was added. Reflux was continued for 24 h. The precipitate was filtered, the filtrate evaporated to dryness on a rotary evaporator, and the residue washed with ether followed with methanol. The combined precipitates were treated with 50 mL of chloroform, and the filtrate passed through a column of alumina. The fluorescent fraction was collected, the chloroform evaporated, and the residue crystallized from xylene: mp >500 °C; IR (Nujol) 1600, 1550, 1480, 1280, 1235, 1220, 1150, 955, 940, 910, 805, and 790 cm^{-1}; NMR ($CDCl_3$) δ 9.64 (s, 2, H-18 and H-19), 9.16 (dd, 2, H-2 and H-15, J_{H2-H3} = 4 Hz, H_{H2-H4} = 2 Hz), 8.22 (dd, 2, H-4 and H-12, J_{H3-H4} = 8 Hz), 8.10 (s, 2, H-5 and H-12), 7.50 (dd, 2, H-3 and H-14), 3.80–3.26 (m, 8, H-6, H-7, H-10, and H-11).

Anal. Calcd for $C_{28}H_{18}N_6$: C, 76.69; H, 4.14; N, 19.17. Found: C, 75.37; H, 4.07; N, 18.99

Acknowledgment. This work was supported in part by the U.S. Army Research Office, Durham, N.C. and by the Research Foundation of the State University of New York (Grant-in-Aid 08352002210730).

Registry No.—**1**, 16357-83-8; **2**, 56685-47-3; **3**, 56644-58-7; **4**, 56644-59-8; **7**, 504-02-9; **8**, 7521-41-7; **9**, 56488-08-5; **10**, 68475-25-2; **11**, 68475-26-3; **12**, 68475-27-4; **13**, 68475-28-5; **14**, 68475-29-6; **15**, 68475-30-9; **16**, 57694-96-9; **17**, 68475-31-0; α-tetralone, 529-34-0.

References and Notes

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(2) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **40**, 2566 (1975).
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(4) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **40**, 3407 (1975).
(5) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **41**, 1058 (1976).
(6) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **39**, 720 (1974).
(7) K. D. Bartle and D. W. Jones, *Adv. Org. Chem.*, **8**, 317 (1972).
(8) To facilitate comparison of the polycyclic systems represented in Figure 1, the central 1,8-naphthyridine unit is kept constant. This results in the correct orientation for **15** and **17**, but not for **12** and **15'**, according to IUPAC rule A-22. [A. D. McNaught, *Adv. Heterocycl. Chem.*, **20**, 175 (1976).]
(9) Although **15** is identical with **15'**, two IUPAC names may be derived, namely 6,7,16,17-tetrahydropyrido[2',3'-2,3]1,7-phenanthrolino[8,9-*b*]pyrido-[2,3-*j*]-1,7-phenanthroline and 6,7,16,17-tetrahydropyrido[2',3'-8,9]-1,7-phenanthrolino[2,3-*j*]pyrido[2,3-*b*]-1,7-phenanthroline.
(10) The shaded rings in Figure 2 do not represent branching points for the polycyclic system. They indicate the position for the ring common in the two different modes of ring annelation.

Study of the Pictet–Spengler Reaction in Aprotic Media: Synthesis of the β-Galactosidase Inhibitor, Pyridindolol[1c]

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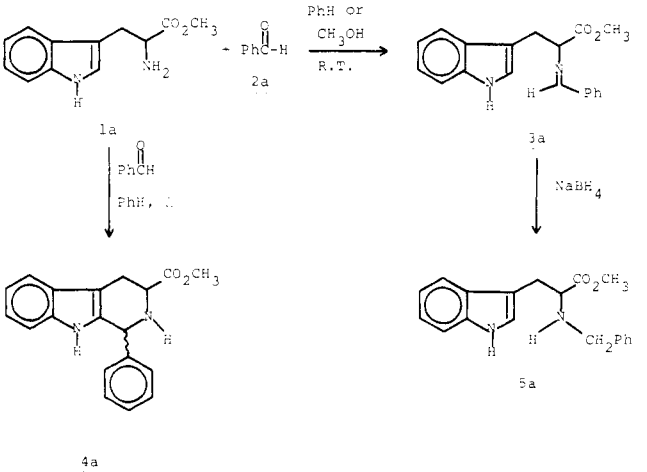
Factors which influence the Pictet–Spengler reaction in nonacidic, aprotic media have been studied. The condensation has been shown to work well with aldehydes when tryptophan methyl ester derivatives and N_b-benzyltryptamines were employed as substrates. The optimum conditions were realized when the N_b-benzyl derivatives were stirred with aldehydes in refluxing toluene. The factors (electrophilic character of the intermediate imine) which determine the ease of cyclization have been examined, as well as the effect of temperature on the condensation. The synthesis of many tetrahydro-β-carbolines, **6a–6i, 7a,** and **7b,** heretofore difficult to prepare, have been accomplished in good yield in the aprotic medium. This methodology has permitted the synthesis of the antibiotic pyridindolol (**16**).

In the course of work directed toward the construction of potential antihypertensive agents,[1a] the need arose for a preparation of N_b-benzyltryptophan methyl ester. This ester can be prepared by stirring tryptophan methyl ester (**1a**) and benzaldehyde (**2a**) in benzene at room temperature, followed by reduction of the resulting imine (**3a**) with sodium borohydride, similar to the work of Yoneda.[2] To improve the conversion of ester (**1a**) to imine (**3a**), the aldehyde (**2a**) and amine were heated in refluxing benzene, while a Dean-Stark trap was employed to remove water which formed in the reaction (Scheme I). Although the imine (**3a**) was initially observed, after prolonged heating the products of this sequence, isolated in 95% yield,[1b] were the cis and trans isomers of 1-phenyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**4a**).[3]

The result in the aprotic solvent was surprising, for generally the Pictet–Spengler reaction is carried out in a protic solvent with acid catalysts.[4–7] Reports in the literature are well-documented which indicate that furfural and tryptamine yielded only imine[8] when heated in refluxing benzene, while similar findings have been observed by Jackson and Smith[9] with tryptamine (**1f**) and benzaldehyde (**2a**). Both bases would not cyclize to tetrahydro-β-carbolines unless hydrochloric acid was added to the solution.[8,9] Presumably, the Pictet–Spengler reaction in the tryptophan methyl ester (**1a**) case had occurred without the aid of acid catalysis; therefore, it was decided to make a detailed study of this observation.

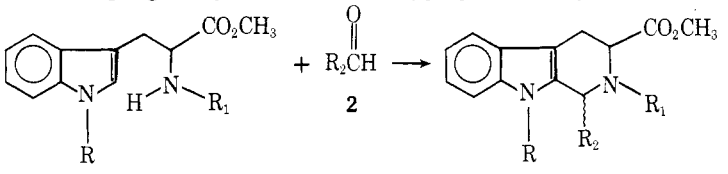
A variety of tryptophan methyl ester (**1**) derivatives have been employed in this condensation; some of these are outlined in Table I. Excellent yields of tetrahydro-β-carbolines (**4a–e**) were obtained with N_b-benzyltryptophan methyl ester

Scheme I



0022-3263/79/1944-0535$01.00/0

Table I. Pictet–Spengler Cyclization with Tryptophan Methyl Ester Derivatives

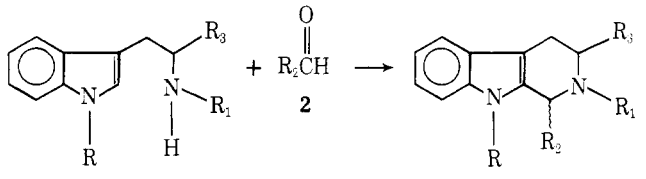


1 4

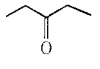
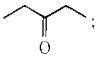
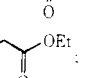
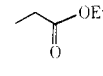
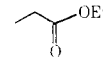
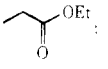
amine	aldehyde	product	% yield (aprotic med.)[a]	% yield (aqueous med.)[a]
1a, R = H; R_1 = H	**2a**, R_2 = phenyl	**4a**, R = H; R_1 = H; R_2 = phenyl	95	90
1a, R = H; R_1 = H	**2b**, R_2 = cyclohexyl	**4b**, R = H; R_2 = H; R_2 = cyclohexyl	85	73
5a, R = H; R_1 = benzyl	**2a**, R_2 = phenyl	**4c**, R = H; R_1 = benzyl; R_2 = phenyl	95	
5a, R = H; R_1 = benzyl	**2b**, R_2 = cyclohexyl	**4d**, R = H; R_1 = benzyl; R_2 = cyclohexyl	87	
1b, R = CH_3; R_1 = benzyl	**2b**, R_2 = cyclohexyl	**4e**, R = CH_3; R_1 = benzyl; R_2 = cyclohexyl	87	68
1c, R = H; R_1 = isopropyl	**2c**, R_2 = ethyl propionate	**4f**, R = H; R_1 = isopropyl; R_2 = ethyl propionate	40	<25

[a] **4a**, **4b**, and **4f** are composed of cis and trans isomers.

Table II. Reaction with Acid-Labile Aldehydes



1 6

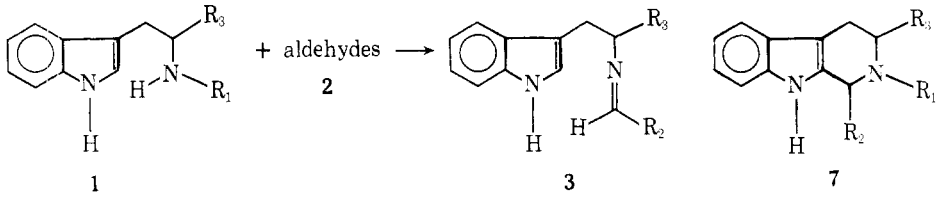
amine	aldehyde	product	% yield (aprotic med.)	% yield (aqueous med.)[a]
1b, R = CH_3; R_1 = CH_2Ph; R_3 = CO_2CH_3	**2d**, R_2 = $HC(OEt)_2$	**6a**, R = CH_3; R_1 = CH_2Ph; R_2 = $HC(OEt)_2$; R_3 = CO_2CH_3	90	<20[a]
1d, R = H; R_1 = CH_2Ph; R_3 = H	**2d**, R_2 = $HC(OEt)_2$	**6b**, R = H; R_1 = CH_2Ph; R_2 = $HC(OEt)_2$; R_3 = H	92	<25[a]
1e, R = CH_3; R_1 = H; R_3 = CO_2CH_3	**2d**, R_2 = $HC(OEt)_2$	**6c**, R = CH_3; R_1 = H; R_2 = $HC(OEt)_2$; R_3 = CO_2CH_3	65	<15[a]
1a, R = H; R_1 = H; R_3 = CO_2CH_3	**2d**, R_2 = $HC(OEt)_2$	**6d**, R = H; R_1 = H; R_2 = $HC(OEt)_2$; R_3 = CO_2CH_3	62	<15[a]
5a, R = H; R_1 = CH_2Ph; R_3 = CO_2CH_3	**2d**, R_2 = $HC(OEt)_2$	**6e**, R = H; R_1 = CH_2Ph; R_2 = $HC(OEt)_2$; R_3 = CO_2CH_3	75	<25[a]
1b, R = CH_3; R_1 = CH_2Ph; R_3 = CO_2CH_3	**2e**, R_2 = 	**6f**, R = CH_3; R_1 = CH_2Ph; R_2 =  ; R_3 = CO_2CH_3	94	25[b]
1b, R = CH_3; R_1 = CH_2Ph; R_3 = CO_2CH_3	**2f**, 	**6g**, R = CH_3; R_1 = CH_2Ph; R_2 =  ; R_3 = CO_2CH_3	97	
5a, R = H; R_1 = CH_2Ph; R_3 = CO_2CH_3	**2g**, R_2 = 	**6h**, R = H; R_1 = CH_2Ph; R_2 = ; R_3 = CO_2CH_3	80	50[a]
1b, R = CH_3; R_1 = CH_2Ph; R_3 = CO_2CH_3	**2g**, R_2 = 	**6i**, R = CH_3; R_1 = CH_2Ph; R_2 =  ; R_3 = CO_2CH_3	75	59[c]

[a] The amine·HCl and aldehyde were heated in a 50:50 methanol–water solution. [b] **1b** and 4-oxohexanal ethylene ketal were heated in acidic solution (methanol–water–HCl). [c] See ref 2; in our hands the yield in acidic solution was 50%.

(**5a**) and N_a-methyl-N_b-benzyltryptophan methyl ester (**1b**), as well as with the parent ester (**1a**).

It is apparent from examination of the data in Table I that yields of the Pictet–Spengler reaction can be greatly improved in the aprotic media, and certainly this would expand the scope of this reaction. Nowhere is this more obvious than when acid-labile aldehydes were employed as substrates as illustrated in Table II. Glyoxal diethyl acetal (**2d**), prepared by the method of Grohman,[10] was condensed in refluxing benzene with the tryptophan methyl ester derivatives (**1b**, **1e**, **1a**, and **5a**) to provide good to excellent yields of the corresponding 1-(formyl diethyl acetal)-1,2,3,4-tetrahydro-β-carbolines (**6a**, **6c**, **6d**, and **6e**),[11] respectively. In addition, N_b-benzyltryptamine (**1d**) was also reacted with glyoxal diethyl acetal (**2d**) to provide a 92% yield of the desired β-carboline derivative (**6b**) in contrast to the very poor results (<25%) found in the

Table III. Influence of the Electrophilic Character of the Imine on the Pictet–Spengler Reaction



1 3 7

amine	aldehyde	product	medium	yield, % imine 3	yield, % P–S[d]
1a, R_1 = H; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**3b**, R_2 = *o*-hydroxyphenyl; R_3 = CO_2CH_3	benzene, Δ	100	
1a, R_1 = H; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**3b**, R_2 = *o*-hydroxyphenyl; R_3 = CO_2CH_3	toluene, Δ	100	
1a, R_1 = H; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**7a**, R_1 = H; R_2 = *o*-hydroxyphenyl; R_3 = CO_2CH_3	$CH_3OH/H_2O/H^+$, Δ		3.5[a]
5a, R_1 = CH_2Ph; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**7b**, R_1 = CH_2Ph; R_2 = *o*-hydroxylphenyl; R_3 = CO_2CH_3	benzene, Δ		62
5a, R_1 = CH_2Ph; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**7b**, R_1 = CH_2Ph; R_2 = *o*-hydroxyphenyl; R_3 = CO_2CH_3	toluene, Δ		97
1a, R_1 = H; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**8**, R_2 = *o*-hydroxyphenyl; R_3 = CO_2CH_3	toluene/HOAc, Δ	β-carboline[b]	
1a, R_1 = H; R_3 = CO_2CH_3	**2h**, salicylaldehyde	**8**, R_2 = *o*-hydroxyphenyl; R_3 = CO_2CH_3	toluene/pTSA, Δ	β-carboline[b]	
1a, R_1 = H; R_3 = CO_2CH_3	**2i**, acetylsalicylaldehyde	**7c**, R_1 = H; R_2 = *o*-acetylphenyl; R_3 = CO_2CH_3	benzene, Δ		40[c]
1f, R_1 = H; R_3 = H	**2a**, benzaldehyde	**3c**, R_2 = phenyl; R_3 = H	benzene, Δ	100	
1d, R_1 = CH_2Ph; R_3 = H	**2a**, benzaldehyde	**7d**, R_1 = CH_2PH; R_2 = Ph; R_3 = H	benzene, Δ		98.5
1a, R_1 = H; R_3 = CO_2CH_3	**2a**, benzaldehyde	**3a**, R_2 = Ph; R_3 = CO_2CH_3	benzene, room temperature	100	
1a, R_1 = H; R_3 = CO_2CH_3	**2a**, benzaldehyde	**4a** (see Scheme I, also Table I)	benzene, Δ		90

[a] See ref 3. [b] Ring C is aromatized. [c] Yields varied from 24 to 40%; the actual tetrahydro-β-carboline isolated was the N_b-acetamide derivative derived from rearrangement of the *o*-acetyl group to the N_b-nitrogen function. [d] P–S = Pictet–Spengler product.

aqueous, acidic medium. The figures (Table II) for yields in the aprotic medium were generally 300–400% better than those in aqueous acid.[12]

Other acid-labile aldehydes have also been employed in this sequence as illustrated in Table II. Of particular interest are the tetrahydro-β-carbolines **6f** and **6g** (Table II), which are important intermediates employed in work toward the total synthesis of natural products such as isoajmaline, ajmaline,[13] and suaveoline.[14] The syntheses of **6f** and **6g** have been much improved in the aprotic media over the published methods.[13-15]

From the data in Table II it is obvious that the Pictet–Spengler reaction can be extended to include aldehydes containing functionality such as acetals, esters, amides, and acetonides (see below), heretofore too labile to be practical for this condensation.

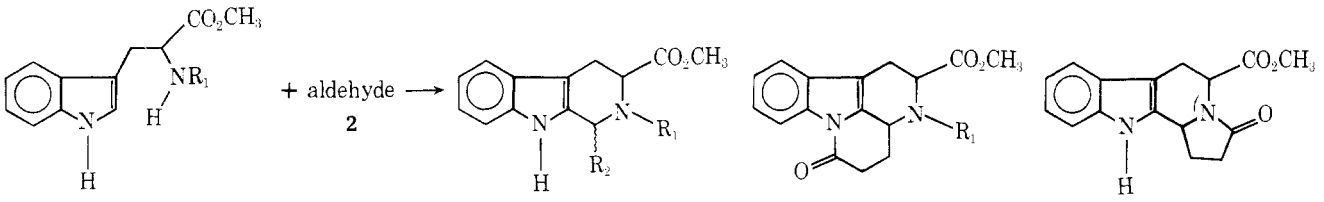
Two possible mechanisms for the Pictet–Spengler cyclization of carbonyl compounds with tryptamine derivatives have been extensively studied by Jackson[16a-c] and co-workers and have been reviewed.[16d] However, regardless of the path which is followed, it is the electrophilic nature of the imine double bond which is the driving force in this cyclization.[11] Performing the reaction in nonacidic, aprotic media permitted a study of the correlation between the electron density on the aliphatic nitrogen with the ease of cyclization since protonation of nitrogen by solvent was no longer a complicating factor.

The failure of the Schiff base **3c** to cyclize in refluxing benzene vs. the facile cyclization for the analogous reaction with tryptophan methyl ester **1a** (Table III) can be rationalized by examination of the pK_a values for the two bases: tryptamine, pK_a = 10.2;[17] tryptophan methyl ester, pK_a = 7.29.[18] Clearly, the carbon–nitrogen double bond in the tryptamine case is less electrophilic, for the nitrogen carries a higher electron density than that found for the tryptophan methyl ester "imine" **3a** intermediate. This difference in behavior could not be attributed to the presence of trace amounts of acidic impurities, for even in the presence of small amounts of tryptophan or tryptophan methyl ester·HCl the tryptamine intermediate **3c** failed to cyclize (see Experimental Section).

In 1974 Hamaguchi et al.[3] reported that **1a** and salicylaldehyde (**2h**) condensed in acidic media to provide the Pictet–Spengler product (**7a**, cis and trans isomers) in 3.7% overall yield (see Table III). When this same condensation was carried out in our hands with **1a** in refluxing benzene or toluene, only the imine (**3b**) formed. The failure of the imine (**3b**) to undergo cyclization can be understood in terms of the mesomeric effect of the phenolic oxygen; electron release by this atom rendered the imine double bond in **3b** less electrophilic in comparison to the same bond in **3a**. This hypothesis was supported by the formation of the cis and trans isomers of the acetoxyphenyl-1,2,3,4-tetrahydro-β-carboline (**7c**) prepared in moderate yield (see Table III) from the condensation of acetylsalicylaldehyde (**2i**) and **1a** in refluxing toluene. The electron-donating capability of the phenolic oxygen (**3**) is retarded by the acetyl group, and the cyclization proceeded in the desired manner to give the tetrahydro-β-carboline (**7c**).

To effect cyclization of **3b** it was necessary to heat the imine

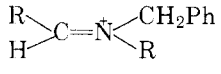
Table IV. Effect of Temperature in the Aprotic Medium



amine	aldehyde	product	yield, %	medium
5a, $R_1 = CH_2Ph$	**2f**, 2-oxoglutaric acid	**7e**, $R_1 = CH_2Ph$; $R_2 = CH_2CH_2CO_2H$	20.5	benzene, Δ
		11, $R_1 = CH_2Ph$	47.5	
5a·HCl, $R_1 = CH_2Ph$	**2f**, 2-oxoglutaric acid	no Pictet–Spengler product		EtOH, Δ
5a, $R_1 = CH_2Ph$	**2f**, 2-oxoglutaric acid	2-oxoglutarate salt of **5a**		$CHCl_3$, Δ
5a, $R_1 = CH_2Ph$	**2f**, 2-oxoglutaric acid	**7e**, $R_1 = CH_2Ph$; $R_2 = CH_2CH_2CO_2H$	56.4	benzene/
		11, $R_1 = CH_2Ph$	39.1	dioxane, Δ
1a, $R_1 = H$	**2f**, 2-oxoglutaric acid	**12**	80	benzene, Δ
1a·HCl, $R_1 = H$	**2f**, 2-oxoglutaric acid	**12**	42	EtOH, Δ
1a, $R_1 = H$	**2j**, *p*-anisaldehyde	**7f**, $R_1 = H$; $R_2 = p$-CH_3OPh–	trace	toluene, Δ
1a, $R_1 = H$	**2j**, *p*-anisaldehyde	**7f**, $R_1 = H$; $R_2 = p$-CH_3OPh–	15	*p*-xylene, Δ
1a·HCl, $R_1 = H$	**2j**, *p*-anisaldehyde	**7f**, $R_1 = H$; $R_2 = p$-CH_3OPh–	0	MeOH/H_2O, Δ
5a, $R_1 = CH_2Ph$	**2j**, *p*-anisaldehyde	**7g**, $R_1 = CH_2Ph$; $R_2 = p$-CH_3OPh–	40	*p*-xylene, Δ

in toluene for 48 h in the presence of *p*-toluenesulfonic acid or acetic acid. The harsh conditions of prolonged heating and acid yielded not the desired tetrahydro-β-carboline (**7a**), but gave the fully aromatic β-carboline (**8**).

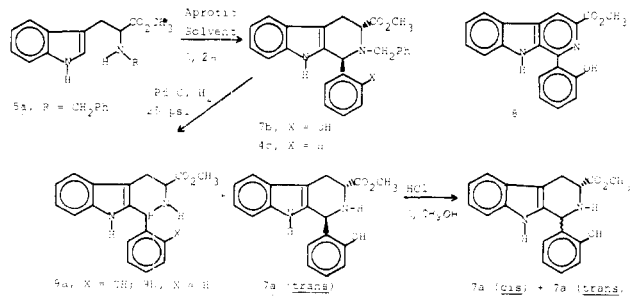
Indeed, if the electrophilic character of the C=N bond was the limiting factor in the nonacidic, aprotic medium, a method to increase the electrophilic character was necessary. The use of the N_b-benzyl group provided the more electrophilic iminium ion intermediate A, and the benzyl group could be removed later by catalytic hydrogenation. The results of this investigation are shown in Scheme II, and the yields are listed in Table III. N_b-benzyltryptophan methyl ester (**5a**) was heated in refluxing benzene with salicylaldehyde (**2h**) to provide a 62% yield of the 1-(*o*-hydroxyphenyl)-2-benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**7b**, 97% when refluxing toluene was employed). Catalytic debenzylation of **7b** over Pd/C[2,7] at 25 psi[19] gave the *trans*-tetrahydro-β-carboline (**7a**) in 55–70% yield. Also isolated was the 2-benzyl derivative[20] (**9a**), the product of a second hydrogenolysis.[21] The cis isomer of **7a** was obtained by epimerization of the trans isomer in hot methanolic hydrogen chloride (see Experimental Section).



A

In every case that we have examined the effect of substitution of a benzyl group on the aliphatic nitrogen of either tryptamine (**1f**) or tryptophan methyl ester (**1a**) has been to speed the rate of the cyclization and to improve the yield.[11]

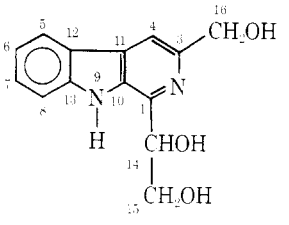
Scheme II



Furthermore, the N_b-isopropyl group (see Table I) leads to lower yields of product which may be due to steric, electronic, or both effects, but in fact is in accord with the greater electron-releasing[22] properties of the isopropyl group as compared to that of the benzyl moiety.

The potential of employing high boiling solvents to facilitate the Pictet–Spengler cyclization, without decomposing the aldehydes, is an important advantage of the cyclization in aprotic medium (Table IV).[23]

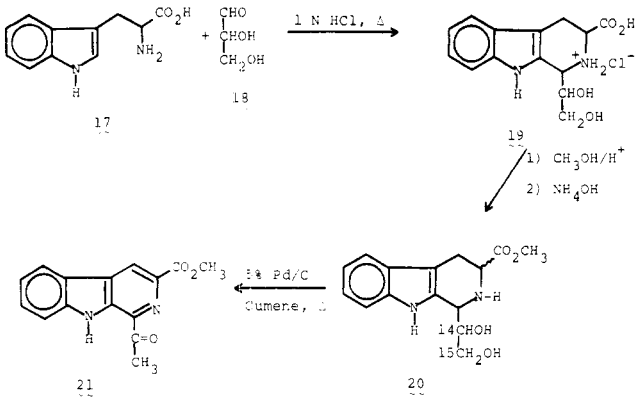
Synthesis of the Antibiotic, Pyridindolol (16). In 1975 Umezawa and co-workers reported the isolation[24a] of the β-carboline alkaloid pyridindolol (**16**) produced by *Streptomyces alboverticillatus;* the alkaloid is a specific inhibitor of neutral bovine liver β-galactosidase. The structure and absolute configuration (*R*) of this base were determined by X-ray analysis later that year.[24b] A detailed structure–activity study has been reported;[24c] essentially the data indicated that two and probably all three of the hydroxyl functions contained in **16** are necessary for activity. The unique structure of this β-carboline (**16**), coupled with its biological activity, stimulated interest in the synthesis of this molecule.



16

The first attempts to synthesize **16** were based on a biogenetic approach, as outlined in Scheme III. Pictet–Spengler condensation of *dl*-tryptophan (**17**) with *dl*-glyceraldehyde (**18**) in an acidic medium[25] provided the diol (**19**) in moderate yield. The amorphous solid (**19**) was then esterified with methanolic hydrogen chloride to provide the methyl ester (**20**), which was subsequently treated with 5% Pd/C to generate the fully aromatic β-carboline system. However, instead of the desired 3-methoxycarbonyl derivative of **16**, the product of this oxidation was the methyl ketone (**21**). Loss of water had occurred from C-15 of **20** in such a fashion as to generate the ketone function at C-14 during this oxidation.

Scheme III



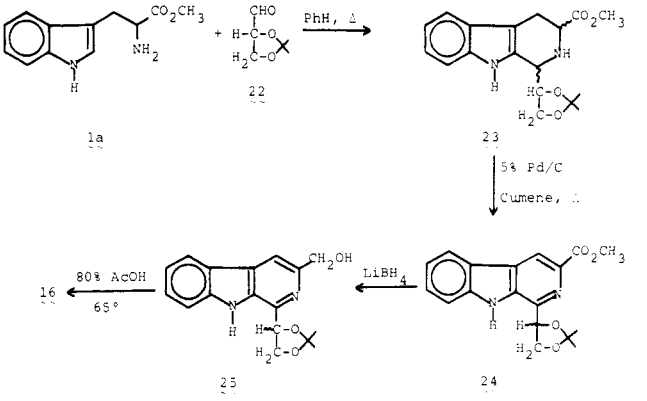
From the very beginning of this work, it was felt that some difficulty might be encountered in converting **20** to the β-carboline (**16**) since 1,2,3,4-tetrahydro-β-carbolines with hydroxymethyl substituents attached to position 1 are rather labile;[25,26] indeed, Spenser had taken advantage of this earlier in the synthesis of harmalan.[25] Furthermore, the conversion of **20** to **21** over Pd/C in refluxing cumene served to illustrate that the hydroxy function at C-15 was not very stable either.

Clearly, a method for protecting the diol of **20** was necessary; however, to be effective this would have to be done before the tetrahydro-β-carboline skeleton was constructed. The Pictet–Spengler reaction in nonacidic, aprotic media was the simplest solution to this problem, for these conditions would permit the use of a protected glyceraldehyde molecule which would otherwise be labile in acidic media. Many simple attempts to prepare a functionalized glyceraldehyde species were unsuccessful; however, the acetonide of D-glyceraldehyde (**22**) was obtained relatively easily from D-mannitol by the combined methods of Vargha[27] and Fischer.[28]

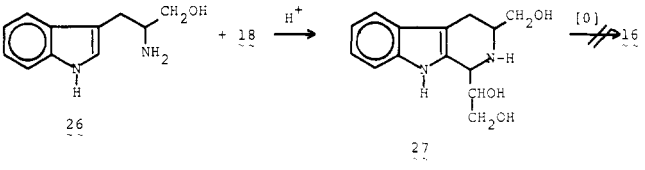
Pictet–Spengler condensation of *dl*-tryptophan methyl ester (**1a**) with the optically active aldehyde (**22**) in refluxing benzene gave a 90% yield of a mixture of diastereomers represented by structure **23** as shown in Scheme IV. Since the chirality at positions 1 and 3 of ring C would be destroyed on conversion to the β-carboline (**24**), no attempt was made to separate these isomers. The mixture of diastereomers (**23**) showed an overall rotation in the levorotatory direction, which indicated that complete racemization had not occurred during the reaction in refluxing benzene; heating **1a** and **22** in an aqueous acidic medium led to intractable tars which showed no optical rotation. Aromatization of **23** with 5% Pd/C in refluxing cumene gave the β-carboline (**24**) in good yield; however, this base was optically inactive. Not only had the chirality at positions 1 and 3 been destroyed under these conditions, but racemization of the D-acetonide had also occurred. The methyl ester (**24**) was reduced to the alcohol **25** by stirring with sodium borohydride in refluxing methanol[29] or with lithium borohydride. Removal of the acetonide group was carried out in 70% yield by warming the hydroxyacetonide (**25**) in 80% acetic acid at 65 °C for 25 h.[30] The spectral data for synthetic, racemic pyridindolol [**16**; mp 169–170 °C (lit.[24a] mp 167–168 °C)] were identical in all respects with the published data, except for the optical rotation which in our case was 0. This constituted the first synthesis of pyridindolol (35% overall yield from tryptophan methyl ester, Scheme IV).

Shortly after the synthesis of **16** was completed,[31] a report appeared from a Japanese group[32] which supported our contention that the hydroxy groups of **20** must be protected before oxidation. They reported that tryptophol (**26**) was reacted with glyceraldehyde (**18**) in aqueous, acidic media to provide the trihydroxy-1,2,3,4-tetrahydro-β-carboline **27**;[32] however, dehydrogenation of this triol with Pd/C did not lead to pyridindolol (**16**), but gave 3-(hydroxymethyl)-β-carboline. It was also reported that any other oxidative method to obtain **16** was unsuccessful,[32] as illustrated in Scheme V.

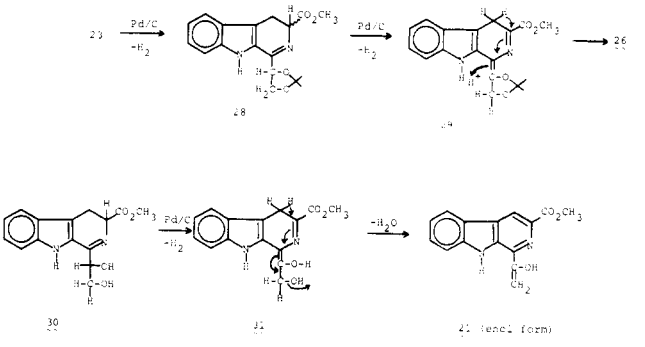
Scheme IV



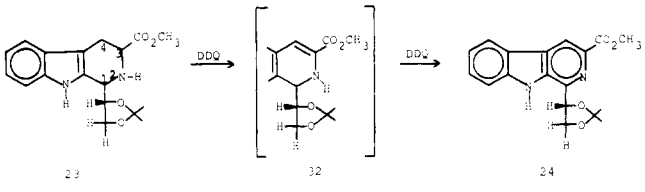
Scheme V



Scheme VI



Scheme VII



A possible mechanism for the racemization of the chiral center of the acetonide during the aromatization process, which is also consistent with the formation of the methyl ketone (**21**) generated from **20**, is outlined in Scheme VI. The common feature of both pathways is the introduction of the 1,2 double bond in ring C of the tetrahydro-β-carbolines (**28**) (acetonide) and **30** (diol) with the first Pd/C oxidation. The acetonide (**28**) then loses two additional hydrogen atoms to generate the exo/endo diene (**29**), which undergoes a prototropic shift to give racemic **26**. In the case of the diol **30**, loss of two hydrogen atoms would give the exo/endo diene (**31**), which could lose water in the manner illustrated to produce **21** (enol form).[33]

To test this hypothesis, other methods to convert **23** to **24** were considered. The introduction of unsaturation at the 3,4 position of ring C (**32**) followed by removal of hydrogen atoms across the C(1)–N(2) bond (Scheme VII) to furnish the fully aromatic β-carboline (**24**) seemed particularly attractive. This would prohibit racemization of **28** via enamine–imine equilibra, nor would it allow formation of species **29**.

Oikawa and Yonemitsu have recently reported that the 4 position of tetrahydrocarbazole was selectively attacked by DDQ in aqueous solution[34] to provide 4-oxotetrahydrocarbazole, while LeQuesne and co-workers[35] have found that indole-3-propionitrile was dehydrogenated to the α,β-unsaturated nitrile in high yield on treatment with DDQ. Therefore, the tetrahydro-β-carboline (**23**) enriched in the *S* isomer ($[\alpha]_D$ −11°) was stirred with DDQ in benzene. The yield of the reaction was 45%; however, the β-carboline (**24**) obtained was optically active with a rotation ($[\alpha]^{23}_D$ 5.5°) in the dextrorotatory direction. Reduction of the methyl ester and cleavage of the acetonide (see above) provided **16** ($[\alpha]^{23}_D$ 7.7°). The retention of much of the optical activity contained in **23** strongly supports the mechanisms outlined in Scheme VI (Pd/C) and Scheme VII (DDQ).

Pyridindolol (**16**) enriched in either the (+) isomer (D-acetonide) or the natural isomer (L-acetonide) can be prepared by this method from D-mannitol and L-mannitol, respectively. However, the optically active glyceraldehyde acetonides racemize overnight,[36] even on standing at low temperature. The acetonide must be used immediately, and we were never able to isolate **22** on a preparative scale in greater than 60% optical purity. The Pictet–Spengler product (**23**) was obtained on a 10-g scale ($[\alpha]^{23}_D$ −11°) and was converted in three steps to pyridindolol ($[\alpha]^{23}_D$ 7.7°). With much smaller amounts of material (0.005 mol) the tetrahydro-β-carboline (**23**) could be obtained in higher optical purity ($[\alpha]^{23}_D$ −25°).

The natural product (**10**) has an optical rotation of −49°;[24a] therefore, pyridindolol prepared by this method has retained 15% of the optical purity [25% based on the optical purity of the starting acetonide (**22**)]. It is believed that some epimerization occurred during the initial Pictet–Spengler reaction via an imine–enamine equilibrium.

Conclusion

The synthetic potential of the Pictet–Spengler reaction in aprotic media with either tryptophan methyl ester derivatives or N_b-benzyltryptamines is quite general and can be employed with a variety of aldehydes which may or may not contain labile functional groups. The optimum conditions for this modification appear to be the use of N_b-benzyl derivatives in refluxing toluene. Care must be taken to assure that the boiling point of the aldehyde is higher than that of the solvent; aldehydes such as acetaldehyde distill into the Dean-Stark trap and give poor yields of tetrahydro-β-carboline. For substrates that are not soluble in benzene or toluene, dioxane can be added to the reaction medium.

This modification should permit the use of the Pictet–Spengler reaction in a wider variety of indole alkaloid syntheses without fear of yield loss during the formation of the 1,2,3,4-tetrahydro-β-carboline ring system.

Experimental Section

Microanalyses were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60 MHz spectrometer and a Varian CFT-20 ^{13}C NMR spectrometer. Infrared spectra were taken on a Beckman Acculab-1 instrument, and mass spectra were recorded on Hitachi RMU-6 and AEI-MS-902 mass spectrometers.

Analytical TLC plates used were E. Merck Brinkman UV active silica gel or alumina on plastic. The TLC plates were developed with the spray reagent ceric ammonium sulfate in 50% sulfuric acid. *dl*-Tryptophan, tryptamine·HCl, salicylaldehyde, cyclohexanecarboxaldehyde, and benzaldehyde were purchased from Aldrich Chemical Co. Ethyl 3-formylpropionate was purchased from Pressure Chemical. The platinum oxide (Adam's catalyst) and palladium on carbon were obtained from Pfaltz and Bauer, Inc.

3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-benzene (4a). Tryptophan methyl ester (**1a;** 2.2 g, 0.01 mol) and benzaldehyde (**2a;** 1.0 g, 0.01 mol) were dissolved in dry benzene (50 mL). The mixture was refluxed for 48 h, and the solvent was subsequently removed under reduced pressure to provide 3.2 g of a yellow-white solid which was chromatographed on silica (benzene–methylene chloride–ethyl acetate, gradient elution). Two compounds were obtained and found to be the cis and trans isomers of the 1-phenyl-β-carboline **4a** (overall yield 95%). The trans isomer predominated in the mixture (~60%). *cis*-**4a:** mp 201–203 °C (lit.[3] mp 220–223 °C); R_f 0.56 (silica; CH_2Cl_2–CH_3OH, 24:1); M^+ = *m/e* 306. *trans*-**4a:** mp 175–177 °C (lit.[3] mp 176–177 °C); R_f 0.43; M^+ = *m/e* 306. The two isomers could also be separated by dissolving the mixture in benzene, followed by freezing and then rethawing. The cis isomer could be obtained in pure form by this method for it does not redissolve readily in the benzene solution.

The above two compounds were found to be identical with the β-carbolines (cis, 201–203 °C; trans, 176–178 °C) obtained from heating tryptophan methyl ester·HCl with benzaldehyde in a methanol–water solvent mixture following the work of Hamaguchi,[3] although the yield (90%) was lower in the aqueous medium. The assignment of stereochemistry was based on ^{13}C NMR spectra (see ref 37).

Cis: IR (KBr) 3400, 3300, and 1745 cm^{-1}; NMR (Me_2SO-d_6) 2.8–3.2 (2 H, m), 3.70 (3 H, s, OCH_3), 3.80–4.10 (1 H, m), 5.25 (1 H, broad singlet), 6.80–7.60 (10 H, m); M^+ at *m/e* 306.

Trans: IR (KBr) 3150 and 1740 cm^{-1}; NMR (Me_2SO-d_6) δ 3.00 (2 H, m), 3.60 (3 H, s, OCH_3), 3.65–4.00 (1 H, m), 5.34 (1 H, s), 6.80–7.60 (10 H, m); M^+ at *m/e* 306.

3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-cyclohexane (4b). Tryptophan methyl ester (**1a;** 9.7 g, 0.044 mol) was dissolved in dry benzene (125 mL), and cyclohexanecarboxaldehyde (**2b;** 5.2 g, 0.046 mol) was added. The mixture was refluxed for 16 h and then cooled in a refrigerator for several days. White crystals were filtered from the solution and washed with benzene to provide 11.60 g of **4b** (85% yield) as a mixture of cis and trans isomers. The diastereomers were separated by careful column chromatography on silica (benzene–CH_2Cl_2–ethyl acetate, gradient elution). The trans isomer predominated in the mixture to the extent of approximately 60%. *cis*-**4b:** mp 153–155 °C; R_f on silica, 0.70 (CH_2Cl_2–CH_3OH, 24:1); IR (KBr) 3350 (NH) and 1725 (ester) cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.20 (12 H, m, a singlet can be seen at δ 1.96), 2.6–3.2 (2 H, m), 3.65 (1 H, multiplet which resembles a doublet), 3.80 (3 H, s, OCH_3), 4.12 (1 H, broad singlet), 6.95–7.60 (4 H, m), 7.90 (1 H, broad singlet, N–H); M^+ at *m/e* 312.

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.07; H, 7.69; N, 8.97. Found: C, 72.80; H, 7.50; N, 8.67.

trans-**4b:** mp 147–149 °C: R_f on silica, 0.59 (CH_2Cl_2–CH_3OH, 24:1); IR (KBr) 3150 (NH), 3060, and 1730 (ester) cm^{-1}; NMR ($CDCl_3$) δ 0.80–2.00 (11 H, m), 2.23 (1 H, s), 3.00 (2 H, d), 3.70 (3 H, s, OCH_3), 3.98 (2 H, broad distorted t), 6.90–7.60 (4 H, m), 7.90 (1 H, s); M^+ at *m/e* 312.

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.07; H, 7.69; N, 8.97. Found: C, 73.35; H, 7.80; N, 8.85.

The same reaction was repeated in an aqueous methanol medium using tryptophan methyl ester·HCl; however, the yields were generally less than 70% and the highest yield obtained was 73%. The assignment of cis and trans stereochemistry was made based on work outlined in ref 37.

2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-benzene. N_b-Benzyltryptophan methyl ester (**5a;** 1.61 g, 0.005 mol) was liberated from its HCl salt by treatment with 14% NH_3 followed by extraction with $CHCl_3$ and dried over K_2CO_3. The resulting oil was dissolved in dry benzene (100 mL) and refluxed for 16 h with benzaldehyde (**2a;** 0.583 g, 0.0055 mol) with water separation via a Dean-Stark trap. The solvent was removed under reduced pressure to give an orange oil which recrystallized from methanol. **4c:** 1.88 g, 95% yield; mp 224–225 °C; IR (KBr) 3360 (s, NH) and 1715 (s, ester) cm^{-1}; NMR ($CDCl_3$) δ 3.2 (d, 2 H, J = 4 Hz), 3.6 (s, 3 H, OCH_3), 3.87 (s, 2 H), 3.95 (d, 1 H, J = 4 Hz), 5.43 (s, 1 H), 7.0–7.8 (m, 15 H); mass spectrum (70 eV), *m/e* 397 (M + 1, 5), 396 (M^+, 18), 337 (12), 319 (100).

Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.06. Found: C, 78.50; H, 5.95; N, 7.00.

2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-cyclohexane (4d). To a solution of N_b-benzyltryptophan methyl ester (**5a;** 3.0 g, 0.01 mol) in benzene (125 mL) was added cyclohexanecarboxaldehyde (**2b;** 1.7 g, 0.015 mol), and the mixture was refluxed for 12 h. The solvent was then removed under reduced pressure, and the oil that remained was crystallized from methanol to provide an 87% yield (3.5 g) of **4d:** mp 167–169 °C; IR (KBr) 3400 (NH) and 1720 (ester) cm^{-1}; NMR ($CDCl_3$) δ 0.60–2.00 (10 H, m), 2.01–2.45 (1 H, m), 2.9–3.60 (5 H, 3 overlapping multiplets), 3.75 (3 H, s, OCH_3), 3.85–4.40 (1 H, m), 7.00–7.80 (10 H, m); M^+ at *m/e* 402.

Anal. Calcd for $C_{26}H_{30}O_2N_2$: C, 77.61; H, 7.46; N, 6.96. Found: C, 77.41; H, 7.30; N, 6.66.

2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-cyclohexane (4e). N_a-Methyl-N_b-benzyltryptophan methyl ester (**1b;** 1.31 g, 0.004 mol) and cyclohexanecarboxaldehyde (**2b;** 0.56 g, 0.005 mol) were dissolved in 120 mL of dry benzene and refluxed for 22 h with water separation in a Dean-Stark trap. After removal of solvent, the faint yellow oil was chromatographed on 25 g of silica gel. Elution with 1:1 benzene–hexane gave a colorless oil (**4e**): 1.48 g, homogeneous by TLC which crystallized upon addition of 9:1 CH_3OH–benzene; 87% yield of mp 118–120 °C; IR (KBr) 1732 cm^{-1} (s); NMR ($CDCl_3$) δ 0.8–1.83 (m, 10 H), 2.12 (m, 1 H), 3.05 (d, 2 H), 3.28 (s, 2 H), 3.5 (s, 3 H, OCH_3), 3.73 (t, 1 H), 3.85 (s, 3 H), 4.28 (t, 1 H), 7.33 (m, 9 H); mass spectrum (70 eV), *m/e* 416 (M^+, 1), 357 (3), 334 (50), 333 (100), 183 (26), 91 (92).

Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; H, 6.72. Found: C, 78.16; H, 7.94; N, 6.68.

Ethyl 2-Isopropyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (4f). N_b-Isopropyltryptophan methyl ester (**1c;** 1.30 g, 0.005 mol) was refluxed in 150 mL of dry benzene with ethyl 3-formylpropionate (**2c;** 0.715 g, 0.005 mol) for 40 h with water separation by a Dean-Stark trap. The benzene was removed with a rotary evaporator, and the resultant oil was chromatographed on 20 g of silica gel. Elution with 10% $CHCl_3$–benzene gave a crude oil, 1.488 g, which failed to crystallize (yield 40–60%). **4f:** IR (neat) 3370 (s, NH), 1720 (s, ester), and 1710 (s, ester) cm^{-1}; NMR ($CDCl_3$) δ 1.0 (d, 6 H, J = 6 Hz), 1.3 (t, 3 H, J = 8 Hz), 1.98 (m, 1 H), 2.64 (m, 2 H), 2.8–3.25 (m, 5 H), 3.52 (s, 3 H, OCH_3), 3.85 (m, 1 H), 3.86–4.27 (q, 2 H, J = 8 Hz), 6.9–7.6 (m, 4 H), 8.4 (s, 1 H, NH); the NMR spectrum indicated the formation of two isomers in a ratio of approximately 4:1); mass spectrum (70 eV), *m/e* 372 (M^+, 2), 371 (5), 370 (22), 245 (36), 243 (63), 239 (100), 199 (12), 198 (14), 197 (50), 195 (36), 187 (25), 169 (25).

Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.5; N, 7.52. Found: C, 67.50; H, 7.39; N, 7.35.

The same reaction was repeated by heating the aldehyde **2d** and amine in a 50:50 CH_3OH–H_2O solution in the presence of hydrochloric acid (1 mL). The yield of 1,2,3,4-tetrahydro-β-carboline was less than 25%.

2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-formyl Diethyl Acetal (6a). A solution of benzene (100 mL) containing N_a-methyl-N_b-benzyltryptophan methyl ester (**1b;** 2.0 g, 0.006 mol) and glyoxal diethyl acetal (**2d;** 2.0 g, 0.015 mol) was refluxed with stirring for 14 h (water was removed by a Dean-Stark trap). After the solvent was removed, the solid was crystallized from MeOH to give pale yellow crystals of **6a** (2.5 g, 90% yield): mp 156 °C; IR (KBr) 3500 (N–H) and 1725 (ester) cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, 3 H), 3.3 (s, 3 H), 3.5 (s, 2 H), 3.0–3.9 (m, 7 H), 4.0–4.6 (m, 1 H), 4.8 (d, 1 H, J = 4 Hz), 7.0–7.7 (m, 9 H), 8.1 (s, 1 H); mass spectrum (70 eV), *m/e* 334 (98, M^+), 330 (58), 275 (100), 258 (32), 243 (87), 183 (73), 168 (47), 157 (96), 91 (73).

Anal. Calcd for $C_{26}H_{32}O_4N_2$: C, 71.53; H, 7.39; N, 6.41. Found: C, 71.40; H, 7.25; N, 6.30.

This same reaction was repeated by heating N_a-methyl-N_b-benzyltryptophan methyl ester·HCl and glyoxal diethyl acetal in aqueous methanol (1:1); however, at least five compounds were observed by TLC. The isolated yield of the desired tetrahydro-β-carboline (**6a**) was 18%.

2-Benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-formyl Diethyl Acetal (6b). A solution of N_b-benzyltryptamine (**1d;** 4.35 g, 0.027 mol) and glyoxal diethyl acetal (**2d;** 4.5 g, 0.034 mol) was heated to reflux in benzene (100 mL) with stirring. The water produced in the reaction was removed via a Dean-Stark trap. The solvent was removed under reduced pressure, and the resulting solid crystallized from MeOH to yield white crystals of **6b** (92% yield): mp 130 °C; IR (KBr) 3400 cm^{-1} (s, NH); NMR ($CDCl_3$) δ 1.2 (t, 6 H), 2.8–3.8 (m, 8 H), 4.4 (broad s, 2 H), 4.5 (d, 1 H, J = 6 Hz), 4.6 (d, 1 H, J = 6 Hz), 7.6–7.1 (m, 9 H), 8.5 (s, 1 H).

Anal. Calcd for $C_{23}H_{28}O_2N_2$: C, 75.82; H, 10.14; N, 10.14. Found: C, 75.56; H, 10.10; N, 10.01.

More than four compounds were formed when this reaction was carried out under aqueous, acidic conditions.

3-(Methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-formyl Diethyl Acetal (6v). A solution of N_a-methyltryptophan methyl ester (**1e;** 2.0 g, 0.015 mol) and glyoxal diethyl acetal (**2d;** 2.0 g, 0.015 mol) was heated to reflux in benzene (100 mL) for 14 h. After the solvent was removed under reduced pressure, the resulting solid was crystallized from methanol to give pale yellow crystals of **6c** (2.0 g, 65% yield): mp 150 °C; IR (KBr) 3500 (w, NH) and 1725 (ester) cm^{-}; NMR ($CDCl_3$) δ 1.2 (t, 6 H), 2.1 (s, 1 H), 3.3 (s, 3 H), 3.5 (s, 3 H), 3.0–3.8 (m, 8 H), 4.0–4.6 (m, 2 H), 4.8 (d, 1 H, J = 4 Hz), 7.0–7.6 (m, 4 H), 8.0 (s, 1 H); mass spectrum (70 eV), *m/e* 330 (7.0), 272 (7), 258 (36), 244 (100), 240 (50), 199 (21), 185 (29), 182 (57), 157 (96).

Anal. Calcd for $C_{19}H_{26}O_4N_2$: C, 65.87; H, 7.56; N, 8.08. Found: C, 65.60; H, 7.45; N, 8.00.

3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-formyl Diethyl Acetal (6d). A solution of tryptophan methyl ester (**1a;** 5.5 g, 0.025 mol) and glyoxal diethyl acetal (**2d;** 4.0 g, 0.030 mol) was heated in dry benzene (100 mL) to reflux for 14 h. The solvent was removed under reduced pressure, and the residual yellow oil was chromatographed on silica with benzene to yield two stereoisomers in 62% total yield (R_f 0.69 and 0.75): mp 125 and 98 °C, respectively; IR (KBr) 3500 (s, NH) and 1725 (ester) cm^{-1}; mass spectrum (70 eV), *m/e* 332 (M^+, 24), 286 (29), 257 (13), 240 (22), 229 (100). *cis*-**6d:** R_f 0.69; NMR ($CDCl_3$) δ 1.2 (t, 6 H), 2.6 (s, 1 H), 3.0–3.2 (d of d, 3 H, $J_{ax,eq}$ = 4 Hz, $J_{ax,ax}$ = 9 Hz), 3.6 (s, 3 H), 3.6–4.1 (m, 4 H), 4.3 (m, 1 H), 4.5 (d, 1 H, J = 6 Hz), 7.0–7.5 (m, 4 H), 8.2 (s, 1 H). *trans*-**6d:** R_f 0.75; NMR ($CDCl_3$) δ 1.2 (t, 6 H), 2.7 (s, 1 H), 3.0–3.2 (d of d, 3 H, $J_{ax,eq}$ = 4 Hz, $J_{ax,ax}$ = 9 Hz), 3.6 (s, 3 H), 3.5–4.0 (m, 4 H), 4.1–4.3 (m, 1 H), 4.6 (d, 1 H, J = 6 Hz), 7.0–7.5 (m, 4 H), 8.6 (s, 1 H).

Anal. Calcd for $C_{18}H_{24}O_2N_2$: C, 65.03; H, 7.28; N, 8.43. Found: C, 64.65; H, 7.27; N, 8.25.

2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-formyl Diethyl Acetal (6e). To a solution of N_b-benzyltryptophan methyl ester (**5a;** 28 g, 0.09 mol) in benzene (200 mL) was added glyoxal diethyl acetal (**2d;** 11.8 g, 0.09 mol) slowly. The mixture was stirred at reflux for 14 h with separation of water via a Dean-Stark trap. After removal of solvent, the resulting yellow solid was crystallized ffrom EtOH to give 29.0 g of white crystals of **6e** (75% yield): mp 125 °C; IR (KBr) 3400 (s, NH) and 1725 (s, ester) cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, 6 H), 3.0 (s, 1 H), 3.8 (s, 3 H), 3.6–4.0 (m, 4 H), 4.2 (m, 1 H), 4.5 (d, 1 H, J = 4 Hz), 7.0–7.6 (m, 10 H), 8.0 (s, 1 H); mass spectrum (70 eV), M^+ at *m/e* 376 (38), 284 (100), 269 (50), 256 (88), 240 (88), 182 (50).

Anal. Calcd for $C_{25}H_{30}O_4N_2$: C, 71.06; H, 7.157; N, 6.632. Found: C, 71.08; H, 7.05; N, 6.57.

2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-(3-pentanone) 6f. N_a-Methyl-N_b-benzyltryptophan methyl ester (**1b;** 8.37 g, 0.026 mol) and 4-oxohexanal (**2e;** 2.97 g, 0.026 mol) were dissolved in 150 mL of dry benzene and refluxed for 8 h; water was removed via a Dean-Stark trap. Following removal of solvent, the resultant oil was chromatographed on silica gel (120 g) packed in hexane and eluted with benzene to provide 10.2 g of product which was a mixture of cis and trans isomers of **6f** (93.9% overall yield): mp 117–119 °C (high R_f isomer), mp 95–97 °C (low R_f isomer); IR (KBr) 1740 (s) and 1705 (s) cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H), 1.66 (m, 2 H), 2.16 (q, 2 H), 2.8 (m, 2 H), 3.16 (d, 2 H), 3.47 (t, 1 H), 3.63 (s, 3 H, NCH_3), 3.7 (s, 3 H, OCH_3), 3.8 (m, 3 H), 7.3 (m, 9 H); mass spectrum (70 eV), *m/e* 418 (M^+, 6), 359 (9), 334 (34), 333 (100), 273 (12), 267 (7), 241 (6), 209 (8), 195 (6), 184 (12), 183 (34).

Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.69. Found: C, 74.90; H, 7.31; N, 6.70.

2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (6g). To a refluxing solution of N_a-methyl-N_b-benzyltryptophan methyl ester (**1b;** 6.70 g, 0.0208 mol) in benzene (100 mL) was added, dropwise, a solution of 2-oxoglutaric acid (**2f;** 3.44 g, 0.023 mol) in 50 mL of dioxane. After refluxing for 20 h, with water removal via a Dean-Stark trap, the solvent was removed to furnish an orange oil which crystallized from 8:1 methanol–benzene to give 4.46 g of colorless crystals (**6g**). Column chromatography of the residue on silica gel provided an additional 3.74 g upon elution with $CHCl_3$: overall yield 8.2 g, 97% yield; mp 197–199 °C; IR (KBr) 1725 (ester) and 1705 (acid) cm^{-1}; NMR ($CDCl_3$) δ 1.83–2.66 (m, 4 H), 3.13 (d, 2 H), 3.56 (s, 3 H), 3.83 (s, 3 H), 7.3 (m, 9 H).

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.71; H, 6.46; N, 6.92.

Ethyl 2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (6h). A 1-L flask equipped with a condenser and a Dean-Stark trap was charged with N_b-benzyltryptophan methyl ester (**5a;** 11.2 g, 0.23 mol) and ethyl 3-formylpropionate (**2g;** 33 g, 0.25 mol) in 500 mL of benzene. The reaction mixture was refluxed for 20 h with water removed by means of a Dean-Stark trap. Removal of solvent under reduced pressure provided an orange oil which gave colorless crystals (68.0 g) from methanol. Column chromatography of the mother liquor on silica with benzene as the eluent gave an additional 9.6 g of **6h** (80% yield): mp 127–129.5 °C (CH_3OH); IR (KBr) 1730 and 1710 (ester) cm^{-1}; NMR ($CDCl_3$) δ 1.13 (3 H, t), 1.8 (1 H, s, NH), 2.05 (4 H, m), 3.14 (2 H, d, J

= 8 Hz), 3.37 (1 H, t, J = 8 Hz), 3.56–4.03 (8 H, m, quartet, singlet distinguishable), 7.2 (9 H, m), 8.1 (1 H, broad s); mass spectrum, M^+ at m/e 420 (6), 374 (2), 361 (9), 329 (19), 320 (26), 319 (100), 283 (3), 269 (4), 259 (7), 229 (10).

Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.40; H, 6.71; N, 6.66. Found: C, 71.44; H, 6.68; N, 6.33.

Preparation of N_b-Benzylidenetryptophan Methyl Ester (3a). Tryptophan methyl ester (**1a**; 2.18 g, 0.01 mol) and benzaldehyde (**2a**; 1.37 g, 0.013 mol) were dissolved in dry benzene, and the solution was stirred at room temperature. After stirring for several hours, anhydrous sodium sulfate (10 g) was added and the mixture was stirred at room temperature for 4 h. The white precipitate which formed was dissolved in methylene chloride and separated from the sodium sulfate. Evaporation of solvent under reduced pressure provided a yellow solid which was crystallized from methanol to provide an 80% yield (2.4 g) of **3a**: mp 120 °C; IR (KBr) 1735 (ester C=O) and 1630 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.30 (1 H, d, J = 9 Hz), 3.50 (1 H, d, J = 5 Hz), 3.75 (3 H, s, OCH_3), 4.30 (1 H, d of d, J_1 = 9 Hz, J_2 = 5 Hz), 6.70–7.80 (10 H, m), 7.90 (1 H, s, HC=N), 8.15 (1 H, broad singlet); M^+ at m/e 306.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.50; H, 5.88; N, 9.15. Found: C, 74.30; H, 5.80; N, 9.00.

2-Benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-benzene (7d). N_b-Benzyltryptamine (**1d**; 1.0 g, 0.004 mol), prepared by reaction of tryptamine and benzaldehyde in the presence of $NaCNBH_3$, was dissolved in dry benzene (50 mL), and benzaldehyde (**2a**; 0.50 g, 0.0047 mol) was added. The solution was refluxed for 24 h and the water (0.07 mL) removed by means of a Dean-Stark trap. The solvent was removed under reduced pressure to provide a solid (**7d**) which was recrystallized from methanol, yield 1.33 g (98.5%): mp 171–172 °C (MeOH); IR (KBr) 3420 (NH) and 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (3 H, m), 3.08 (1 H, m), 3.30 (1 H, d, J = 13.5 Hz), 3.9 (1 H, d, J = 13.5 Hz), 4.60 (s, 1 H), 6.95–7.60 (m, 15 H); M^+ at m/e 338.

The methylene protons of the benzyl group are diastereotopic and are split into doublets (J = 13.5 Hz).

Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.20; H, 6.50; N, 8.28. Found: C, 85.00; H, 6.20; N, 8.00.

1,2,3,4-Tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-benzene (10). 1-Phenyl-1,2,3,4-tetrahydro-β-carboline (**10**) was prepared by the method of Jackson et al.,[16a] mp 168 °C (petrol) (lit.[39] mp 168 °C). An authentic sample of the imine, N_b-benzylidenetryptamine (**3c**), was also prepared by published methods:[16a] mp 118–120 °C (petrol) (lit.[39] mp 120–121 °C); IR (KBr) 3140 (broad NH) and 1645 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.15 (2 H, t, J = 8 Hz), 3.40 (0.5 H, s), 3.90 (2 H, t, J = 8 Hz), 6.80–7.80 (9 H, m), 8.05 (1 H, s, HC=N); M^+ at m/e 248.

Attempted Cyclization of N_b-Benzylidenetryptamine (3c) in Refluxing Benzene. **3c** (2 g) was dissolved in dry benzene, and the solution was refluxed for 8 h. Evaporation of solvent under reduced pressure furnished a quantitative recovery of the benzylidene derivative (**3c**), identical in all respects with that described above. This reaction was repeated and refluxed for 24 h. Again, none of the cyclized β-carboline (**10**) was found; the only compound isolated was N_b-benzylidenetryptamine (**3c**).

Attempted Cyclization of N_b-Benzylidenetryptamine (3c) in the Presence of Tryptophan. In order to determine if traces of tryptophan were responsible for the cyclization of amines and aldehydes to tetrahydro-β-carbolines when heated in refluxing benzene, the following experiment was carried out. Tryptamine (55 mg) and benzaldehyde (40 mg) were dissolved in dry benzene (7 mL). A catalytic amount (2–5 mg) of tryptophan was added, and the mixture was refluxed for 30 h. None of the cyclized β-carboline (**10**) was obtained. The same experiments were repeated employing 2–5 mg of tryptophan methyl ester·HCl, and again no β-carboline (**10**) was isolated.

Preparation of the Schiff Base (3b) of Tryptophan Methyl Ester (1a) and Salicylaldehyde (h). Tryptophan methyl ester (**1a**; 6.0 g, 0.027 mol) and salicylaldehyde (**2h**; 3.0 g, 0.024 mol) were dissolved in dry benzene (100 mL), and the resulting solution was refluxed for 1 h. The water was removed from the reaction by use of a Dean-Stark trap. Removal of solvent under reduced pressure provided an oil (7 g) which was shown by spectroscopic and chemical data to be the imine **3b**: IR (neat) 3410 (NH, OH), 1735 (ester C=O), and 1630 (C=N) cm^{-1}; NMR ($CDCl_3$) 3.35 (1 H, d, J = 9 Hz), 3.52 (1 H, d, J = 5 Hz), 3.75 (3 H, s, OCH_3), 4.28 (1 H, d of d, J_1 = 9 Hz, J_2 = 5 Hz), 6.60–7.70 (8 H, m), 7.80 (1 H, s, HC=N), 8.05 (1 H, broad singlet, NH), 10.05 (1 H, s); M^+ at m/e 322.

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.59; N, 8.69. Found: C, 70.60; H, 5.40; N, 8.50.

The Schiff base (**3b**) was stirred in a 50:50 methanol–water solution (50 mL) at room temperature in the presence of acetic acid (1 mL). The imine reverted to tryptophan methyl ester (**1a**) and salicylaldehyde (**2h**).

Attempted Cyclization of the Schiff Base 3b to 3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-(2-hydroxybenzene) 7a in Refluxing Benzene. The Schiff base (**3b**, 2 g) was heated in refluxing dry benzene (50 mL) for 24 h. Evaporation of solvent under reduced pressure gave an oil identified as the Schiff base (**3b**) by comparison of spectral data with an authentic sample. The same reaction was carried out in dry, refluxing toluene (2 days), but again only the starting material (**3b**) was isolated. Careful examination of the reaction indicated that none of the 1,2,3,4-tetrahydro-β-carboline (**7a**) had formed.

1-(2-Hydroxyphenyl)-3-(methoxycarbonyl)-β-carboline (8). The Schiff base (**3b**, 5 g) obtained from the previous experiment and acetic acid (5 mL) were dissolved in toluene (50 mL), and the solution was refluxed for 48 h. Evaporation of solvent under reduced pressure, treatment of the residual oil with ammonium hydroxide (14 g), and extraction of the alkaline solution with methylene chloride provided a 4.5% yield of the fully aromatic β-carboline (**8**) as a yellow solid: IR (KBr) 3290 (OH and NH) and 1712 (ester C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.95 (3 H, s, OCH_3), 6.80–8.60 (9 H, m), 9.02 (1 H, s), 13.10 (1 H, broad singlet); M^+ at m/e 318.

Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.40; N, 8.80. Found: C, 71.40; H, 4.20; N, 8.60.

The same β-carboline (**8**) was obtained when the Schiff base (**3b**, 5 g) was refluxed in toluene (125 mL) in the presence of p-toluenesulfonic acid (100 mg). From both experiments none of the 1-(2-hydroxyphenyl)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**7a**) was isolated.

3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-acetoxybenzene) (7c). *dl*-Methyl ester tryptophan (**1a**; 2.0 g, 0.0092 mol) and acetylsalicylaldehyde[38] (**2i**; 2.0 g, 0.0122 mol) were condensed in refluxing dry benzene (250 mL), with a Dean-Stark trap to remove the water formed. After 7 days, the solvent was removed in vacuo. The residue contained >40% of **7c** and was recrystallized from benzene to provide the tetrahydro-β-carboline **7c** (0.47 g, 24%): mp 150–152 °C; IR (KBr) 3390, 3000–3070, 1740, and 1700 (ester C=O), *1660* (*C=O amide rearrangement product*), 1600–1580, 1480, and 1460 cm^{-1}. The yield of **7c** decreased markedly on purification; presumably rearrangement to the N_b-acetamide derivative occured: NMR ($CDCl_3$) δ 1.80 (3 H, s, C(=O)CH_3), 2.40 (2 H, d of d, C-4 H, J_1 = 8 Hz, J_2 = 3 Hz), 3.70 (3 H, s, OCH_3), 4.70 (1 H, t, C-3 H, J = 8 Hz), 4.9 (1 H, s, N–H), 5.40 (1 H, s, C-1 H), 6.40–7.60 (9 H, m); mass spectrum, m/e 406 (19, M^+ + 42, impurity), 364 (M^+, 38), 363 (31), 322 (58), 321 (42), 305 (27), 263 (23), 261 (42), 260 (29).

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 74.01; H, 5.73; N, 6.17. Found: C, 73.90; H, 6.09; N, 5.72. The data reported here are actually for the N_b-acetamide derivative of **7c**.

***trans*-2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-(2-hydroxybenzene) (7b).** *dl*-N_b-Benzyltryptophan methyl ester (**5a**; 14.5 g, 0.047 mol) and salicylaldehyde (**2h**; 10 mL, 0.095 mol) were refluxed for 16 h in toluene (150 mL) with a Dean-Stark trap to remove the water which formed. The solution was slowly cooled to room temperature, which resulted in the formation of a white crystalline solid found to be **7b** (18.6 g, 97%): mp 243–245 °C; IR (KBr) 3400 (s, NH), 3060, 3040 (w, aromatic CH), 2950, 2890 (w, aliphatic CH), 1740 (s, C=O ester), 1600, 1575, 1480, 1450 (C=C), 1270, 1240, 1210, 1170 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.10 (2 H, t, C-4 H, J = 4 Hz), 3.60 (3 H, s, OCH_3), 4.00 (3 H, m, benzyl CH_2 and C-3 H), 5.6 (1 H, s, C-1 H), 7.00–7.20 (14 H, m); mass spectrum (electron impact), m/e 412 (2, M^+), 321 (8), 238 (7), 237 (34), 236 (15), 235 (14), 234 (12), 222 (12), 220 (15), 218 (9), 217 (9), 204 (7), 182 (12), 162 (12), 145 (11), 131 (20), 118 (26), 117 (33), 91 (100).

Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.50; H, 5.88; N, 6.79. Found: C, 75.79; H, 6.11; N, 6.81.

***trans*-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole-1-(2-hydroxybenzene) (7a) and 2-(2-Hydroxybenzyl)tryptophan Methyl Ester (9a).** The *trans*-benzylphenol **7b** (2 g, 0.0049 mol) was hydrogenated (25 psi) in a solution of methanol (300 mL) and acetic acid (40 mL) for 8 h over 10% Pd/C (0.2 g). The catalyst was filtered off, and the solvent was removed in vacuo. The residue was basified with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue contained two new compounds (R_f 0.57 and 0.26) by TLC (silica gel; 1% methanol–chloroform).

The mixture was chromatographed on silica gel. The methyl ester of the debenzylated phenol (**7a**) was eluted first from the column (1.1 g, 75%, R_f 0.57): mp 168–169 °C (MeOH) [lit.[3] mp 142–146 °C (MeOH)]; IR (KBr) 3400 (s, indole NH), 3310 (s, NH), 3060, 3030 (w, aromatic CH), 2960, 2920, 2850 (w, aliphatic CH), 1730 (s, C=O ester), 1600, 1580, 1490, 1450 (C=C), 1320, 1290, 1270, 1250, 1210 (s, C–O)

cm^{-1}; NMR ($CDCl_3$) δ 3.18 (2 H, d, J = 5.8 Hz), 3.65 (3 H, s, OCH_3), 3.95 (1 H, t, J = 5.8 Hz), 5.40 (1 H, s, C-1 H), 6.60–7.60 (13 H, m), 7.60 (1 H, s, broad); mass spectrum, M^+ at m/e 322.

The ring-cleaved product **9a** (0.24 g, 14% yield) was eluted next (R_f 0.26): mp 137–139 °C ($CHCl_3$); IR (KBr) 3340 (s, indole NH), 3280 (NH), 3060, 3020 (aromatic C–H), 2950, 2920, 2860 (aliphatic C–H), 1720 (s, C=O ester), 1590 1575, 1480, 1450 (C=C), 1290, 1275, 1240, 1230, 1200 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.20 (2 H, m, ester β-CH_2), 3.70 (4 H, m, OCH_3 plus ester α-CH), 4.05 (2 H, d, benzyl CH_2), 4.40 (3 H, broad band, NH_2 and OH signals), 6.70–7.50 (9 H, m), 7.80 (1 H, s). The peaks at δ 7.8 and 4.4 disappeared on addition of D_2O. Mass spectrum (electron impact): m/e 324 (10, M^+), 322 (17), 318 (12), 317 (9), 306 (12), 293 (25), 292 (100), 275 (13), 274 (9), 265 (15), 264 (47), 263 (10), 261 (10), 260 (12), 258 (18), 257 (14), 248 (14), 247 (16), 246 (14), 238 (22), 237 (150), 236 (498), 235 (39), 234 (59), 233 (17).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.95; H, 6.52; N, 8.66.

***cis*-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-(2-hydroxybenzene) (7a).** The *trans*-phenol **7a** was refluxed in methanolic hydrogen chloride for 2 days. The solvent was evaporated in vacuo; the residue was basified with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The cis diastereomer of **7a** had a higher mobility (R_f 0.75) than did the trans diastereomer of **7a** (R_f 0.60). The diastereomers were separated best by column chromatography on aluminum oxide; silica gel epimerized the trans diastereomer (**7a**), resulting in mixed fractions after some of the cis diastereomer (**7a**) had been removed (*cis*-**7a**): mp 189–192 °C (MeOH) (lit.[3] mp 186 °C); IR (KBr) 3360 (s, indole N–H), 3300 (s, N–H), 3060, 3010 (w, aromatic C–H), 2960, 2930, 2860 (aliphatic C–H), 1730 (s, C=O ester), 1610, 1590, 1465 (C=C), 1300, 1250, 1240, 1220 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.20 (2 H, m, C-4 H), 3.80 (4 H, OCH_3 and C-3 H), 5.10 (1 H, s, C-1 H), 6.70–7.50 (9 H, m); mass spectrum (electron impact), m/e 322 (25, M^+), 318 (11), 305 (7), 279 (22), 263 (10), 261 (14), 258 (12), 238 (10), 237 (39), 236 (19), 235 (20), 234 (22), 229 (9), 222 (17), 220 (18), 149 (100).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.81; H, 5.59; N, 8.70. Found: C, 70.59; H, 5.39; N, 8.56.

The ratio of cis/trans isomers after epimerization was 1:2.

2-Benzyltryptophan Methyl Ester (9b). The phenylcarboline **4c** (0.813 g, 0.0026 mol) was dissolved in ethanol (150 mL) and acetic acid (45 mL). The mixture was hydrogenated (50 psi) at room temperature over 10% Pd/C (0.111 g) for 24 h. The solvent was removed under reduced pressure. The residue was basified with ammonium hydroxide (14%) and the solution extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel, and the ring-cleaved indole **9b** (0.3 g, 48% yield) was recovered: mp 127–130 °C (MeOH); IR (KBr) 3350 (s, indole N–H), 3290 (s, NH_2), 3140, 3100, 3060, 3020 (s, aromatic C–H), 2940, 2860, 2770 (aliphatic C–H), 1725 (s, C=O ester), 1620, 1600, 1580, 1550, 1490 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 3.12 (2 H, d, J = 5 Hz), 3.60–3.80 (4 H, OCH_3 and α ester C–H), 4.10 (2 H, s, CH_2), 6.90–7.80 (10 H, m).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.03; H, 6.49; N, 9.09. Found: C, 74.44; H, 6.48; N, 9.13.

***trans*-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-(2-acetoxybenzene), Derivative 14.** The N_b-benzylphenol **7b** was dissolved in pyridine, and excess acetic anhydride was added. After 3 days, ice was added and the resulting solid was filtered. The solid was recrystallized from ether and found to be the acetyltetrahydro-β-carboline **14**: mp 158–160 °C (Et_2O); IR (KBr) 3400 (s, N–H), 3060, 3030 (w, aromatic C–H), 2950, 2910, 2880, 2850 (w, aliphatic C–H), 1730–1750 (s, C=O ester), 1620, 1475, 1460 (C=C), 1260, 1220, 1180, 1160 (s, C–O) cm^{-1}; NMR ($CDCl_3$) δ 2.40 (3 H, s, C(=O)CH_3), 3.20 (2 H, d of d, J_1 = 4 Hz, J_2 = 2 Hz), 3.60 (3 H, s, OCH_3), 3.80 (3 H, m, benzyl CH_2 and C-3 H), 5.70 (1 H, s, C-1 H), 6.90–7.60 (13 H, m), 8.10 (1 H, s); mass spectrum (electron impact), m/e 455 (42, $M^+ + 1$), 454 (99, M^+), 411 (11), 400 (55), 395 (95), 365 (11), 364 (60), 363 (100), 322 (20), 321 (62), 319 (16), 303 (13), 279 (41), 278 (29), 277 (25), 262 (21), 261 (48), 260 (22), 237 (27), 236 (50), 234 (50).

Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 74.01; H, 5.73; N, 6.17. Found: C, 73.90; H, 6.09; N, 5.72.

2-(2-Acetoxybenzyl)-N_b-benzyltryptophan Methyl Ester (15). The acetylcarboline **14** (1.15 g, 0.0025 mol) was hydrogenated (50 psi) in acetic acid (100 mL) over PtO_2 (45 mg) for 12 h at room temperature. The catalyst was filtered from the solution, and the acetic acid was removed under reduced pressure. The residue was basified with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4), and removed under reduced pressure. The residue was chromatographed on silica gel. The starting material (**14**) was eluted from the column first [0.8 g, mp 158–160 °C (Et_2O)] and then the ring-cleaved indole **15** was recovered: 0.3 g; mp 130–132 °C (Et_2O); IR (KBr) 3310, (w, N–H), 3070, 3040 (w, aromatic C–H), 2960, 2860 (w, aliphatic C–H), 1760, 1740 (C=O ester), 1485, 1460 (C=C), 1210, 1195, 1175 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 2.20 and 2.00 (3 H, 2 singlets, 66 and 24%, respectively, acetate CH_3), 3.20 (2 H, d, CH_2, J = 6 Hz), 3.50–3.70 (6 H, m, OCH_3 (s), ester α-CH (m), and indole 2-benzyl CH_2), 3.90 (2 H, s, N–CH_2), 6.90–7.50 (13 H, m), 7.90 (1 H, s, indole N–H).

Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.68; H, 6.14; N, 6.14. Found: C, 73.74; H, 6.02; N, 6.19.

Synthesis of Methyl 1,2,3,3a,4,5-Hexahydro-6-oxocanthine-2-carboxylate (11) and 2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (7e). To a refluxing solution of N_b-benzyltryptophan methyl ester (**5a**; 6.26 g, 0.02 mol) in dry benzene (100 mL) was added, slowly, 2-oxoglutaric acid (**2f**; 3.70 g, 0.025 mol) in dry dioxane (50 mL). Reflux was continued for 48 h with water separation via a Dean-Stark trap. After removal of solvent, the reaction mixture was chromatographed on 300 g of silica gel. Elution with $CHCl_3$ gave methyl 1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate (**11**) as a green oil which crystallized from 1:1 CH_3OH–EtOAc: 3.55 g, 47.5% yield; mp 170–171 °C; IR (KBr) 1725 (s, ester) and 1690 (s, amide) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (2 H, m), 2.83–3.1 (4 H, m), 3.7 (3 H, s), 3.76–4.43 (4 H, m), 7.00–8.00 (4 H, m); mass spectrum (70 eV), m/e 375 (13), 374 (M^+, 46), 319 (5), 316 (10), 315 (42), 305 (5), 287 (7), 284 (28), 283 (100), 249 (6), 224 (6), 223 (34), 199 (6), 198 (42), 197 (32), 184 (24), 168 (32).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.88; H, 6.12; N, 7.28.

Elution with EtOAc gave 2-benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic acid (**7e**): 1.6 g, 20.5% yield; mp 204–205 °C dec; IR (KBr) 3340 (s), 1720 (s, ester), and 1700 (s, acid) cm^{-1}; mass spectrum (70 eV), m/e 393 ($M + 1$, 2), 392 (M^+, 8), 374 (6), 333 (20), 321 (4), 320 (25), 319 (100), 301 (15), 283 (4), 259 (6), 225 (13), 224 (6), 170 (8), 169 (18), 168 (11), 167 (5).

Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.55; H, 6.27; N, 7.02.

When the condensation was performed in refluxing absolute ethanol using N_b-benzyltryptophan methyl ester·HCl, only diethyl 2-oxoglutarate and starting materials were isolated. The same reaction using the free base in refluxing $CHCl_3$ resulted in precipitation of the 2-oxoglutarate salt of N_b-benzyltryptophan methyl ester. Finally, employing a 1:1 refluxing mixture of toluene and dioxane, N_b-benzyltryptophan methyl ester (**5a**; 1.54 g, 0.005 mol) and 2-oxoglutaric acid (**2f**; 0.8 g, 0.0055 mol) were condensed to give 2-benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic acid (**7e**; 1.04 g, 56.4% yield) and methyl 1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylate (**11**; 0.73 g, 39% yield), overall yield 95.5%. Both products were identical in all respects with those previously isolated.

Synthesis of the Tetracyclic Lactam 12. Tryptophan methyl ester (**1a**; 4.7 g, 0.018 mol) was dissolved in dry benzene (1.50 mL), and 2-oxoglutaric acid (**2f**; 2.7 g, 0.018 mol) was added in small portions to the refluxing solution. Reflux was continued, after addition, for 20 h with water removal via a Dean-Stark trap. After removal of solvent, the reaction mixture was chromatographed on silica gel (eluted with 30% EtOAc–CH_2Cl_2) to provide a yellow oil which solidified on standing (**12**; 4.14 g, 79.2% yield): mp 184–186 °C; IR (KBr) 3200 (s, N–H), 1740 (s, ester), and 1670 (s, amide) cm^{-1}; NMR ($CDCl_3$) δ 1.88 (2 H, t), 2.53 (2 H, m), 3.33 (2 H, d), 3.63 (3 H, s, OCH_3), 5.22 (2 H, m), 7.25 (4 H, m), 8.33 (s, 1 H, N–H); mass spectrum (70 eV), m/e 285 ($M + 1$, 18), 284 (M^+, 64), 283 (21), 226 (18), 225 (89), 223 (30), 198 (34), 197 (100), 182 (10), 181 (11), 170 (22), 169 (54), 168 (60), 167 (15), 155 (11).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.38; H, 5.76; N, 9.67.

The reaction was also done in refluxing absolute ethanol with tryptophan methyl ester·HCl (10.2 g, 0.04 mol) and 2-oxoglutaric acid (5.84 g, 0.04 mol). Chromatography, as above, gave **12** (4.91 g, 41.7% yield), mp 184–187 °C. The NMR spectrum indicated that a 3:1 mixture of ethyl and methyl esters was present which was not separated.

3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-*p*-anisidine (7f). Tryptophan methyl ester (**1a**; 4.1 g, 0.0188 mol) and *p*-anisaldehyde (**2j**; 2.6 g, 0.019 mol) were refluxed in dry toluene (125 mL) for 30 h. Analysis by TLC (10% CH_3OH–benzene) indicated a trace of product plus starting materials; TLC at 40 h indicated no further reaction. The toluene was removed under reduced pressure and replaced with *p*-xylene (125 mL), and the solution was refluxed for an additional 25 h. The *p*-xylene was removed under

reduced pressure, and the reaction mixture was chromatographed on silica (elution with 50% CH_2Cl_2–PhH) to give a pale yellow oil which crystallized from CH_3OH, overall yield (**7f**; 0.93 g, 15.1%) of cis and trans isomers: mp 147–149 °C; IR (KBr) 1725 (s, ester) and 1600 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.22 (s, 1 H, N–H), 3.17 (d, 2 H, J = 6 Hz), 3.68 (s, 3 H), 3.77 (s, 3 H), 3.95 (t, 1 H, J = 7 Hz), 5.48 (s, 1 H), 6.73–7.62 (m, 9 H); mass spectrum (70 eV), m/e 337 (M + 1, 14), 336 (M^+, 100), 319 (34), 277 (28), 275 (24), 252 (36), 251 (36), 250 (60), 218 (32), 169 (18), 144 (29).

Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.57; H, 6.03; N, 8.40.

2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-*p*-anisidine (7g). N_b-Benzyltryptophan methyl ester (**5a**; 4.31 g, 0.014 mol) and *p*-anisaldehyde (**2j**; 2.11 g, 0.0154 mol) were refluxed in *p*-xylene (125 mL) for 96 h with water removed via a Dean-Stark trap. Removal of solvent under reduced pressure and chromatography on silica gave a colorless oil which crystallized from CH_3OH (**7g**; 2.40 g, 40.0% yield): mp 199–200.5 °C; IR (KBr) 1725 (s, ester) and 1600 (m) cm^{-1}; NMR ($CDCl_3$) δ 3.16 (d, 2 H, J = 6 Hz), 3.56 (s, 3 H), 3.73 (s, 3 H), 3.83 (s, 2 H), 3.9 (t, 1 H, J = 6 Hz, partially obscured), 5.33 (s, 1 H), 6.7–7.52 (m, 14 H); mass spectrum (70 eV), m/e 427 (M + 1, 12), 426 (M^+, 38), 367 (58), 335 (100), 319 (46), 251 (36), 250 (58), 218 (36), 135 (34), 91 (70), 78 (58).

Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.04; H, 6.14; N, 6.57. Found: C, 76.40; H, 6.13; N, 6.57.

1-Acetyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indole (21). *dl*-Tryptophan (**17**; 1.02 g, 0.005 mol) was dissolved in hydrochloric acid (1 N, 5 mL), and *dl*-glyceraldehyde (**18**; 0.495 g, 0.0055 mol) was added. The mixture was gently refluxed for 2 h[25] until a sample no longer gave a precipitate with 2,4-dinitrophenylhydrazine. The mixture was concentrated in vacuo, and final amounts of water were azeotroped from the oil by treatment with benzene. The brown residue was dissolved in methanol (30 mL) and saturated with anhydrous hydrogen chloride. The solution was refluxed for 12 h and subsequently filtered through activated charcoal. The filtrate was concentrated in vacuo to an oil which was then treated with sodium bicarbonate solution until the pH 8 was attained. The aqueous solution was extracted with dichloromethane (3 × 50 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide a yellow solid, albeit in poor yield (**20**): m/e 290 (M^+), 272 ($M^+ - 18$), 268 ($M^+ - 22$); IR ($CDCl_3$) 3400–3200 (OH and NH) and 1735 (ester) cm^{-1}. The solid was dissolved in *p*-xylene, palladium on carbon (0.5 g of 5%) was added, and the mixture was refluxed for 2 days. The solution was filtered and the solvent removed under reduced pressure. TLC (Al_2O_3; $CHCl_3$–MeOH, 100:1) indicated the presence of a new compound (R_f 0.80) as well as smaller amounts of starting tetrahydro-β-carboline **20** (R_f 0.40). The mixture was chromatographed on silica to provide 200 mg of the ketone **21**: mp 222–224 °C from CH_3OH; IR ($CHCl_3$) 3420 (NH), 1720 (ester), and 1670 (ketone) cm^{-1}; NMR ($CDCl_3$) δ 2.90 (s, 3 H), 4.05 (s, 3 H), 7.20–7.70 (m, 3 H), 8.10 (d, J = 8 Hz, 1 H), 8.90 (s, 1 H), 10.40 (s, 1 H); mass spectrum, m/e 268 (M^+).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.83; H, 4.61; N, 10.31.

Preparation of the Pictet–Spengler Product of Tryptophan Methyl Ester (1a) and Glyceraldehyde D-Acetonide (23). Tryptophan methyl ester (**1a**; 10.9 g, 0.05 mol) and glyceraldehyde D-acetonide (**22**; 7.0 g, 0.055 mol) were dissolved in benzene (250 mL, dry, distilled). The solution was refluxed for 2 h, at which time TLC indicated that only a small amount of tryptophan methyl ester remained. The solution was refluxed for 20 additional hours, after which the solvent was removed under reduced pressure to furnish an oil (19.5 g). The oil was crystallized from methanol to provide a solid (15 g, 90% yield) composed of a mixture of diastereomers represented by structure **23**: mp 180–191 °C; IR (film) 3435 (NH), 3400 (NH), and 1740 (ester) cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.50 (s, 3 H), 2.22 (s, 1 H), 2.90 (m, 2 H), 3.50–4.50 (m, overlapping with 3 sharp singlets, 8 H including diastereomeric methoxyl signals), 6.90–7.60 (m, 4 H), 8.40 (s, 1 H); mass spectrum, m/e 330 (M^+, 15), 326 (8), 315 (6), 271 (20), 268 (30), 255 (30), 247 (18), 229 (100), 169 (100); $[\alpha]^{RT}_D$ −11° (c 6.25, $CHCl_3$), from glyceraldehyde D-acetonide $[\alpha]^{RT}_D$ +27° (c 8) (lit.[28] value 64.9°).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.45; H, 6.66; N, 8.48. Found: C, 65.30; H, 6.38; N, 8.30.

1-[1(±),2-Dihydroxyethyl]-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indole Acetonide (24). The mixture of diastereomers **23** (4.3 g) was dissolved in cumene (300 mL), and 5% Pd/C (3.5 g) was added. The mixture was refluxed for 20 h, after which the catalyst was removed by filtration. After the solvent was removed under reduced pressure, the oil which remained was crystallized from methanol to provide white needles of **24** (3.0 g, 70% yield); additional amounts of **24** were obtained on alumina chromatography of the mother liquor (hexane–chloroform): mp 220–222 °C (methanol); IR (film) 3430 (NH), 1720 (ester), 1620, and 1250 cm^{-1}; NMR ($CDCl_3$) δ 1.55 and 1.60 (2s, 6 H), 4.05 (s, 3 H), 4.50 (m, 2 H), 5.65 (t, 1 H, J = 6.2 Hz), 7.15–7.65 (m, 3 H), 8.10 (d, 1 H, J = 7.5 Hz), 8.70 (s, 1 H), 9.60 (s, 1 H); mass spectrum, m/e 326 (M^+); $[\alpha]^{RT}_D$ 0° (c 10).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.59. Found: C, 66.20; H, 5.40; N, 8.40.

1-[1(*S*),2-Dihydroxyethyl]-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indole Acetonide (26). The tetrahydro-β-carboline **23** (2.8 g, $[\alpha]^{23}_D$ −11°) was dissolved in dry benzene (300 mL), and the solution was cooled to 16 °C by use of a water bath. Dichlorodicyanoquinone (4.8 g) was added in one portion and the resulting mixture stirred for 1.5 h. The color of the solution became black and then changed to reddish brown. The benzene solution was washed with ammonium hydroxide (300 mL of 15%), and the organic layer was separated. The aqueous layer was washed several times with chloroform, and the combined organic layers were then dried (K_2CO_3). The solvent was removed under reduced pressure, and the oil which remained was chromatographed on alumina (benzene–chloroform) to provide a yellow solid (**24**; 1.3 g, 46% yield), mp 220–222 °C (from CH_3OH), identical in most respects with the sample of **24** prepared in the previous experiment; however, this sample had an optical rotation in the positive direction, $[\alpha]^{23}_D$ 5.56°.

1-[1(±),2-Dihydroxyethyl]-3-(hydroxymethyl)-9*H*-pyrido-[3,4-*b*]indole 1-Acetonide (25). The ester **24** (3 g, 0.0092 mol) was dissolved in methanol (50 mL, distilled), and sodium borohydride (1 g) was added. The mixture was refluxed for 45 h. Additional amounts of sodium borohydride (1.5 g) were added over the 45-h period. A major protion of the solvent was removed under reduced pressure. Ether and ammonium hydroxide (14%) were added, and the organic layer was separated. The aqueous layer was extracted several times with ether, and the combined organic layers were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure to provide a yellow oil which was crystallized from methanol–methylene chloride to furnish 2.2 g (80% yield) of **25**: mp 124–125 °C; IR (film) 3435 (NH), 3420–3100 (NH and OH), and 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 6 H), 4.40 (m, 2 H), 4.80 (s, 2 H), 5.52 (t, 1 H, J = 6.2 Hz), 7.00–7.56 (m, 3 H), 7.78 (s, 1 H), 8.00 (d, J = 8 Hz, 1 H), 9.15 (s, 1 H); mass spectrum, M^+ at m/e 298 (20), 283 (8), 268 (8), 255 (3), 240 (100), 225 (20), 224 (18), 223 (25), 222 (25), 212 (28), 211 (25), 210 (30), 209 (28), 197 (18), 196 (18), 195 (25), 194 (95), 193 (80), 192 (5).

Anal. Calcd for $C_{17}H_{18}O_3N_2$: C, 68.45; H, 6.04; N, 9.39. Found: C, 68.15; H, 6.15; N, 9.25.

1-[1(±),2-Dihydroxyethyl]-3-(hydroxymethyl)-9*H*-pyrido-[3,4-*b*]indole (16). The acetonide **25** (1.5 g, 0.005 mol) was dissolved in acetic acid (60 mL of 80%), and the solution was heated to 65 °C for 25 h. The acetic acid was removed under reduced pressure, and the oily residue was dissolved in ammonium hydroxide. The triol was not very soluble in chloroform; therefore, the solution was extracted with butanol (3 × 50 mL). The organic layer was dried and the solvent removed under reduced pressure to provide an oil (1.0 g) which crystallized from ethyl acetate–methanol (**16**) (0.9 g, 70% yield): mp 169–170 °C (lit.[24a] mp 167–168 °C); $[\alpha]^{RT}_D$ 0° (c 1); the IR and NMR spectra were identical with those reported for **16** by Umezawa and co-workers;[24a] mass spectrum (electron impact), M^+ at m/e 258 ($M^+ - 22$); mass spectrum (chemical ionization) (NH_3), 259 ($M^+ + 1$) = 258 molecular ion.

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.99; H, 5.58; N, 10.57.

1-[1(*S*),2-Dihydroxyethyl]-3-(hydroxymethyl)-9*H*-pyrido-[3,4-*b*]indole. The acetonide **24** (0.55 g, 0.0016 mol) isolated from the dicyanodichloroquinone oxidation (rotation in the dextrorotary direction) was dissolved in distilled tetrahydrofuran (15 mL), and lithium borohydride (0.37 g, 10 molar ratio) was added. The mixture was stirred at room temperature for 1 h, poured into water, and extracted with chloroform (3 × 50 mL). Removal of solvent under reduced pressure provided an oil which was chromatographed on silica gel (CH_2Cl_2–CH_3OH, gradient elution) to provide 0.51 g of the monol **25**. This alcohol **25** was added to acetic acid (20 mL of 80%) and held at 60–65 °C for 18 h. Removal of solvent and workup as in the previous experiment yielded the triol **16** (0.3 g), which crystallized from CH_3OH–EtOAc (1:1): overall yield for the two steps, 73%; mp 168–170 °C; $[\alpha]^{RT}_D$ +7.7°.

Methyl 2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate. 2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole-1-propionic acid (52.8 g, 0.13 mol) was dissolved in 250 mL of methanolic hydrogen chloride and refluxed for 2.5 h. After removal of solvent, the residue was dissolved in 200 mL of CH_2Cl_2, neutralized with aqueous ammonia (14%), washed with brine, and dried over

K_2CO_3. The product solidified upon removal of CH_2Cl_2. Recrystallization from CH_3OH gave 49.6 g of the diester: 91% yield; mp 137–140 °C (lit.[2] mp 137–140 °C); IR (KBr) 1730 cm^{-1} (ester) (lit. 1730 cm^{-1}); NMR ($CDCl_3$) δ 2.0 (m, 2 H), 2.43 (m, 2 H), 3.05 (d, 2 H, J = 8 Hz), 3.43 (s, 3 H), 3.6 (s, 3 H), 3.73 (s, 2 H, benzyl methylene), 3.76 (s, 3 H), 4.0 (m, 2 H), 7.0–7.6 (m, 9 H); mass spectrum (70 eV), m/e 421 (M^+ + 1, 8), 420 (M^+, 24), 362 (8), 361 (24), 334 (12), 333 (100), 273 (20), 243 (18), 184 (26), 183 (60), 182 (26), 170 (26), 169 (14), 168 (28).

Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.72; N, 6.66. Found: C, 71.37; H, 6.43; N, 6.70.

Methyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (i). The β-keto ester was prepared according to the method of Yoneda.[2] To a solution of the diester (above) (10.5 g, 0.025 mol) in 50 mL of toluene was added NaH (1.66 g, 0.069 mol) in 50 mL of toluene. The reaction mixture was brought slowly to reflux followed by the dropwise addition of a solution composed of 1 mL of CH_3OH and 9 mL of toluene. The mixture was refluxed for 2 h after the addition and then was stirred at room temperature overnight. Acetic acid was added (5 mL), and then the mixture was saturated with $NaHCO_3$ until neutral pH. The mixture was extracted with benzene and dried (Na_2SO_4). Removal of solvent and addition of CH_3OH gave 8.28 g of crystalline product: 85.3% yield; mp (CH_3OH) 146–148 °C (lit.[2] mp 148–150 °C); IR (KBr) 1670 and 1630 (β-keto ester) cm^{-1} (lit. 1670 and 1625 cm^{-1}); NMR ($CDCl_3$) δ 1.2 (m, 2 H), 2.4 (m, 1 H), 2.8 (m, 1 H), 3.05 (m, 2 H), 3.6 (s, 3 H), 3.66 (s, 3 H), 3.73 (s, 2 H, benzyl methylene), 4.1 (m, 1 H), 7.0–7.6 (m, 9 H); mass spectrum (70 eV), m/e 389 (M + 1, 4), 388 (M^+, 15), 315 (57), 297 (69), 283 (87), 223 (48), 220 (39), 197 (37), 170 (98), 91 (100), 78 (88).

Registry No.—**1a,** 4299-70-1; **1b,** 21469-60-3; **1c,** 65048-62-6; **1d,** 15741-79-4; **1e,** 724-42-5; **1f,** 61-54-1; **2a,** 100-52-7; **2b,** 2043-61-0; **2c,** 10138-10-0; **2d,** 5344-23-0; **2e,** 25346-59-2; **2f,** 328-50-7; **2h,** 90-02-8; **2i,** 5663-67-2; **2j,** 123-11-5; **3a,** 67628-15-3; **3b,** 68014-31-3; **3c,** 16979-93-4; *cis*-**4a,** 60702-94-5; *trans*-**4a,** 60702-95-6; *cis*-**4b,** 60702-90-1; *trans*-**4b,** 60702-91-2; **4c,** 68036-75-9; **4d,** 68014-25-5; **4e,** 68014-26-6; *cis*-**4f,** 68014-38-0; *trans*-**4f,** 68014-39-1; **5a,** 63229-68-5; **5a** 2-oxoglutarate salt, 68014-35-7; **6a,** 68014-27-7; **6b,** 68014-28-8; **6c,** 68014-29-9; *cis*-**6d,** 68014-40-4; *trans*-**6d,** 68014-41-5; **6e,** 68014-30-2; *cis*-**6f,** 68014-42-6; *trans*-**6f,** 68014-43-7; **6g,** 60702-96-7; **6h,** 65048-61-5; **6i,** 60702-93-4; *trans*-**7a,** 68014-44-8; *cis*-**7a,** 68014-45-9; **7b,** 68014-32-4; **7c,** 68014-34-6; **7d,** 65048-57-9; **7e,** 60702-97-8; **7f,** 68014-36-8; **7g,** 68014-37-9; **8,** 68014-33-5; **9a,** 68014-46-0; **9b,** 68014-47-1; **10,** 3790-45-2; **11,** 60702-98-9; **12,** 32283-52-6; **14,** 68014-48-2; **15,** 68014-49-3; **16,** 66183-62-8; **17,** 54-12-6; **18,** 56-82-6; **20,** 66154-39-0; **21,** 66154-37-8; **22,** 15186-48-8; **23,** 66154-40-3; **24,** 66154-41-4; **25,** 66154-42-5; **26,** 2899-29-8; **27,** 65474-78-4; methyl 2-benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate, 19171-89-2; 2-benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic acid, 60702-96-7; i, 2738-25-2.

References and Notes

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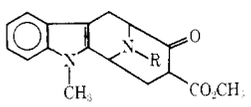

i, R = -CH_2Ph

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