into **66b** in CF_3COOD (with no deuterium incorporation) provide the best evidence, to date, that epimerization of *cis*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines into their *trans* counterparts is mediated via scission across the C(1)−N(2) bond (see **44**)[10] and not by intermediates **45** or **46** (Figure 1). In addition, conversion of *cis* **64a** into *trans* **64b** mediated by $ZnCl_2$ also supports the carbocation C(1)−N(2) scission mechanism proposed here. The lack of evidence to support the intermediacy of compounds such as **45** or **46** provides additional support for the C(1)−N(2) scission mechanism earlier proposed for the isomerization of reserpine into isoreserpine reported from our laboratory.[32]

Conclusion

Pictet−Spengler condensation of aldehydes with either an N_b-benzyl or N_b-diphenylmethyl-substituted tryptophan derivative resulted in the preferential formation of 1,3-*trans* diastereomers. This is contrary to the traditional condensations devoid of a substituent at the N_b-nitrogen atom whereby *cis* diastereomers are often times formed preferentially.[1] The diastereochemical ratio of the products obtained in the Pictet−Spengler cyclization of N_b-substituted-tryptophan alkyl esters was dependent upon the steric bulk of the incoming carbonyl compound, the substituents on the N_b-nitrogen atom, and the size of the ester function. As the size of the aldehyde increased, so too did the ratio of *trans* diastereomer to *cis* isomer. Under the nonacidic aprotic conditions of benzene at reflux, aldehydes such as acetaldehyde undergo the Pictet−Spengler condensation to provide only modest diastereoselectivity (**7a**, **7b**--26:74). Cyclohexanecarboxaldehyde, however, reacts to provide a high yield of solely the *trans* diastereomer **9** with 100% stereoselectivity. Increased steric interaction from the ester function imparted a slight increase in the amount of *trans* diastereomer which was formed. This was most evident in the nonacidic aprotic condensations of butyraldehyde with N_b-benzyltryptophan methyl ester (**8a**:**8b**--*cis*:*trans*--23:77) and N_b-benzyltryptophan isopropyl ester (**11a**:**11b**--*cis*:*trans*--13:87). Replacement of the benzyl function by the larger diphenylmethyl group also increased the *trans* stereoselectivity. When the N_b-diphenylmethyl substituent was introduced into the nonacidic aprotic condensation it was evident that an appreciable amount of steric hindrance was present since no reaction was observed in the cases with bulky aldehydes. However, in those cases which did react, substantial increases in the diastereomeric excess were observed.

The ratios observed under nonacidic aprotic conditions are the result of kinetic trapping experiments. Upon exposure to acid, the diastereomeric ratios shift to provide increased amounts of the *trans* diastereomers. The marked increases in the amount of the *trans* diastereomer formed in each case upon addition of acid and the fact that the *cis* diastereomer **8a** epimerizes irreversibly to the *trans* congener **8b** indicate that the *trans* diastereomer in the N_b-alkyl cases is the thermodynamically more stable diastereomer. Furthermore, there is strong evidence to support the mechanism of C-1−N-2 bond cleavage which results in the epimerization of *cis* **8a** to *trans* **8b**. The isolation of **67** from the carbocation-trapping experiment ($NaBH_4/CF_3COOH$) with **66a** strongly supports this hypothesis.

Scheme 13



Recently, Reddy et al. reported[27,30] the synthesis of two *Roemaria* alkaloids roeharmine and (−)-1,2,3,4-tetrahydroeharmine (**68**) isolated by Gozler et al. The 100% *trans* stereoselectivity in the Pictet−Spengler reaction of 6-methoxytryptophan **47** with α-ketoglutaric acid provided much needed insight for the enantiospecific synthesis of the 6,7-dimethoxy indole alkaloid **68** by Reddy. The specific rotation for the natural product **68** had been reported to be −4.0° ($c = 0.12$, MeOH). Consideration of the mechanism of epimerization described above in the 6-methoxy series (see Scheme 10) suggested that **68** might readily undergo C(1)−N(2) bond cleavage under the acidic conditions of isolation by Gozler.[27,30] Therefore, Reddy designed the synthesis of THβC **68** utilizing the Moody azide pyrolysis process and the Pictet−Spengler condensation under nonacidic aprotic conditions.[14,30] The spectral properties of synthetic **68** were identical to the natural product except for the optical rotation which was −18.0° ($c = 1.04$, MeOH). It was believed that the natural 1,2,3,4-tetrahydroeharmine **68** had undergone partial racemization during the acid/base-mediated isolation procedure facilitated by the 7-methoxy group. This hypothesis was tested by exposing optically pure **68** to trifluoroacetic acid in CH_2Cl_2 at room temperature as illustrated in Scheme 13. The ^{1}H NMR and R_f of the alkaloid which resulted were unchanged; however, the optical rotation of the product was approximately −0.8°. Racemization was believed to occur through the C(1)−N(2) scission pathway related to **44** in which the 6-methoxy group (7 in THβC nomenclature) was felt to contribute to stabilization of the ring-cleaved [C(1)−N(2)] carbocation. When optically pure **68** was allowed to stir with CF_3COOD in CH_2Cl_2 at 25 °C (Scheme 13), the optical rotation of the reaction product **68** was again found to be near zero as expected. Although deuterium incorporation had occurred at C(5) and C(8) no deuterium was found at C(1) as illustrated in Scheme 13 (see ^{2}H-**68**). An alternate mechanism would result from formation of an olefinic intermediate related to **45** whereupon protonation at C(1) would provide racemic material. If this alternate pathway had operated during this epimerization, the above reaction with CF_3COOD would have provided **68** in which a deuterium atom would appear at C(1). This was not observed. Analysis of the deuterium labeling experiment supports the cationic-mediated mechanism via scission across the C(1)−N(2) bond after which protonation from both faces led to racemic material.[27] These results should therefore be considered a warning to those who isolate ring-A methoxylated indole alkaloids when strongly acidic conditions are employed in the extraction process; there is a definite risk of epimerization at C(1) of the tetrahydro-β-carboline nucleus.

Experimental Section

All starting materials were purchased from Aldrich Chemical Co. unless otherwise noted. All aldehydes were distilled at reduced pressure under an atmosphere of nitrogen gas to remove acidic impurities as evidenced by IR spectroscopy. Thin layer chromatography was performed on Merck silica gel 60 F-254 TLC plates. Visualization of the indolic products was achieved by spraying with an acidic cerric ammonium sulfate solution and development in a stream of warm air for several minutes. Unless otherwise noted, all spectral and analytical data were recorded as described in reference 6. Optical rotations were measured with a JASCO DIP-370 polarimeter. Spectral data for compounds **4**,[36] **7**,[35] and **9**[14] were identical to those previously reported.

General Procedure for Catalytic Transfer Hydrogenation (CTH).[37] The N_b-alkyltetrahydro-β-carboline to be hydrogenated was placed into a round-bottomed flask, and to it was added solid, dry ammonium formate (20 mol equiv). This mixture was dissolved in a minimal amount of absolute methanol. Freshly activated 10%Pd/C (1 mass equiv relative to the compound to be hydrogenated) was carefully slurried in absolute methanol and the ammonium formate solution added. This mixture was stirred under an atmosphere of dry nitrogen gas until complete removal of the alkyl group was indicated by TLC (silica gel; 1:9, ethyl acetate:benzene). The solution was filtered through Celite and the Celite thoroughly washed with ether. The organic solution which resulted was washed with brine to remove the residual ammonium formate. Solvent removal was achieved under reduced pressure to yield the N_b-hydrogen bases in yields that ranged between 90% and 97%.

***cis*-3-(Methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4a) and *trans*-3-(Methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4b).** Upon subjection of compounds **7a** and **7b** to CTH (catalytic transfer hydrogenation), a 94% and 96% yield of **4a** and **4b**, respectively, was realized, the ^{1}H NMR spectra of each being identical to those published previously.[15,36] **4a**: ^{1}H NMR ($CDCl_3$) δ 1.49 (d, $J = 6.6$ Hz, 3H), 1.90 (br, 1H), 2.86 (m, 1H), 3.13 (m, 1H), 3.80 (s, 3H), 3.85 (dd, $J = 4.5$ and 11.5 Hz, 1H), 4.28 (br, 1H), 7.12 (br, 2H), 7.33 (br, 1H), 7.48 (br, 1H), 7.83 (br, 1H). **4b**: ^{1}H NMR ($CDCl_3$) δ 1.49 (d, $J = 6.6$ Hz, 3H), 2.10 (br, 1H), 2.90 (m, 1H), 3.12 (m, 1H), 3.77 (s, 3H), 3.97 (dd, $J = 4.5$ and 11.5 Hz, 1H), 4.41 (br, 1H), 7.10 (br, 2H), 7.35 (br, 1H), 7.50 (br, 1H), 7.86 (br, 1H).

(1*R*,3*R*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8a) and (1*S*,3*R*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8b). Optically active N_b-benzyl-(D)tryptophan methyl ester was prepared according to the method of Zhang[18] and is known.[38] A mixture of this ester (6.0 g, 0.020 mol), dry benzene (100 mL), and butyraldehyde (2.8 g, 0.039 mol) was brought to reflux and reacted under a nitrogen atmosphere for 72 h. The solvent was removed under reduced pressure and the *cis* and *trans* diastereomers separated by gravity chromatography on silica gel (CH_2Cl_2) to yield **8b** (4.9 g) as a white solid and **8a** (0.54 g) as a yellow oil for a combined yield of 77%. **8a**: $[\alpha]^{25}_D = -13.3°$ ($c = 1$, benzene); IR (KBr) 3320−3180, 1718 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.76 (t, $J = 7.0$ Hz, 3H), 1.38−1.60 (m, 4H), 2.94 (dd, $J = 15.9$ and 5.8 Hz, 1H), 3.18 (dd, $J = 16.0$ and 5.0 Hz, 1H), 3.41 (s, 3H), 3.74 (t, $J = 4.9$ Hz, 1H), 3.92 (broad, 3H), 7.05−7.52 (broad, 9H), 7.65 (s, 1H); ^{13}C NMR (C_6D_6) δ 14.3, 19.8, 19.9, 36.8, 51.3, 58.0, 58.9, 59.3, 106.3, 111.1, 118.6, 119.6, 121.9, 127.3, 127.6, 128.4, 128.9, 129.2, 134.5, 136.7, 139.5, 140.3,

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(36) Deng, L. M.S. Thesis, University of Wisconsin−Milwaukee, 1991.
(37) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929.
(38) Shimizu, M.; Ishikawa, M.; Komoda, Y.; Nakajima, T.; Yamaguchi, K.; Sakai, S.-i. *Chem. Pharm. Bull.* **1984**, *32*, 1313.

174.7; MS (CI, CH_4) *m/z* (relative intensity) 363 (M + 1, 100%). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.20; H, 7.23; N, 7.73. Found: C, 76.55; H, 6.99; N, 8.01. **8b**: mp 149.2−152.4 °C. $[\alpha]^{25}_D = -50.4°$ (*c* = 1, benzene); IR (KBr) 3340−3260, 1700 cm^{-1}; ^1H NMR (C_6D_6) δ 0.75 (t, *J* = 6.85 Hz, 3H), 1.30−1.47 (m, 4H), 2.96 (dd, *J* = 6.8 and 17.5 Hz, 1H), 3.16 (dd, *J* = 9.2 and 15.8 Hz, 1H), 3.33 (s, 3H), 3.52 (d, *J* = 13.7 Hz, 1H), 3.70 (m, 1H), 3.95 (m, 2H), 6.45 (s, 1H), 7.16 (m, 6H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (C_6D_6) δ 14.2, 19.1, 21.6, 36.6, 51.2, 53.7, 55.7, 57.0, 107.2, 111.0, 116.5, 119.7, 121.8, 127.3, 127.6, 128.0, 128.4, 129.5, 135.1, 140.5, 173.0; MS (CI, CH_4) *m/z* (relative intensity) 363 (M + 1, 100%). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.20; H, 7.23; N, 7.73. Found: C, 76.40; H, 7.25; N, 7.73.

(1*R*,3*R*)-(+)-3-(Methoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole. CTH of **8a** provided the optically active N_b-H isomer ($R^1 = CH_2CH_2CH_3$, $R^3 = CH_3$) in 91% yield, the spectral properties of which [^{13}C NMR ($CDCl_3$) δ 56.40 (C-1), 52.45 (C-3)], were identical to the (1*S*,3*S*) enantiomer.[39,42] Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.73; H, 7.90; N, 9.98.

(1*S*,3*R*)-(+)-3-(Methoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole. CTH of **8b** provided the optically active N_b-H isomer ($R^1 = CH_2CH_2CH_3$, $R^3 = CH_3$) in 96% yield, the spectral properties of which [^{13}C NMR ($CDCl_3$) δ 52.44 (C-1), 49.99 (C-3)], were identical to the (1*R*,3*S*)-enantiomer.[39,42] Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.40; H, 7.25; N, 10.53. When the *cis* isomer **8a** was stirred in CF_3COOD it was converted into the *trans* isomer **8b** $[\alpha]^{25}_D = -50.4°$ (*c* = 1, benzene). The *trans* isomer **8b** did not contain deuterium (NMR, MS).

***trans*-1-Cyclohexyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6b).** CTH of **9** provided a 95% yield of **6b**; mp 147−148 °C the spectral data of which were identical to those reported previously:[11]

Isopropyl (±)-tryptophanoate (20). Anhydrous HBr (g) was passed through dry 2-propanol (1.1 L) at 0 °C to form a saturated solution. In one portion, (D/L)-tryptophan (80.0 g, 0.392 mol) was added to the viscous solution. This stirred suspension was warmed to reflux, and the resulting homogeneous solution took on a deep red coloration. After 7 h the flask was cooled and the precipitate isolated by vacuum filtration. Additional material was obtained from the mother liquors and recrystallization from 2-propanol. Combination of the individual crops yielded 101.67 g (79.3%) of the pure ester hydrobromide salt (**20**): mp 228.1 °C dec; IR (KBr) 3200, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, free base) δ 1.18 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.61 (broad, 2H), 2.99 (dd, *J* = 14.4 and 7.8 Hz, 1H), 3.26 (dd, *J* = 14.2 and 4.9 Hz, 1H), 3.76 (broad, 1H), 5.00 (heptet, *J* = 6.3 Hz, 1H), 7.04 (s, 1H), 7.07−7.21 (m, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (DMSO-d_6, HBr salt) δ 20.9, 21.3, 26.2, 52.7, 69.6, 106.4, 111.5, 118.0, 118.5, 121.1, 124.7, 126.7, 136.1, 166.8; MS (CI, CH_4), *m/z* (relative intensity) 247 (M + 1, 33). HRMS calculated for $C_{14}H_{18}N_2O_2$: 246.1368. Found: 246.1396. Anal. Calcd for $C_{14}H_{18}N_2O_2 \cdot HBr$: C, 51.39; H, 5.85; N, 8.56. Found: C, 51.31; H, 5.82; N, 8.49.

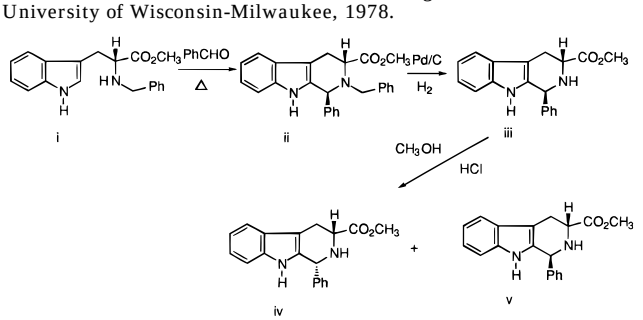
Isopropyl N_b-Benzyl-(±)-tryptophanoate (26). Benzaldehyde (11.38 g, 0.107 mol) was added to a solution of methanol (140 mL) and tryptophan isopropyl ester **20** (24 g, 0.098 mol). This solution was allowed to stir for 11 h at 25 °C after which it was cooled to 0 °C, and $NaBH_4$ (0.9 g, 0.048 mol) was added portionwise over 30 min. After 6 h, ice−water (2.1 mL) was added and the volume reduced under vacuum. The residue was dissolved in $CHCl_3$ (180 mL) and the solution washed with brine (2 × 60 mL) and dried over Na_2SO_4. Purification by flash chromatography (ethyl acetate:hexanes-30:70 v/v on silica gel) yielded 20 g (61%) of pure N_b-benzyltryptophan isopropyl ester **26**: mp 55.5−56.8 °C; IR (KBr) 3720, 3070, 2950, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.81 (broad, 1H), 3.13 (d, *J* = 6.9 Hz, 2H), 3.60 (t, *J* = 6.7 Hz, 1H), 3.64 (d, *J* = 6.7 Hz, 1H), 3.81 (d, *J* = 13.1 Hz, 1H), 4.95 (heptet, *J* = 6.3 Hz, 1H), 7.02−7.35 (m, 8H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.99 (s, *1*H); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.8, 29.3, 52.0, 61.4, 66.1, 111.0, 111.2, 118.8, 119.2, 121.9, 122.8, 126.9, 127.5, 128.1, 128.3, 136.1, 139.7, 174.5; MS (CI, CH_4) *m/z* (relative intensity) 337 (M + 1, 100%). HRMS calculated for $C_{21}H_{24}N_2O_2$: 336.1838. Found: 336.1809. Anal. Calcd for $C_{21}H_{24}N_2O_2 \cdot HCl$: C, 67.65; H, 6.71; N, 7.52. Found: C, 67.07; H, 6.89; N, 7.27.

***cis*-2-Benzyl-3-(isopropoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (10a) and *trans*-2-Benzyl-3-(isopropoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (10b).** Acetaldehyde (0.7 g, 14.6 mmol), N_b-benzyltryptophan isopropyl ester **26** (0.464 g, 1.38 mmol), and dry benzene (10 mL) were sealed under vacuum in a glass tube and heated for 36 h in an oven at 80 °C. The reaction mixture was cooled and transferred to a round-bottomed flask where the solvent was removed under reduced pressure. A short silica gel wash column provided 0.430 g (86%) of a mixture of the *trans* and *cis* isomers. Further chromatography ($CHCl_3$, silica gel) was used to separate the isomers. Anal. Calcd (for the mixture of diastereomers) $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.45; H, 7.25; N, 7.73. **10a**: ^1H NMR ($CDCl_3$) δ 1.20 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.33 (d, *J* = 6.9 Hz, 3H), 2.97 (dd, *J* = 7.1 and 5.5 Hz, 1H), 3.20 (dd, *J* = 15.7 and 8.1 Hz, 1H), 3.86 (t, *J* = 6.2 Hz, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 4.03 (d, *J* = 15.0 Hz, 1H), 4.27 (q, *J* = 6.9 Hz, 1H), 4.98 (heptet, *J* = 6.3 Hz, 1H), 7.00−7.55 (m, 9H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.4, 21.8, 22.4, 53.2, 54.4, 60.6, 68.3, 106.7, 110.7, 118.2, 119.5, 121.5, 126.8, 128.2, 128.3, 135.4, 135.9, 140.3, 173.1; MS (CI, CH_4) *m/z* (relative intensity) 363 (M + 1, 100) 419 (M + 28, 18.7). HRMS calculated for $C_{23}H_{26}N_2O_2$: 362.1994. Found: 362.1959. CTH of **10a** provided a compound (N_b-H) which had spectral properties identical to **29a**.[42] **10b**: ^1H NMR ($CDCl_3$) δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 2.98 (dd, *J* = 15.7 and 5.4 Hz, 1H), 3.09 (dd, *J* = 15.7 and 7.1 Hz, 1H), 3.77 (d, *J* = 14.4 Hz, 1H), 3.88 (d, *J* = 14.3 Hz, 1H), 3.92 (dd, *J* = 7.1 and 5.5 Hz, 1H), 4.14 (q, *J* = 6.6 Hz, 1H), 5.01 (heptet, *J* = 6.2 Hz, 1H), 7.00−7.55 (multiplet, 9H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.5, 22.3, 51.0, 53.8, 57.0, 68.0, 106.4, 110.7, 118.1, 119.4, 121.4, 126.9, 128.3, 128.4, 136.1, 136.2, 140.1, 172.7; MS (CI, CH_4) *m/z* (relative intensity) 363 (M + 1, 100). HRMS calculated for $C_{23}H_{26}N_2O_2$: 362.1994. Found: 362.1965. CTH of **10b** provided a compound (N_b-H) which had spectral properties identical to **29b**.[42] Anal. Calcd (as a mixture of diastereomers) for $C_{23}H_{26}N_2O_2 \cdot HCl \cdot {}^3/_4H_2O$: C, 66.99; H, 6.73; N, 6.80. Found: C, 67.26; H, 6.66; N, 6.45.

(39) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, *4*, 431.

(40) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(41) Not only does the N_b-benzyl group promote *trans* stereoselectivity in the Pictet−Spengler reaction itself (see results in PhH, Δ)[4] but also promotes *trans* stereochemistry during the acid-mediated equilibration at C(1). In the racemic series Ungemach demonstrated that stereospecific formation of **ii** (from **i**) occurred as reported in the N_b-benzyl series under acidic or nonacidic conditions. However after the *trans* diastereomer **ii** was converted into the corresponding N_b-H *trans* isomer **iii** *via* catalytic debenzylation, this pure *trans* isomer **iii** (N_b-H) was transformed into an approximate 40:60 mixture of *cis* to *trans* diastereomers (**iv** and **v**) on heating under acidic conditions. In the absence of the N_b-benzyl group a considerable amount of *cis*-isomer **iv** formed under these acidic conditions. Ungemach, F. MS Thesis, University of Wisconsin-Milwaukee, 1978.



(42) K. Czerwinski, Ph.D. Thesis, University of Wisconsin−Milwaukee, Milwaukee, WI, 1995.

***cis*-2-Benzyl-3-(isopropoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (11a) and *trans*-2-Benzyl-3-(isopropoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (11b).** Butanal (0.432 g, 6.0 mmol) was added to a solution of N_b-benzyl tryptophan isopropyl ester **26** (1.0 g, 3.0 mmol) in dry benzene (50 mL). This solution was heated to reflux, and after 36 h the reaction was cooled to 25 °C, the solvent was removed under vacuum and a small amount of the crude material removed for spectroscopy. The mixture of *cis* and *trans* diastereomers (0.927 g, 82%) was separated by flash chromatography (CH_2Cl_2, silica gel). Anal. Calcd (for the mixture of diastereomers) $C_{25}H_{30}N_2O_2 \cdot {}^1/_4H_2O$: C, 76.04; H, 7.73; N, 7.09. Found: C, 75.88; H, 7.76; N, 7.10. **11a**: ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.2 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.5 Hz, 3H), 1.40−1.80 (m, 4H), 2.94 (dd, J = 15.7 and 5.8 Hz, 1H), 3.18 (dd, J = 15.7 and 5.0 Hz, 1H), 3.78 (t, J = 5.0 Hz, 1H), 3.92 (broad, 3H), 4.94 (heptet, J = 6.3 Hz, 1H), 7.05−7.52 (broad, 9H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.8, 20.7, 21.7, 21.8, 36.1, 58.1, 58.2, 59.7, 66.3, 106.7, 110.6, 118.1, 119.4, 121.5, 124.0, 127.1, 128.1, 128.7, 134.8, 136.0, 139.8, 173.2; MS (CI, CH_4) *m*/*z* (relative intensity) 391 (M + 1, 100%) 419 (M + 28, 18.7%). HRMS calculated for $C_{25}H_{30}N_2O_2$: 390.2307. Found: 390.2294. CTH of *cis* **11a** provided a compound (N_b-H) which had spectral properties identical to **30a**.[42] **11b**: mp 137.2−138.1 °C; ^{1}H NMR ($CDCl_3$) δ 0.73 (t, J = 7.4 Hz, 3H), 1.19−1.80 (m, 10H), 2.96 (dd, J = 16.2 and 5.3 Hz, 1H), 3.10 (dd, J = 15.8 and 9.0 Hz, 1H), 3.56 (d, J = 13.8 Hz, 1H), 3.81−3.86 (m, 2H), 3.96 (dd, J = 9.0 and 5.3 Hz, 1H), 5.06 (heptet, J = 6.2 Hz, 1H), 7.08−7.40 (broad, 8H), 7.51 (d, J = 7.0 Hz, 1H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.8, 21.1, 21.9, 36.8, 53.2, 55.4, 56.7, 68.1, 107.4, 110.7, 118.1, 119.4, 121.4, 126.9, 127.1, 128.1, 129.0, 135.4, 136.0, 139.8, 172.8; MS (CI, CH_4) *m*/*z* (relative intensity) 391 (M + 1, 100%) 419 (M + 28, 19.2%). Anal. Calcd for $C_{25}H_{30}N_2O_2 \cdot {}^1/_4H_2O$: C, 76.04; H, 7.73; N, 7.09. Found: C, 75.88; H, 7.76; N, 7.10. CTH of *trans* **11b** provided a compound (N_b-H) which had spectral properties identical to **30b**.[42]

***trans*-2-Benzyl-1-cyclohexyl-3-(isopropoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (12).** Cyclohexanecarboxaldehyde (0.51 g, 4.5 mmol) was added to a solution of N_b-benzyltryptophan isopropyl ester **26** (1.0 g, 3.0 mmol) in dry benzene (100 mL). This solution was heated to reflux using a Dean−Stark trap for water removal. After 36 h the reaction was cooled, and a small amount of the crude material was removed for spectroscopy. Removal of the solvent under reduced pressure and recrystallization from methanol afforded 1.16 g (89%) of the pure material with mp 185.0−187.3 °C: IR (KBr) 3450, 1730, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.60−1.30 (m, 5H), 1.28 (d, J = 6.2 Hz, 3H), 1.30 (d, J = 6.2 Hz, 3H), 1.40−1.90 (broad, 5H), 2.20−2.30 (broad, 5H), 2.85 (dd, J = 14.2 and 5.5 Hz, 1H), 2.96 (dd, J = 14.2 and 10.0 Hz, 1H), 3.20 (d, J = 8.5 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.66 (d, J = 13.8 Hz, 1H), 4.09 (q, J = 5.0 Hz, 1H), 4.98 (heptet, J = 6.0 Hz, 1H), 6.95−7.45 (broad, 9H), 10.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.9, 26.3, 30.4, 42.0, 53.1, 57.0, 61.4, 68.1, 107.6, 110.6, 118.1, 119.3, 121.5, 126.9, 127.9, 129.1, 134.4, 135.8, 139.8, 172.7; MS (CI, CH_4) *m*/*z* (relative intensity) 431 (M + 1, 100%). HRMS calculated for $C_{28}H_{34}N_2O_2$: 430.2620. Found: 430.2635. Anal. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.27; H, 8.23; N, 6.57. The stereochemical configuration of **12** was confirmed as *trans* by single crystal X-ray crystallography.[40]

Isopropyl N_b-(Diphenylmethylene)-(±)-tryptophanoate (24). Into a 1 L flask were placed a suspension of tryptophan isopropyl ester hydrobromide salt (14.08 g, 0.043 mol) in CH_2Cl_2 (500 mL) and an equimolar amount of benzophenone imine (7.80 g). This mixture was stirred for 24 h under nitrogen. Filtration to remove NH_4Br and solvent removal under reduced pressure yielded a tan oil. The oil was taken up in ether and the solution filtered, washed with distilled water, and dried over K_2CO_3. Filtration and solvent removal followed by recrystallization from ether/hexane yielded 15.9 g (90%) of **24** as white solid: mp 118.9-120.8 °C; IR (KBr) 3455, 3190, 1725 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.04 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.3 Hz, 3H), 3.02 (dd, J = 6.5 and 7.3 Hz, 1H), 3.30 (dd, J = 6.0 and 7.3 Hz, 1H), 4.14 (t, J = 6.8 Hz, 1H), 4.83 (m, J = 6.3 Hz, 1H), 6.73-7.72 (m, 15H), 10.76 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.4, 29.0, 66.5, 67.5, 109.8, 111.1, 118.0, 120.7, 123.6, 127.3, 127.9, 130.3, 135.5, 135.9, 138.9, 169.1, 170.7; MS (CI, CH_4) *m*/*z* (relative intensity) 411 (M + 1, 100%). Anal. Calcd for $C_{27}H_{26}N_2O_2$: C, 79.03; H, 6.38; N, 6.82. Found: C, 78.83; H, 6.31; N, 6.63.

Isopropyl N_b-(Diphenylmethyl)-(±)-tryptophanoate (28). A solution of anhydrous methanol (500 mL) and imine **24** (11.80 g, 0.029 mol) was stirred at pH 6 (adjusted by the addition of glacial acetic acid). Sodium cyanoborohydride (3.62 g, 0.058 mol) was added portionwise while the reaction was monitored by TLC. Additional glacial acetic acid was added to maintain the pH at 6. The observation that the starting material was no longer visible by TLC (silica gel; 1:9 ethyl acetate:benzene v/v) prompted the addition of excess distilled water until the solution took on a white color. The pH was adjusted to 8 with $NaHCO_3$ and the solution extracted with $CHCl_3$. Removal of the solvent under reduced pressure furnished a tan oil. The oil was taken up in ether and the hydrochloride salt formed by the addition of 1.5 mol equiv of anhydrous HCl (g) dissolved in ether. The stoppered solution was held overnight at 0 °C, and the resultant white precipitate was collected by vacuum filtration and thoroughly washed with cold ether to yield, upon drying, 12.33 g (95%) of **28** as a white powder: mp 212.6 °C dec; IR (KBr) 3280, 1740 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.82 (d, J = 6.2 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H), 3.20 (m, 2H), 3.76 (t, J = 6.6 Hz, 1H), 4.96 (m, J = 6.3 Hz, 1H), 5.05 (s, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.68 (broad, 1H), 6.98−7.19 (m, 10H), 7.36 (d, J = 7.0 Hz, 2H), 7.44 (d, J = 7.1 Hz, 2H), 7.67 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 20.5, 21.2, 59.3, 64.4, 69.3, 108.1, 111.4, 118.0, 118.4, 121.1, 124.2, 128.2, 128.8, 136.2, 168.9; MS (CI, CH_4) *m*/*z* (relative intensity) 413 (M + 1, 100%). Anal. Calcd for $C_{27}H_{28}N_2O_2 \cdot$ HCl: C, 72.23; H, 6.51; N, 6.24. Found: C, 72.54; H, 6.63; N, 6.17.

Methyl N_b-(Diphenylmethyl)-(±)-tryptophanoate (25). Tryptophan methyl ester hydrobromide salt (11.318 g) was converted into the imine **21** by the method of Polt and O'Donnell.[22] The product of this preparation was then immediately dissolved in anhydrous methanol and the pH of the solution adjusted to 6 with glacial acetic acid. Addition of $NaCNBH_3$ (7.50 g) over a 1 h period and further stirring while the reaction was monitored by TLC (silica gel; 1:9 ethyl acetate:benzene v/v) indicated reaction completion in 4 h. Concomitant additions of acetic acid over the course of the reduction were necessary to maintain the pH at 6. Distilled water was added until a cloudy white precipitate persisted. The pH was adjusted to 8 with concentrated aqueous ammonia and the mixture extracted with $CHCl_3$. The combined organic extracts were dried over K_2CO_3. The filtrate was concentrated under reduced pressure and dissolved in a minimal amount of anhydrous ether. Addition of an ether solution of 1.5 mol equiv of HCl and storage at −20 °C overnight yielded a fluffy white powder which was filtered off and washed with cold ether. The white solid was dried to provide 21.4 g (80% from the tryptophan methyl ester hydrobromide salt) of the substituted amine **25**: mp 254 °C dec; IR (neat) 3428, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, free base) δ 2.23 (s, 1H), 3.16 (d, J = 6.4 Hz, 2H), 3.58 (s, 3H), 4.80 (s, 1H), 6.99−7.35 (m, 15H), 7.52 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.5, 52.6, 66.2, 70.6, 110.1, 112.8, 118.0, 118.7, 121.3, 123.3, 127.5−128.8 (m), 130.3, 135.9, 136.0, 168.9; MS (CI, CH_4) *m*/*z* (relative intensity) 385 (M + 1, 45.7%). Anal. Calcd for $C_{25}H_{24}N_2O_2 \cdot$ HCl: C, 71.33; H, 5.99; N, 6.65. Found: C, 71.01; H, 6.34; N, 6.22.

***trans*-3-(Methoxycarbonyl)-1-methyl-2-(diphenylmethyl)-1,2,3,4-tetrahydro-9*H*-pyridp[3,4-*b*]indole (13b).** A solution of **23** (76 mg, 0.2 mmol) and dry benzene (7 mL) was placed in a glass tube and cooled to 0 °C after which acetaldehyde (0.166 mL, 3.0 mmol) was added to it. (The volume of the solution was not allowed to exceed one-tenth the total volume of the glass tube.) The tube was sealed at atmospheric pressure and carefully thawed. After heating at 80 °C for 36 h, the tube was cooled to 25 °C prior to opening, and the solvent was removed under reduced pressure to

provide a yellow oil. The residue was subjected to a wash column (silica gel, CH_2Cl_2) followed by separation of the diastereomers by flash chromatography (silica gel, toluene) to yield **13b** (28 mg, 34%) as a pale yellow oil: IR (neat) 3520, 1750 cm^{-1}; ^1H NMR (C_6D_6, free base) δ 1.22 (d, J = 7.0 Hz, 3H), 2.82 (q, J = 7.0 Hz, 1H), 3.24 (s, 3H), 3.27 (d, J = 14.2 Hz, 1H), 4.07 (q, J = 6.0 Hz, 2H), 5.23 (s, 1H), 6.17 (s, 1H), 7.05 (m, 8H), 7.56 (m, 6H); ^{13}C NMR (C_6D_6) δ 19.4, 20.4, 21.4, 49.4, 51.1, 54.4, 72.1, 106.0, 111.0, 118.7, 119.7, 121.7, 127.4, 127.5, 127.8, 128.2, 128.3, 128.5, 129.0, 129.0, 129.3, 135.2, 136.7, 143.5, 144.6, 174.5; MS (CI, CH_4) m/z (relative intensity) 411 (M + 1, 56.8%). Anal. Calcd for $C_{27}H_{26}N_2O_2$·HCl: C, 72.55; H, 6.09; N, 6.27. Found: C, 72.59; H, 6.02; N, 6.74. CTH of **13** provided a compound which had spectral properties identical to *trans*-**4b**.

***trans*-3-(Methoxycarbonyl)-2-(diphenylmethyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (14).** A solution of **23** (1.17 g, 3.05 mmol), butyraldehyde (0.242 g, 3.36 mmol), and dry benzene (50 mL) was heated to reflux under a nitrogen atmosphere for 36 h. Analysis by TLC indicated very little product formation. A further period of heating (5 d) provided tetrahydro-β-carboline for study. Removal of the solvent under reduced pressure and purification by flash chromatography yielded 0.720 g (59%) of a waxy foam **14**: IR (neat) 3430, 1736 cm^{-1}; ^1H NMR (C_6D_6, free base) δ 0.87 (t, J = 6.4 Hz, 3H), 1.16 (m, 1H), 1.33 (m, 1H), 1.60 (m, 1H), 1.88 (m, 1H), 2.10 (s, 1H), 2.85 (dd, J = 5.9 and 8.1 Hz, 1H), 3.28 (d, J = 13.4 Hz, 1H), 3.36 (s, 3H), 3.74 (dd, J = 5.4 and 4.3 Hz, 1H), 4.11 (d, J = 6.8 Hz, 1H), 4.80 (s, 1H), 6.18 (s, 1H), 6.97−7.27 (m, 10H), 7.38 (d, J = 7.1 Hz, 1H), 7.63 (t, J = 7.0 Hz, 2H); ^{13}C NMR (C_6D_6) δ 15.1, 18.0, 21.4, 21.9, 38.8, 51.9, 54.7, 55.1, 73.4, 105.9, 111.4, 119.3, 120.2, 122.3, 126.1, 128.8, 134.6, 137.1, 144.4, 144.7, 174.7; MS (CI, CH_4) m/z (relative intensity) 439 (M + 1, 61%). Anal. Calcd for $C_{29}H_{30}N_2O_2$·HCl: C, 73.33; H, 6.58; N, 5.90. Found: C, 73.01; H, 6.66; N, 5.96. CTH of **14** provided a compound which had spectral properties identical to the *trans* N_b-H isomer related to **5b** with (R^1 = $CH_2CH_2CH_3$, R^3 = CH_3).[42]

***trans*-1-Cyclohexyl-3-(methoxycarbonyl)-2-(diphenylmethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (15).** A solution of **23** (1.01 g, 2.63 mmol), anhydrous benzene (50 mL), and cyclohexanecarboxaldehyde (0.324 g, 2.88 mmol) was placed into a round-bottomed flask. To this solution TFA (0.329 g, 2.89 mmol) was added. The solution was heated to reflux and after 36 h the reaction mixture was cooled, washed with 15% aqueous ammonia, brine, and dried over K_2CO_3. Filtration and solvent removal under reduced pressure yielded a yellow oil. Flash chromatography on silica gel (toluene) resulted in 0.391 g of **15** (31%): IR (neat) 3444, 1735 cm^{-1}; ^1H NMR (C_6D_6, free base) δ 1.39 (m, broad 7H), 2.04 (d, J = 5.8 Hz, 4H), 2.51 (s, 1H), 2.29 (m, 2H), 2.32 (s, 3H), 3.66 (t, J = 6.2 Hz, 1H), 5.08 (s, 1H), 6.31 (s, 1H), 6.92 (s, 1H), 7.19 (m, 7H), 7.44 (m, 4H), 7.73 (d, J = 7.5 Hz, 1H); ^{13}C NMR (C_6D_6) δ 21.5, 26.7, 27.6, 28.6, 28.7, 30.0, 33.5, 51.2, 60.2, 66.1, 110.6, 111.7, 117.3, 119.5, 120.0, 122.4, 125.7, 127.3, 127.7, 128.4, 128.5, 128.6, 128.7, 128.8, 129.4, 137.5, 139.4, 143.6, 145.0, 175.3; MS (CI, CH_4) m/z (relative intensity) 479 (M + 1, 45%). Anal. Calcd for $C_{32}H_{34}N_2O_2$·HCl: C, 74.62; H, 6.85; N, 5.44. Found: C, 74.40; H, 7.23; N, 6.01. CTH of **15** provided a compound which had spectral properties identical to *trans* **6b** (R^1 = C_6H_{11}, R^3 = CH_3).[42]

***trans*-2-(Diphenylmethyl)-3-(isopropoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (16).** A solution of **24** (0.50 g, 1.3 mmol) and dry benzene (7 mL) was placed in a tube for sealing. After cooling the solution to 0 °C, acetaldehyde (0.20 mL, 3.6 mmol, also at 0 °C) was added. The solution was cooled further in liquid nitrogen, sealed under vacuum, and carefully thawed. The solution was heated for 36 h at 80 °C followed by removal of the solvent under reduced pressure to give a brown oil. Flash chromatography on silica gel (CH_2Cl_2) yielded **16** (0.165 g, 31%) as a white foam: mp 235 °C dec; ^1H NMR (C_6D_6, free base) δ 0.91 (d, J = 6.3 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H), 2.85 (q, J = 7.0 Hz, 1H), 3.33 (d, J = 15.6 Hz, 1H), 4.09 (q, J = 6.3 Hz, 2H), 4.87 (m, J = 6.2 Hz, 1H), 5.33 (s, 1H), 6.18 (s, 1H), 7.10 (m, 8H), 7.61 (d, J = 8.9 Hz, 5H), 7.69 (d, J = 7.1 Hz, 1H); ^{13}C NMR (C_6D_6) δ 19.5, 20.8, 21.6, 21.7, 49.4, 54.9, 67.8, 72.0, 106.1, 110.6, 118.7, 119.7, 121.6, 127.5, 128.1, 128.5, 128.9, 129.0, 130.2, 132.0, 135.4, 136.7, 143.7, 144.5, 173.7; IR (neat) 1400, 1710, 2875, 3405; MS (CI, CH_4) m/z (relative intensity) 439 (M + 1, 97%). Anal. Calcd for $C_{29}H_{30}N_2O_2$·HCl: C, 73.33; H, 6.58; N, 5.90. Found: C, 72.89; H, 6.84; N, 5.99. CTH of **16** provided a compound (N_b-H) which had spectral properties identical to *trans* **29b** [R^1 = CH_3, R^3 = $CH(CH_3)_2$].[42]

***trans*-2-(Diphenylmethyl)-3-(isopropoxycarbonyl)-1-propyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (17).** A solution of the hydrochloride salt of **24** (1.29 g, 2.9 mmol), butyraldehyde (1.03 g, 14.3 mmol), TFA (0.65 g, 5.7 mmol), and dry benzene (75 mL) was heated to reflux. After 36 h the solution was cooled and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 14% ammonia (aq) and brine, and dried (K_2CO_3). Flash chromatography on silica gel (CH_2Cl_2) yielded **17** (0.27 g, 20% yield): IR (neat) 3450, 3110, 1772 cm^{-1}; ^1H NMR (C_6D_6, free base) δ 0.90 (m, 6H), 1.04 (d, J = 6.1 Hz, 3H), 1.18 (m, 1H), 1.30 (m, 1H), 1.58 (m, 1H), 1.91 (m, 1H), 2.20 (s, 1H), 2.86 (d, J = 6.0 and 8.2 Hz, 1H), 3.30 (d, J = 14.0 Hz, 1H), 3.81 (dd, J = 5.2 and 4.2 Hz, 1H), 4.16 (d, J = 7.1 Hz, 1H), 4.86 (s, 1H), 4.98 (m, 1H), 6.22 (s, 1H), 6.90−7.24 (m, 10H), 7.38 (d, J = 7.4 Hz, 1H), 7.59 (t, J = 7.2 Hz, 2H); ^{13}C NMR (C_6D_6) δ 15.6, 18.1, 21.3, 21.7, 21.9, 29.8, 39.0, 51.7, 54.8, 56.1, 72.9, 106.1, 112.1, 120.3, 120.7, 122.2, 127.0, 128.7, 134.1, 136.9, 144.9, 145.2, 175.1; MS (CI, CH_4) m/z (relative intensity) 467 (M + 1, 100%). Anal. Calcd for $C_{31}H_{34}N_2O_2$·HCl: C, 74.00; H, 6.81; N, 5.57. Found: C, 73.60; H, 6.67; N, 5.92. CTH of **17** provided a compound (N_b-H) which had spectral properties identical to *trans* **30b** [R^1 = $CH_2CH_2CH_3$, R^3 = $CH(CH_3)_2$].[42]

***trans*-1-Cyclohexyl-2-(diphenylmethyl)-3-(isopropoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (18).** A mixture of the hydrochloride salt of **24** (1.50 g), cyclohexanecarboxaldehyde (0.56 g), dry benzene (70 mL), and TFA (0.38 g) was heated to reflux for 36 h. After cooling, the solvent was removed under vacuum and the tan residue taken up in CH_2Cl_2. This solution was washed with $NaHCO_3$ (saturated) and brine and then dried ($MgSO_4$). Filtration and removal of the solvent under reduced pressure gave a tan oil. Flash chromatography on silica gel (CH_2Cl_2) yielded a yellow oil (0.423 g, 25%): IR (neat) 3417, 3123, 1770 cm^{-1}; ^1H NMR (C_6D_6, free base) δ 0.95 (d, J = 6.2 Hz, 3H), 1.03 (d, J = 6.2 Hz, 3H), 1.11−1.82 (m, 7H), 2.07 (dd, J = 4.9 and 6.0 Hz, 4H), 2.51 (s, 1H), 3.29 (t, J = 6.7 Hz, 2H), 3.82 (t, J = 6.4 Hz, 1H), 5.01 (m, J = 6.2 Hz, 1H), 5.09 (s, 1H), 6.33 (s, 1H), 6.92 (s, 1H), 7.02−7.61 (m, 11H), 7.76 (d, J = 6.9 Hz, 2H); ^{13}C NMR (C_6D_6) δ 21.6, 21.8, 27.6, 28.5, 28.6, 30.0, 33.5, 53.4, 60.4, 66.0, 67.9, 110.5, 111.9, 117.3, 119.6, 119.9, 122.3, 127.3, 127.8, 127.9, 128.6, 128.7, 128.9, 129.4, 130.0, 130.2, 132.1, 137.4, 139.3, 143.5, 145.1, 174.4; MS (CI, CH_4) m/z (relative intensity) 507 (M + 1, 100%). Anal. Calcd for $C_{34}H_{38}N_2O_2$·HCl: C, 75.19; H, 7.24; N, 5.16. Found: C, 74.75; H, 7.00; N, 5.19. Spectral data obtained after CTH of **18** were identical to those of *trans* **31** [R^1 = C_6H_{11}, R^3 = $CH(CH_3)_2$].[42]

(+)-6-Methoxy-N_a-methyl-N_b-benzyl-(D)tryptophan Ethyl Ester (47). To a solution of (−)-N_a-methyl-6-methoxy-(D)-tryptophan ethyl ester[29,33] (4.1 g, 15 mmol) in anhydrous methanol (25 mL) was added freshly distilled benzaldehyde (1.59 g, 15 mmol). The solution which resulted was stirred for 2.5 h at room temperature. The mixture was then cooled in a large ice−salt bath to −5 °C (reaction mixture temperature), and sodium borohydride (0.72 g, 18.9 mmol) was added in 2 portions over a period of 45 min without allowing the temperature to rise above 0 °C. The reaction was monitored by TLC on silica gel with MeOH/EtOAc (10:90) as the developing solvent for the formation of the imine (R_f = 0.6) and EtOAc/hexane (50:50) for the formation of the amine **47** (R_f = 0.3). The solution was allowed to stir for an additional 0.5 h followed by the addition of ice−water (1 mL). The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and extracted with water (2 × 20 mL). The organic layer was washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to provide the crude N_b-benzyltryptophan **47** which was purified by flash chromatography on silica gel with EtOAc/hexane (30:70) to yield the free

base **47** as an oil (5.1 g, 93%); $[\alpha]^{25}_D = +4.75°$ ($c = 1.6$, $CHCl_3$); IR (neat) 2936, 2835, 1730, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, $J = 7.1$ Hz, 3H), 1.77 (br, s, 1H), 3.08 (dd, $J = 6.9$ and 2.7 Hz, 2H), 3.61 (m, 3H), 3.65 (s, 3H), 3.80 (d, $J = 13.2$ Hz, 1H), 3.84 (s, 3H), 4.07 (q, $J = 7.1$ Hz, 2H), 6.72 (m, 3H), 7.25 (m, 5H), 7.40 (d, $J = 9.0$ Hz, 1H); CI MS (CH_4) *m/e* (relative intensity) 367 ($M^+ + 1$, 100). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.93; H, 7.10; N, 7.53. The optical purity of N_b-benzyltryptophan **47** was assessed in the exact same manner as in the N_a-sulfonamido case **51** employing the europium chiral shift reagent described in references 29 and 33. The methyl signal in the ^1H NMR spectrum (δ 1.14) did not split even after 10 additions of the chiral shift reagent, thereby indicating an optical purity of greater than 98% ee.

***trans*-(1*S*,3*R*)-(−)-2-Benzyl-3-(ethoxycarbonyl)-1-(2′-carboxyethyl)-7-methoxy-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (48).** The (+)-6-methoxy-(D)-N_a-methyl-N_b-benzyltryptophan ethyl ester **47** (21.5 g, 0.0587 mol) was dissolved in toluene (800 mL) and dioxane (800 mL) in a three-neck round-bottom (3 L) flask equipped with a Dean−Stark trap (DST) and a reflux condenser. The solution was heated to reflux followed by the dropwise addition of a solution of α-ketoglutaric acid (8.6 g, 0.0588 mol) in dioxane (90 mL). The reaction mixture was held at reflux for 11 h with continuous removal of water. The solution was allowed to cool followed by the removal of solvent under reduced pressure to provide exclusively the *trans* acid (^{13}C NMR). Further purification of the crude solid was carried out on a short wash column of silica gel with EtOAc/hexane (50:50) to yield the pure *trans* acid **48** as an amorphous solid (21.9 g, 83.0%): $[\alpha]^{25}_D = -24.0°$ ($c = 1.2$, $CHCl_3$); IR ($CHCl_3$) 3254, 2937, 1732, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, $J = 7.1$ Hz, 3H), 1.93−2.04 (m, 2H), 2.45 (qt, $J = 30.0$, 17.5 and 5.8 Hz, 1H), 3.09 (d, $J = 8.2$ Hz, 1H), 3.45 (d, $J = 13$ Hz, 1H), 3.53 (s, 3H), 3.63 (d, $J = 6.3$ Hz, 1H), 3.67 (s, 3H), 3.96 (d, $J = 13$ Hz, 1H), 4.09 (t, $J = 8.5$ Hz, 1H), 4.28 (dq, $J = 7.2$ and 3.6 Hz, 2H), 6.79 (s, 1H), 6.82 (d, $J = 2.1$ Hz, 1H), 7.22−7.44 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.25, 20.48, 27.91, 29.74, 30.96, 52.92, 54.43, 55.95, 56.16, 60.99, 93.58, 106.56, 108.79, 118.78, 121.07, 127.39, 128.36, 129.48, 133.65, 138.65, 138.51, 156.60, 172.27, 177.17; EIMS (70 eV) *m/e* (relative intensity) 450 (M^+, 6.3), 377 (100), 213 (41.2). Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.30; H, 6.72; N, 6.22. Found: C, 68.90; H, 6.61; N, 6.24.

(−)-6-Methoxy-N_a-(benzenesulfonyl)-N_b-benzyltryptophan Ethyl Ester (51). To a solution of (−)-N_a-(benzenesulfonyl)-6-methoxytryptophan ethyl ester **50**[33] (11.4 g, 0.0284 mol) in anhydrous methanol (45 mL) was added benzaldehyde (3.31 g, 0.312 mol). The solution which resulted was stirred for 3 h at rt. The mixture was then cooled in a large ice−salt bath to −5 °C (solution temperature) and sodium borohydride (1.104 g, 0.0292 mol) was added in portions over a period of 1 h (without allowing the temperature to rise above 0 °C). The reaction was monitored by TLC on silica gel with MeOH/EtOAc (10:90) as the eluent for the formation of the imine (R_f imine = 0.65, R_f starting mat. = 0.30) and EtOAc/hexane (50:50) for the formation of the amine **51** (R_f imine = 0.50, R_f amine = 0.40). The solution was allowed to stir for an additional 2.5 h followed by the addition of ice−water (5 mL). The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and extracted with H_2O (20 mL). The organic layer was washed with brine (2 × 50 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to furnish N_b-benzylamine **51** which was purified by flash chromatography on silica gel with EtOAc/hexane (40:60) to yield the free base **51** (12.2 g, 87.3%); $[\alpha]^{26}_D$ −16.2° ($c = 1.0$, $CHCl_3$); IR (neat) 3339, 2980, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.08 (t, 3H, $J = 7.12$ Hz), 1.83 (br s, 1H), 2.96 (d, 2H, $J = 6.7$ Hz), 3.53 (t, 1H, $J = 7.1$ Hz), 3.61 (d, 1H, $J = 13.1$ Hz), 3.77 (d, 1H, $J = 13.1$ Hz), 3.65 (s, 3H), 4.01 (dq, 2H, $J = 7.2$ and 2.5 Hz), 6.81 (dd, 1H, $J = 8.7$ and 2.3 Hz), 7.21−7.51 (m, 11H), 7.79 (d, 2H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.03, 28.97, 51.96, 55.68, 60.26, 60.67, 98.06, 112.15, 118.73, 120.00, 122.91, 124.69, 126.51, 126.98, 128.02, 128.27, 129.07, 133.56, 136.12, 138.14, 139.49, 158.03, 174.23; EIMS (70 e/V) *m/e* (relative intensity) 492 (M^+, 2.0), 192 (100), 160 (78). Anal. Calcd for $C_{27}H_{28}N_2O_5S$: C, 65.85; H, 5.69; N, 5.69. Found: C, 65.96; H, 5.81; N, 5.62.

The optical purity of **51** was determined by ^1H NMR in the presence of the chiral shift reagent tris[3-[(trifluoromethyl)-hydroxymethylene]-(+)-camphorato]europium III.[29,33] The ^1H NMR of racemic **51** in $CDCl_3$ was run as the standard spectrum. The ^1H NMR spectrum was taken after the addition of 2 drops of the chiral shift reagent in $CDCl_3$ (50% solution), and this process was repeated for five additions. The methyl triplet was split immediately (δ 1.07) when the first two drops were added to (±)-**51**. The separation of the triplets became greater as more chiral shift reagent was added until the signal was integrated. When the above benzyl amine **51** was analyzed in the same manner, the methyl triplet (δ 1.07) never split, indicating an optical purity of at least greater than 98% ee. This was checked vs addition of 3% of spiked material (±).

***cis*- (52a) and *trans*-(1*S*,3*R*)-2-Benzyl-3-(ethoxycarbonyl)-1-(2′-carboxyethyl)-7-methoxy-9-(benzenesulfonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (52b).** The (−)-6-methoxy-N_a-benzenesulfonyl-N_b-benzyltryptophan ethyl ester **51** (1.03 g, 2.2 mmol) was dissolved in toluene (40 mL) and dioxane (40 mL) in a three-neck round-bottom (250 mL) flask equipped with a Dean−Stark trap (DST) and a reflux condenser. The solution was heated to reflux and followed by the dropwise addition of a solution of α-ketoglutaric acid (0.295 g, 2.32 mmol, 1.05 equiv) in dioxane (10 mL). After 7 h at reflux, another portion of α-ketoglutaric acid (0.295 g, 2.32 mmol, total of 2.1 equiv) in dioxane (10 mL) was added. The reaction mixture was held at reflux for 44 h with continuous removal of water via a Dean−Stark trap. The mixture was allowed to cool followed by the removal of solvent under reduced pressure to provide a mixture of *cis* to *trans* acids **52a** (49) and **52b** (51), respectively. Further purification was achieved with a short wash column on silica gel with EtOAc/hexane (50:50) to yield the mixture of diastereomers **52a**,**b** (72 mg, 60%).[29]

***trans* 52b**: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.28 (t, 3H, $J = 7.1$ Hz), 2.05 (m, 1H), 2.41−2.50 (m, 3H), 2.96 (d, 2H, $J = 7.6$ Hz), 3.37 (d, 1H, $J = 13.7$), 3.85 (d, 1H, $J = 13.7$ Hz), 3.87 (s, 3H), 4.05 (t, 1H, $J = 8.1$ Hz), 4.10−4.32 (m, 2H), 6.89 (dd, 1H, $J = 8.6$ and 2.2 Hz), 7.22−7.68 (m, 13H), 7.70 (d, 1H, $J = 2.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.17, 20.63, 28.90, 31.72, 53.44, 54.92, 55.84, 57.73, 61.12, 100.16, 112.69, 117.46, 119.00, 123.42, 126.38, 127.53, 128.30, 128.87, 129.14, 133.68, 134.52, 138.16, 138.39, 158.27, 171.97, 178.76.

***cis*- (53a) and *trans*-(1*S*,3*R*)-2-Benzyl-3-(ethoxycarbonyl)-1-[2′-(ethoxycarbonyl)ethyl]-7-methoxy-9-(benzenesulfonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (53b).** The mixture of *cis* and *trans* acids **53a** and **53b** (50 mg, 0.08 mmol) was dissolved in anhydrous EtOH (10 mL) containing 2% HCl (w/w) and triethyl orthoformate (0.3 mL). The mixture was heated to reflux for 45 min under an atmosphere of N_2. The solvent was removed under reduced pressure, and the residue was brought to pH 9 with aqueous NH_3 (14%) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure to afford a yellow oil which was purified via flash chromatography (silica gel, EtOAc/hexane, 30:70) to provide the *cis* and *trans* diethyl esters **53a**,**b** as a colorless oil (45 mg, 86%) in an approximate 1:1 ratio: ^1H NMR ($CDCl_3$, 250 MHz) of the *trans* isomer **53b** δ 1.21 (t, 3H, $J = 7.1$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz), 2.05 (m, 1H), 2.30−2.51 (m, 3H), 2.90 (d, 2H, $J = 6.7$ Hz), 3.32 (d, 1H, $J = 14.1$ Hz), 3.79 (d, 1H, $J = 14.0$ Hz), 3.83 (s, 3H), 4.06 (q, 4H, $J = 7.3$ Hz), 4.19 (m, 2H), 6.86 (dd, 1H, $J = 8.5$ and 2.2 Hz), 7.25 (d, 1H, $J = 6.9$ Hz), 7.32 (br s, 7H), 7.39 (d, 1H, $J = 8.0$ Hz), 7.51 (d, $J = 5.8$ Hz), 7.55 (d, 1H, $J = 7.1$ Hz), 7.72 (d, 1H, $J = 2.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.09 (q), 14.14 (q), 20.63 (t), 29.34 (t), 31.34 (t), 53.26 (t), 54.77 (d), 55.73 (q), 57.41 (d), 60.05 (t), 60.83 (t), 100.10 (d), 112.47 (d), 117.35 (s), 118.85 (d), 126.31 (d), 126.68 (d), 128.11 (d), 128.55 (d), 129.03 (d), 133.56 (d), 135.03 (s), 138.81 (s), 158.07 (s), 172.16 (s), 173.48 (s).

Attempted *Cis* (53a) to *Trans* (53b) Epimerization of *cis*- and *trans*-(1*S*,3*R*)-2-Benzyl-3-(ethoxycarbonyl)-1-[2′-(ethoxycarbonyl)ethyl]-7-methoxy-9-(benzenesulfonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (53). The mix-

ture of *cis* and *trans* diethyl esters **53a**,**b** (120 mg, 0.20 mmol) was dissolved in anhydrous EtOH (30 mL) containing 2% HCl (w/w). The mixture was allowed to reflux for 3 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure, the residue was brought to pH 9 with aqueous NH_3 (14%) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure to afford a yellow oil which was purified via flash chromatography (silica gel, MeOH/hexane, 5:95) to provide the ring-cleaved benzylamine **51** as the major product (92 mg, 76%). The spectral properties of **51** were identical to that reported above for the benzylation of **50**. Note: the pure *trans* diester **53b** and the pure *cis* diester **53a** were subjected to the above conditions (24 h) and also provided the same N_b-benzylamine **51**.

Ethyl 3-Formylpropionate (59). A solution of γ-butyrolactone **54** (86 g, 1 mol) and concd H_2SO_4 (2 g) in EtOH (500 mL) was stirred at 20 °C for 33 h, after which calcium carbonate (15 g) was added, and the mixture which resulted was stirred for an additional 2 h. The reaction mixture was filtered and the solution poured through a bed of K_2CO_3. (It was found that this reaction was partially reversible if the solvent was removed when the solution was acidic; therefore, the pH of the solution should be neutral before the removal of solvent by first pouring the solution through a bed of K_2CO_3.) The solvent was then removed under reduced pressure at 18 °C to provide 4-hydroxybutyrate (65 g, 55%). To a solution of the EtOH free residue (40 g, 0.30 mol) and dry CH_2Cl_2 (500 mL) was added pyridinium dichromate (265 g, 0.70 mol), and this mixture was stirred via a mechanical stirrer for 48 h at rt. The dark mixture which resulted was diluted with CH_2Cl_2 (300 mL) and then filtered through a short bed of silica gel. The liquid that remained was purified by fractional distillation (90 °C, 0.5 mmHg) to provide pure ethyl 3-formylpropionate **59** (25.3 g, 63%): IR (neat) 2987, 1734, 1718 cm^{-1}; ^1H NMR δ 1.11 (t, 3H, J = 7.1 Hz), 2.46 (t, 2H, J = 6.6 Hz), 2.65 (t, 2H, J = 6.4 Hz), 3.99 (q, 2H, J = 7.1 Hz), 9.65 (s, 1H). Note: It was found the best way to monitor these two reactions was analysis via the ^1H NMR spectrum of samples taken from the reaction mixtures.

***cis*- 60a and *trans*-(1*S*,3*R*)-2-Benzyl-3-(ethoxycarbonyl)-1-[2′-(ethoxycarbonyl)ethyl]-7-methoxy-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (60b).** To a solution of (+)-6-methoxy-N_a-methyl-N_b-benzyl-(D)tryptophan ethyl ester **47** (500 mg, 1.6 mmol) in refluxing benzene (5 mL) was added ethyl 3-formylpropionate **59** (213 mg, 1.6 mmol) dropwise over several minutes. The mixture was held at reflux for 10 h with continuous removal of H_2O via a Dean−Stark trap (DST), after which the solvent was removed under reduced pressure to provide a brown oil. A portion of the crude mixture was employed to determine the ratio of *cis* to *trans* isomers by ^1H and ^{13}C NMR spectroscopy (*cis* **60a**/*trans* **60b** = 39/61). The remainder of the material (338 mg, 52%) was purified via flash chromatography [silica gel, EtOAc/hexane, 20:80; the *trans* isomer **60b** was eluted first (TLC on silica gel; R_f *cis* = 0.26, R_f *trans* = 0.30; MeOH/hexane, 5:95, developed twice)]. The spectral data for *trans* **60b** were identical to that described earlier from the Fischer esterification of the *trans* acid to provide **60b**.[29] The yield of this sequence was not maximized but could be improved greatly employing excess aldehyde.

Epimerization of *cis* 60a into *trans*-(1*S*,3*R*)-2-Benzyl-3-(ethoxycarbonyl)-1-[2′-(ethoxycarbonyl)ethyl]-7-methoxy-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (60b). The mixture of *cis* and *trans* diesters **60a** and **60b** (20 mg, 0.042 mmol) obtained from the reaction immediately above was dissolved in CH_2Cl_2 (10 mL) to which trifluoroacetic acid (TFA, 100 μL) was added. The reaction mixture was stirred at rt for 1.5 h after which additional CH_2Cl_2 (10 mL) was added and the solution basified with aq NH_4OH (14%). The aq layer was washed with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford exclusively the pure *trans* **60b** isomer as a colorless oil (19.2 mg, 96%). The spectral properties of **60b** were identical to that reported immediately above for the *trans* diester **60b**.

***trans*-(1*R*,3*R*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole (63b) and *cis*-(1*S*,3*R*)-(+)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (63a).** Optically active N_b-benzyl-(D)(+)-tryptophan methyl ester **61** (5.0 g, 16.2 mmol) was dissolved in C_6H_6 (50 mL) and dioxane (50 mL) in a 250 mL round-bottom flask which was equipped with a Dean−Stark trap (DST) and a reflux condenser. To this solution, α-ketoglutaric acid (2.6 g, 17.8 mmol) was added. The reaction mixture was heated to reflux for 3 h and then allowed to cool to rt. The solution was diluted with EtOAc (100 mL) and washed with H_2O (2 × 50 mL) and brine (1 × 50 mL). The aq layer was extracted with EtOAc (2 × 30 mL). After removal of solvent from the combined organic layers under reduced pressure followed by purification with flash chromatography (silica gel, EtOAc/hexane, 50/50, v/v), the ester acids were obtained as a mixture of *cis* **62a** and *trans* **62b** diastereomers (4.99 g, 85%). The diastereomeric acids were dissolved in CH_2Cl_2 (50 mL) and the resulting solution cooled to −20 °C. To this stirred solution an excess of ethereal diazomethane was added over a 10 min period at −20 °C. The mixture which resulted was then stirred at rt for an additional 1.5 h. After removal of solvent under reduced pressure followed by separation via flash chromatography (silica gel, EtOAc/hexane, 10/90, v/v) the *trans* diester **63b** (4.0 g, 83% from ester acid) and the *cis* diester **63a** (560 mg, 12% from ester acid) were obtained.

63a: $[\alpha]^{28}_D$ = +0.58° (c = 2.5, $CHCl_3$), lit.[38] $[\alpha]^{17}_D$ = −1.3° (c = 1.0, $CHCl_3$); IR (KBr) 3470, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74−1.90 (m, 1H), 1.90−2.01 (m, 1H), 2.43−2.56 (m, 2H), 2.99 (dd, 1H, J = 6.3 and 15.8 Hz), 3.24 (dd, 1H, J = 3.6 and 15.8 Hz), 3.56 (s, 3H), 3.62 (s, 3H), 3.76−3.94 (m, 2H), 3.84 (dd, 1H, J = 14.0 Hz), 3.94 (dd, 1H, J = 14.0 Hz), 7.02−7.44 (m, 8H), 7.52 (d, 1H, J = 7.2 Hz), 8.01 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 20.03, 29.38, 30.40, 51.48, 51.75, 56.37, 58.82, 59.42, 110.88, 118.24, 119.43, 121.76, 127.30, 128.38, 128.97, 133.47, 136.50, 139.05, 173.88, 174.56; MS (EI) m/z (relative intensity) 406 (M^+, 15%), 347 (14), 319 (100), 259 (13), 169 (25). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.32; N, 6.75.

63b: mp 152−153 °C (lit.[38] 150−151 °C); $[\alpha]^{28}_D$ = −35.5° (c = 1.09, $CHCl_3$) lit.[38] $[\alpha]^{13}_D$ = −38.0° (c = 1.0, $CHCl_3$); IR (KBr) 3310, 1731, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85−2.15 (m, 2H), 2.20−2.50 (m, 2H), 3.03 (dd, 1H, J = 5.3 and 15.8 Hz), 3.12 (dd, 1H, J = 8.8 and 15.8 Hz), 3.48 (s, 3H), 3.75 (s, 3H), 3.59 (d, 1H, J = 13.6 Hz), 3.84 (d, 1H, J = 13.6 Hz), 3.87−3.93 (m, 1H), 3.98 (dd, 1H, J = 5.3 and 8.8 Hz), 7.07−7.35 (m, 8H), 7.43 (d, 1H, J = 7.2 Hz), 7.98 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.39, 28.94, 29.88, 51.45, 51.85, 53.51, 54.81, 56.79, 110.99, 118.16, 119.51, 121.77, 127.08, 127.13, 128.28, 129.13, 134.26, 136.50, 139.41, 173.42, 174.18; MS (EI) m/z (relative intensity) 406 (M^+, 60%), 347 (45), 319 (100), 169 (50). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.88; H, 6.47; N, 6.91.

Acid-Catalyzed Epimerization of *cis*-(1*S*,3*R*)-(+)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (63a) into *trans*-(1*R*,3*R*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole (63b). General procedure: To the *cis* diastereomer **63a** (20 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added CF_3-COOH (10 mL, 0.12 mmol, 2.4 equiv) via syringe. The solution was allowed to stir at rt under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 d the reaction was stopped (TLC indicated that all *cis* isomer **63a** had been consumed) and cooled in an ice bath, after which the mixture was diluted with CH_2Cl_2 (10 mL) and brought to pH = 8 with aq $NaHCO_3$ solution (10%). The aq layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried (K_2CO_3), and the solvent was removed under reduced pressure to furnish an oil. The oil which resulted was purified

by flash chromatography (silica gel, EtOAc/hexane, v/v, 20/80) to furnish pure *trans* **63b** (18 mg) as white crystals in 90% yield. This ester **63b** was spectrometrically identical to that of an authentic sample of *trans* **63b** including the optical rotation.

To the *cis* diastereomer **63a** (20 mg, 0.05 mmol) in dry $CHCl_3$ (1.0 mL) was added CF_3COOH (10 mL, 0.12 mmol, 2.4 equiv) via syringe. This solution was stirred at rt under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 d (TLC indicated that all *cis* isomer **63a** had been consumed) the reaction was stopped, worked up, and purified identically to the above procedure to furnish pure *trans* **63b** (16 mg) in 80% yield. This material was spectrometrically identical to that of an authentic sample of *trans* **63b** including the optical rotation.

To the *cis* diastereomer **63a** (20 mg, 0.05 mmol) in dry C_6H_6 was added CF_3COOH (10 mL, 0.12 mmol, 2.4 equiv) via syringe. This solution was stirred at rt under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 d (TLC indicated that about 70% of the *cis* isomer **63a** had been consumed) the reaction was stopped, worked up, and purified identically to the above procedure to furnish pure *trans* **63b** (12 mg) in 60% yield. This material was spectrometrically identical to that of an authentic sample of *trans* **63b** including the optical rotation. In addition, 4 mg of starting *cis* isomer **63a** were recovered.

To the *cis* diastereomer **63a** (20 mg, 0.05 mmol) in dry THF (1.0 mL) was added CF_3COOH (10 mL, 0.12 mmol, 2.4 equiv) via syringe. The solution was stirred at rt under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 d (TLC indicated that no *trans* isomer **63b** had been formed), the reaction was stopped, worked up, and purified identically to the above procedure to return 17 mg of starting *cis* **63a** (85%) which was spectrometrically identical to that of an authentic sample of *cis* **63a** including the optical rotation.

To the *trans* diastereomer **63b** (20 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added CF_3COOH (10 mL, 0.12 mmol, 2.4 equiv) via syringe. The solution was stirred at rt under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 d (TLC indicated that no new component had been formed), the reaction was stopped, worked up, and purified identically to the above procedure to return 17 mg of starting *trans* **63b** (85%) which was spectrometrically identical to that of an authentic sample of *trans* **63b** including the optical rotation.

To a mixture (1:1) of *cis* diastereomer **63a** and *trans* diastereomer **63b** (20 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added CF_3COOH (10 mL, 0.12 mmol, 2.4 equiv) via syringe. This solution was stirred at rt under N_2 and monitored by TLC (silica gel, EtOAc/hexane, v/v, 20/80). After stirring for 10 d (TLC indicated that all the *cis* isomer had been consumed), the reaction was stopped, worked up, and purified identically to the above procedure to furnish pure *trans* **63b** (18 mg) in 90% yield. This material was spectrometrically identical to that of an authentic sample of *trans* **63b** including the optical rotation.

Acid-Catalyzed Epimerization of *cis*-(1*S*,3*S*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (64a) to *trans*-(1*R*,3*S*)-(+)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (64b). Deuterotrifluoroacetic acid (1.4 g, 12.3 mmol) was added to a solution of the *cis* isomer **64a** (258 mg, 0.614 mmol) in CH_2Cl_2 (16 mL), and the reaction mixture was stirred for 10 d at rt and progress monitored by TLC (silica gel). The reaction mixture was cooled in an ice bath, diluted with CH_2Cl_2 (30 mL), and brought to pH 8 with aq $NaHCO_3$ solution (10%). The aq layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (K_2CO_3), and the solvent was removed under reduced pressure to provide an oil. This material was purified by flash chromatography (silica gel, v/v, EtOAc/hexane, 20:80) to furnish **64b** (237 mg) in 91.8% yield. This white solid was spectrometrically identical to that of an authentic sample of *trans* isomer **64b** including the magnitude of the optical rotation. *Trans* isomer **64b**: $[\alpha]^{28}_D = +54.8°$ ($c = 7.62$, $CHCl_3$);[9] mp 119−120 °C [lit.[9] mp 119−120 °C]; IR (KBr) 1735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.85−2.00 (2H, m), 2.38 (dt, 1H, $J = 17.5$, 5.6 Hz), 2.61 (ddd, 1H, $J = 17.5$, 9.6, 5.6 Hz), 3.05 (dd, 1H, $J = 15.8$, 5.5 Hz), 3.12 (dd, 1H, $J = 15.8$, 11.0 Hz), 3.39-3.81 (AB_q, 2H, $J = 13.1$ Hz), 3.50 (3H, s), 3.65 (3H, s), 3.51 (dd, 1H, $J = 15.7$, 5.2 Hz), 3.84 (3H, s), 4.10 (dd, 1H, $J = 11.0$, 5.5 Hz), 7.12−7.40 (8H, m), 7.60 (d, 1H, $J = 8$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.25, 27.90, 29.60, 29.71, 51.26, 52.00, 52.79, 53.32, 56.12, 106.29, 108.90, 118.12, 119.11, 121.32, 126.52, 126.96, 128.14, 129.29, 135.67, 137.46, 139.25, 173.34, 173.87; MS (CI, CH_4) *m*/*z* (relative intensity) 421 (M + 1, 100).

Trifluoroacetic acid (543 mg, 4.76 mmol) was added to a solution of the *cis* isomer **64a** and *trans* isomer **64b** (*cis*, 280 mg, 0.667 mmol; *trans*, 720 mg, 1.71 mmol) in C_6H_6 (20 mL), and the reaction mixture was heated at reflux for 5 h. Progress was monitored by TLC (silica gel). The reaction mixture was cooled in an ice bath, diluted with C_6H_6 (40 mL), and brought to pH 8 with aq $NaHCO_3$ solution (10%). The aq layer was separated and extracted with C_6H_6 (2 × 25 mL). The combined organic layers were washed with brine (40 mL) and dried (K_2CO_3), and the solvent was removed under reduced pressure to provide an oil. This material was purified by flash chromatography (silica gel, v/v, EtOAc/hexane, 20:80) to furnish *trans* **64b** (880 mg) in 88% yield. This white solid was spectrometrically identical to that of an authentic sample of *trans* isomer **64b** including the optical rotation, $[\alpha]^{28}_D = +54.6°$ ($c = 1.42$, $CHCl_3$).

Zinc Chloride-Catalyzed Epimerization of the *cis*-(1*S*,3*S*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (64a) into the *trans*-(1*R*,3*S*)-(+)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (64b). The *cis* isomer **64a** (200 mg, 0.48 mmol) was dissolved in dry distilled $CHCl_3$ (8 mL). Anhydrous $ZnCl_2$ (99.999%, 300 mg, 2.20 mmol) was added to the above solution in one portion. The mixture was allowed to reflux for 30 h under Ar, after which time it was cooled to rt and filtered. The organic layer was washed with aq $NaHCO_3$ (10%) and brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide an oil. The oil was purified by passage through a short wash column (silica gel, v/v, EtOAc/hexane, 20:80) to provide the *trans* isomer **64b** (185 mg, 92.5%) which was spectrometrically identical to that of an authentic sample of *trans* isomer **64b** including the optical rotation, $[\alpha]^{28}_D = +54.8°$ ($c = 1.97$, $CHCl_3$). As a control experiment the *cis* isomer **64a** was heated under exactly the same conditions in dry distilled $CHCl_3$ (8 mL) in the absence of $ZnCl_2$. Under these conditions no *trans* isomer **64b** was observed, and only starting material **64a** was recovered. (The acid-free dry, distilled $CHCl_3$ was prepared by drying reagent grade $CHCl_3$ over KOH, followed by refluxing over sodium hydride and then distillation under Ar.)

Epimerization of the *cis*-(1*S*,3*S*)-(−)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (64a) Hydrochloride Salt to the *trans*-(1*R*,3*S*)-(+)-2-Benzyl-3-(methoxycarbonyl)-1-[(methoxycarbonyl)ethyl]-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (64b). The anhydrous hydrochloride salt **64a**·HCl was prepared as follows: the *cis* isomer **64a** (200 mg, 0.48 mmol) was dissolved in dry CH_3OH (10 mL) which contained 2% HCl (w/w). The mixture was allowed to stir 10 min at rt to form the hydrochloride salt. The solvent was removed under reduced pressure at rt to provide an oil. The oil was dissolved in dry CH_3OH (1 mL), and cold ether (20 mL) was added to precipitate out the hydrochloride salt of **64a**. The white solid which formed was filtered by vacuum filtration. The solid (**64a**·HCl) was washed with dry cold ether (2 × 10 mL) and dried. The HCl salt of **64a** [analysis by TLC (silica gel) indicated that no epimerization of the HCl salt had occurred] was dissolved in CH_2Cl_2 (10 mL) and the solution stirred for 18 d at rt under N_2. The reaction mixture was washed with 10% aq $NaHCO_3$ (20 mL) and brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced

pressure to provide an oil which was purified by flash chromatography (silica gel, v/v, EtOH/hexane, 20:80) to afford *trans* isomer **64b** (178 mg, 89%) and this material was spectrometrically identical to that of an authentic sample of *trans* **64b** including the optical rotation, $[\alpha]^{28}_D = +55.2°$ (c = 1.62, $CHCl_3$).

***cis*-(1*R*,3*R*)-(−)-2-Benzyl-1-(1,3-dithian-2-ylmethyl)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole (66a) and *trans*-(1*S*,3*R*)-(−)-2-Benzyl-1-(1,3-dithian-2-ylmethyl)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (66b).** Optically pure N_b-benzyl-(D)(+)-tryptophan methyl ester **61** was prepared according to the method of Zhang *et al.*[9,10] A mixture of this ester **61** (3.0 g, 9.7 mmol), dry C_6H_6 (15 mL), and 1,3-dithiane-2-acetaldehyde (**65**) (1.55 g, 9.56 mmol) was heated to reflux under N_2 for 14 h at which time analysis by TLC (silica gel, 4:6 EtOAc:hexanes) indicated the complete consumption of aldehyde. The solvent was removed under reduced pressure and the residue passed through a wash column (silica gel) to provide a mixture of *cis* **66a** and *trans* **66b** diastereomers (4.1 g) in a combined yield of 93% in a ratio of 30:70, respectively (^{1}H NMR). The *cis* and *trans* diastereomers were separated by flash chromatography (silica gel, 99:1, $CHCl_3$/hexanes). *cis* **66a**: R_f = 0.14 (TLC, 99:1, $CHCl_3/CH_3OH$); $[\alpha]^{25}_D = -14.4°$ (c = 1.4, CH_2Cl_2); white solid, mp 100 °C; IR (KBr) 3388, 2900, 1736, 1652, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 4H), 2.88 (m, 5H), 3.27 (dd, 1H, J = 1.17 and 16.23 Hz), 3.67 (s, 3H), 3.83 (dd, 1H, J = 1.8 and 6.4 Hz), 4.02 (q, 2H, J = 11.6 Hz), 4.31 (m, 1H), 4.57 (m, H), 7.16 (m, 2H), 7.33 (m, 4H), 7.49 (d, 1H, J = 6.7 Hz), 7.55 (dd, 1H, J = 1.5 and 7.5 Hz), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 26.2, 29.6, 30.2, 40.3, 44.6, 52.1, 54.6, 56.6, 60.2, 106.9, 110.8, 118.3, 119.5, 121.9, 127.2, 127.3, 128.4, 128.8, 133.1, 136.2, 139.4, 173.9; MS (CI, CH_4) m/z (relative intensity) 452 (M + 1, 100%), 319 (85). Anal. Calcd for $C_{25}H_{28}N_2O_2S_2$: C, 66.34; H, 6.23; N, 6.19. Found: C, 66.44; H, 6.19; N, 6.41. *trans* **66b**: R_f = 0.22 (TLC, 99:1, $CHCl_3/CH_3OH$); $[\alpha]^{25}_D = -12.1°$ (c = 1.4, CH_2Cl_2); white crystals, mp 179−180 °C; IR (KBr) 3381, 2924, 1729, 1462, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1H), 2.06 (m, 3H), 2.62 (m, 2H), 2.84 (m, 2H), 3.07 (m, 2H), 3.45 (d, 1H, J = 13.4 Hz), 3.82 (s, 4H), 4.08 (m, 3H), 7.14−7.42 (m, 8H), 7.56 (d, 1H, J = 7.0 Hz), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5, 25.9, 29.7, 30.2, 40.8, 44.3, 52.0, 53.3, 56.7, 106.1, 111.0, 118.3, 119.7, 122.0, 127.1, 128.2, 129.3, 133.5, 136.3, 139.5, 173.1; MS (CI, CH_4) m/z (relative intensity) 452 (M + 1, 100%). Anal. Calcd for $C_{25}H_{28}N_2O_2S_2$: C, 66.34; H, 6.23; N, 6.19. Found: C, 66.26; H, 6.12; N, 6.18. The structure of this isomer **66b** was verified by single crystal X-ray analysis.

Epimerization of the *cis* Isomer 66a into the *trans* Isomer 66b in CF_3COOH/CH_2Cl_2. To the *cis* diastereomer **66a** (155 mg, 0.34 mmol) in dry CH_2Cl_2 (6 mL) was added via syringe TFA (55 mL, 0.71 mmol, 2.1 equiv). The solution which resulted was stirred at rt under N_2 for 17 h at which time analysis by TLC (silica gel, 99:1, $CHCl_3/CH_3OH$) indicated the absence of starting *cis* isomer **66a**. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with 10% aq NH_4OH and brine, dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was passed through a small plug of silica gel to provide 145 mg of the *trans* diastereomer **66b** as a white solid (94%). The spectral properties and optical rotation of this compound were identical to those for authentic *trans* isomer **66b**.

Epimerization of a Mixture of *cis* 66a and *trans* 66b Isomers into the *trans* Isomer 66b in CF_3COOH/CH_2Cl_2. To a mixture of *cis* **66a** and *trans* **66b** diastereomers (380 mg, 0.84 mmol) 30:70 in dry CH_2Cl_2 (12 mL) was added via syringe TFA (136 mL, 1.76 mmol, 2.1 equiv). The solution which resulted was stirred at rt under N_2 until analysis by TLC (silica gel, 99:1, $CHCl_3/CH_3OH$) indicated that all of the *cis* isomer **66a** had been converted into the *trans* compound **66b**. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 10% aq NH_4OH and brine, dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was passed through a small plug of silica gel to provide 345 mg of the *trans* diastereomer **66b** as a white solid (90%). The spectral properties and optical rotation of this compound were identical to those for authentic *trans* isomer **66b**.

Epimerization of the *Cis* Isomer 66a into the *Trans* Isomer 66b in CF_3COOD/CH_2Cl_2. To the *cis* diastereomer **66a** (10 mg, 0.02 mmol) in dry CH_2Cl_2 (0.5 mL) was added CF_3COOD (5 μL, 0.06 mmol, 2.9 equiv) via micropipet. The solution which resulted was stirred at room temperature under N_2 and monitored by TLC (silica gel, 99:1, $CHCl_3/CH_3OH$). After 48 h the reaction was stopped and worked up identically to the above procedures. Note: a small amount of *cis* isomer **66a** was still present at the time the reaction was stopped. Analysis of the resulting *trans* isomer **66b** by low and high resolution mass spectroscopy as well as ^{1}H NMR indicated no deuterium incorporation in **66b**.

Evidence for a Carbocation Intermediate: Treatment of the *cis* Isomer 66a with $CF_3COOH/NaBH_4$ To Provide the C(1)−N(2) Scission Product 3-[2-(Benzylamino)-2-(methoxycarbonyl)propyl]-2-[2-(1,3-dithian-2-yl)ethyl]-indole (67). To an oven-dried 5 mL round-bottom flask containing dry CH_2Cl_2 (1.0 mL) was added TFA (80 μL, 1.04 mmol) via syringe, and the solution was cooled to 0 °C followed by the addition of $NaBH_4$ (12 mg, 0.32 mmol).[34] The solution bubbled vigorously and was stirred under N_2 at 0 °C for 0.5 h and then allowed to warm to rt. The *cis* diastereomer **66a** (12 mg, 0.03 mmol) was added, and the solution which resulted was stirred at rt for 1.5 h at which time analysis by TLC indicated the formation of a new product. Another 0.4 equiv of TFA was then added to the solution, and it was allowed to stir at rt overnight (~16 h). Analysis of the solution by TLC (silica gel, 3:7, EtOAc/hexanes) indicated approximately 50% of the *cis* isomer **66a** had been converted into a new compound. The material which remained was identical in R_f to the *trans* isomer **66b**. The reaction was diluted with CH_2Cl_2 and washed with H_2O, 10% aq NH_4OH, and brine, and dried (K_2CO_3), and the solvent was removed under reduced pressure to yield a clear oil. The residue was subjected to flash chromatography (silica gel, 1:9, EtOAc/hexanes) to provide 3.4 mg of **67** (25%) as a clear oil. **67**: R_f = 0.22 (TLC, 3:7, EtOAc/hexanes); IR (KBr) 3369, 1728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (m, 1H), 2.05 (m, 3H), 2.75 (m, 4H), 2.92 (m, 2H), 3.09 (m, 2H), 3.53−3.63 (m, 5H), 3.75 (m, 1H), 3.89 (t, 1H, J = 7.2 Hz), 7.03 (t, 1H, J = 8.0 Hz), 7.10 (t, 1H, J = 8.0 Hz), 7.15−7.27 (m, 6H), 7.52 (d, 1H, J = 8.0 Hz), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 26.0, 28.8, 29.7, 30.2, 35.2, 46.4, 51.7, 52.3, 61.6, 106.0, 110.4, 118.5, 119.4, 121.5, 126.9, 128.0, 128.3, 128.7, 135.1, 135.4, 139.8, 152.0, 155.7, 175.5; MS (CI, CH_4) m/z (relative intensity) 454 (M + 1, 100%), 276 (55). A control experiment ($CF_3COOH/NaBH_4$) with *trans* isomer **66b** carried out under identical conditions to that described immediately above returned only *trans* isomer **66b** in 90% yield.

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