DDQ Oxidations in the Indole Area. Synthesis of 4-Alkoxy-β-carbolines Including the Natural Products Crenatine and 1-Methoxycanthin-6-one[1]

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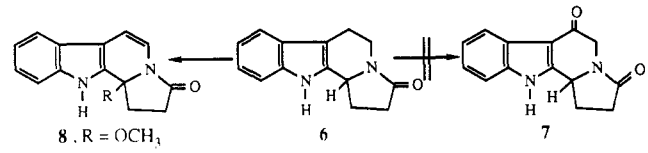
The seven-step synthesis of the cytotoxic, antileukemic alkaloid 1-methoxycanthin-6-one (**2b**) is described. The pivotal steps are represented by the oxidation (DDQ, aqueous THF, room temperature) of 1-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**10**) to provide the 4-oxo-substituted derivative **14** in 78% yield, and conversion of the 4-oxo analogue **7** into 4-methoxy-1-alkyl-β-carboline (**23**) via a methoxylation–oxidation process [CH_3OH, $(CH_3O)_3CH$, pTSA, Δ]. This four-step, one-pot reaction has been shown to be general; 4-oxo-1,2,3,4-tetrahydro-β-carboline (**18**) was converted into the corresponding 4-methoxy-, 4-ethoxy-, 4-(allyloxy)-, and 4-(benzyloxy)-β-carbolines (**19a–d**, respectively) on heating in the appropriate alcohol in the presence of pTSA and a trialkyl orthoformate (Table II). The proposed mechanism for this intriguing transformation is outlined in Scheme IV. Execution of this process has also resulted in a four-step preparation of crenatine (**1a**), a 4-methoxy-1-ethyl-β-carboline alkaloid. Finally, steric and electronic parameters have also been successfully manipulated to direct the DDQ oxidation of 1,2,3,4-tetrahydro-β-carbolines to position 1, regiospecifically. The conversion of tetrahydro-β-carboline **25** into 2-acylindole **38** and benzamide **26** into 1-oxotetrahydro-β-carboline **27** (Table I), respectively, is in agreement with the proposed mechanism for this process.

In recent years increasing numbers of β-carboline alkaloids that contain an oxygen substituent at position 4 have been isolated.[2a,b,3a–e] The 4-methoxy-β-carbolines **1a–h**[3a–e] and canthin-6-ones **2b**, **2c**,[3a,b,4a–d] (Scheme I), as well as several bisindoles[2a,3c,5] serve as representative examples. The diindole, 4-(4,8-dimethoxy-9*H*-pyrido[3,4-*b*]indol-1-yl)-1-(9*H*-pyrido[3,4-*b*]indol-1-yl)-1-butanone, exhibits inhibitory activity against cyclic AMP phosphodiesterase,[2b] while some members of the canthin-6-one series have been shown to possess antileukemic activity.[4c,6] Canthin-6-one (**2a**), 1-methoxycanthin-6-one (**2b**),and 1-hydroxycanthin-6-one (**2c**) (Figure 1) were isolated from *Ailanthus altissima*,[3a,b,4a,b] while **2a**, 11-hydroxycanthin-6-one (**2d**), and 1,11-dimethoxycanthin-6-one (**2e**) were obtained from *Brucea antidysenterica*.[4c] In addition, **2a**, **2b**, and **2e** have recently been isolated from *Soulamea pancheri*.[4d] The alkaloid 1-methoxycanthin-6-one (**2b**) and its congeners have been shown to exhibit cytotoxic activity via their inhibitory effects on DNA synthesis in GPK epithelial cells.[4c,6] Oxygenation of the canthin-6-one skeleton at positions C-1 (C-4 in the β-carboline numbering system) and C-11 greatly enhances the cytotoxic, antileukemic activity of these alkaloids.[4c,6] A versatile approach for the synthesis of 1-oxygen-substituted canthin-6-one alkaloids should provide facile entry into more potent antitumor agents of this class for biological evaluation. In this regard, a general method for the synthesis of 4-alkoxy-β-carbolines from 4-oxo-1,2,3,4-tetrahydro-β-carbolines has been developed, which has resulted in an improved synthesis of crenatine (**1a**)[7,8] and the first synthesis of 1-methoxycanthin-6-one (**2b**).[1]

Scheme I



Relatively few methods for the incorporation of oxygen functionality into position 4 of β-carbolines are available. Deceptively simple syntheses of 4-oxygenated β-carbolines would stem from a Pictet–Spengler[9] or Bischler–Napieralski reaction of the corresponding substituted 3-acyltryptamine; however, both reactions take a different course[2a] (see also ref 1, 10, and 11 for details). Several methods, however, do exist that can be employed to prepare 4-oxo-1,2,3,4-tetrahydro-β-carbolines, and they are listed here: oxidation of 1,2,3,4-tetrahydro-β-carbolines with dichlorodicyanobenzoquinone (DDQ)[7,12,13] or selenium dioxide (SeO_2),[14,15] as well as the intramolecular acylation of an appropriately substituted (position 2) indole.[8,16,17] DDQ is known to form a blue-colored charge-transfer complex (Bergman et al.)[18] with the 2,3-double bond of

(1) A portion of this work was presented in preliminary form. Hagen, T. J.; Cook, J. M. *Tetrahedron Lett.* **1988**, *29*, 2421.
(2) (a) For a list of structures of these alkaloids, see: Hagen, T. J., Ph.D. Thesis, University of Wisconsin—Milwaukee, WI, 1988; pp 164. (b) Sung, Y.-i.; Koike, K.; Nikaido, T.; Ohmoto, T.; Sankawa, U. *Chem. Pharm. Bull.* **1984**, *32*, 1872.
(3) (a) Ohmoto, T.; Tankaka, R.; Nikado, T. *Chem. Pharm. Bull.* **1976**, *24*, 1532. (b) Ohmoto, T.; Koike, K.; Sakamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 390. (c) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1983**, *31*, 3198. (d) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1984**, *32*, 3579. (e) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1986**, *34*, 2090.
(4) (a) Awad, A. T.; Beal, J. L.; Talapatra, S. K.; Cave, M. P. *J. Pharm. Sci.* **1976**, *56*, 279. (b) Kahn, S. A.; Shamussuddin, K. M. *Phytochemistry* **1986**, *20*, 2062. (c) Fukamiya, N.; Okano, M.; Aratani, T. *J. Nat. Prod.* **1986**, *49*, 428. (d) Viola, B. Thesis, Universite de Paris–Sud Centre d'Orsay, France, 1971.
(5) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1982**, *30*, 1204.
(6) Anderson, L. A.; Harris, A.; Phillipson, J. D. *J. Nat. Prod.* **1983**, *46*, 374.
(7) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933. Campus, O.; DiPerro, M.; Cain, M.; Mantei, R.; Gawish, A.; Cook, J. M. *Heterocycles* **1980**, *14*, 975.
(8) Murakami, Y.; Yokoyama, Y.; Aoke, C.; Miyagi, C.; Watanabe, T.; Ohmoto, T. *Heterocycles* **1987**, *26*, 875.
(9) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089.
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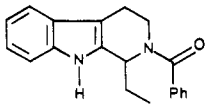
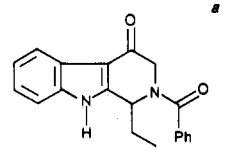
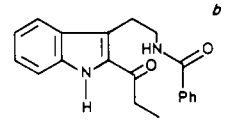
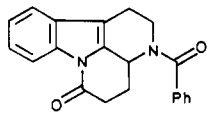
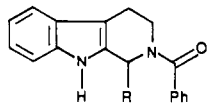
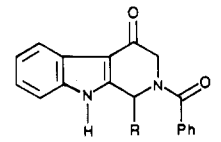
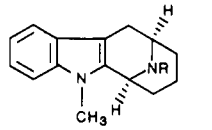
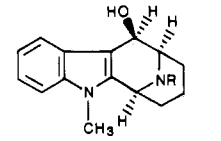
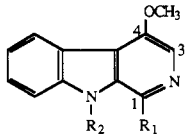
(12) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.
(13) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293.
(14) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907.
(15) Gata, F.; Misiti, D. J. *J. Heterocycl. Chem.* **1987**, *42*, 1213.
(16) Rosenmund, P.; Trommer, W.; Corn-Zachertz, D.; Ewerdwalbesloh, U. *Justus Liebigs Ann. Chem.* **1979**, 1643.
(17) Cain, M. Ph.D. Thesis, University of Wisconsin–Milwaukee, 1982, and references cited therein.

0022-3263/89/1954-2170$01.50/0

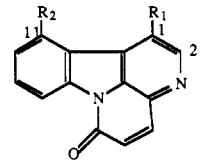
Table I. DDQ Oxidation of Substituted 1,2,3,4-Tetrahydro-β-carbolines

entry	substrate	solvent	reaction conditions	products	% yield	ref
1	 **3**	THF/H_2O	−78 °C → rt	 **4** [a]	71	7
				 **5** [b]	14	7
2	 **9**	THF/H_2O	−78 °C → rt	no reaction		17
3	 **17**	THF/H_2O	−60 °C → rt	 **18**, R = H	56	
4	 **15**, R = COPh	THF/H_2O	rt	 **16**	95	17

[a] These 4-oxo-1,2,3,4-tetrahydro-β-carbolines are also described as 3-acylindoles in the text. [b] These 2-acylindoles are formerly derived from oxidation at position 1 of a 1,2,3,4-tetrahydro-β-carboline.



1a, $R_1 = CH_2CH_3$, $R_2 = H$
1b, $R_1 = CH{=}CH_2$, $R_2 = H$
1c, $R_1 = CH_2CH_2OH$, $R_2 = H$
1d, $R_1 = CH(OH)CH_2OH$, $R_2 = H$
1e, $R_1 = CH(OCH_3)CH_2OH$, $R_2 = H$
1f, $R_1 = COCH_3$, $R_2 = H$
1g, $R_1 = COOCH_3$, $R_2 = H$
1h, $R_1 = CH{=}CH_2$, $R_2 = OCH_3$



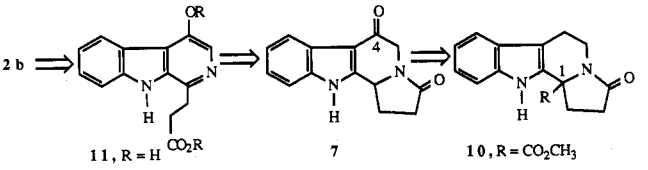
2a, $R_1 = R_2 = H$
2b, $R_1 = OCH_3$, $R_2 = H$
2c, $R_1 = OH$, $R_2 = H$
2d, $R_1 = H$, $R_2 = OH$
2e, $R_1 = R_2 = OCH_3$

Figure 1. Representative examples of 4-methoxy-substituted β-carboline alkaloids.

indole;[7,12,13] consequently, the regiochemistry of the oxidation can better be controlled than in the corresponding case with selenium dioxide.[14] For this reason, a route toward **2b** that centered on the use of DDQ was pursued.

Recently, during work directed toward the synthesis of crenatine (**1a**),[7] it was found that oxidation of amide **3** (Table I, entry 1) when performed at room temperature gave **4** (3-acylindole) and **5** (2-acylindole) in a ratio of 1:1, while this increased to 5:1 at −78 °C. Disappointingly, treatment of the γ-lactam **6** with DDQ (aqueous THF)

Scheme II

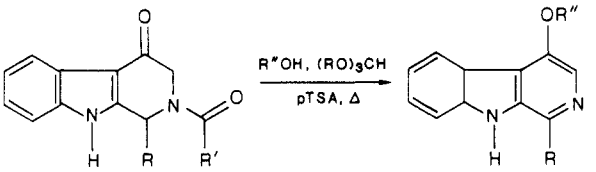


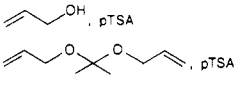
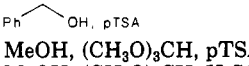
even at low temperature, according to the method of Cain,[7,17] failed to produce the desired 3-acylindole **7**. However, when the oxidation was carried out in methanol at −78 °C, the methyl ether **8** was obtained in 48% yield. In this case the DDQ oxidation has occurred at both positions 1 and 4 despite previous work which indicated that low temperature would favor oxidation at the desired carbon atom (position 4).

In a related study (Table I, entry 2), the DDQ-mediated oxidation of the hexahydrocanthin-6-one **9** was attempted. The hexahydrocanthin-6-one ring system was easily constructed via the reaction between N_b-benzyltryptamine and 2-ketoglutaric acid.[7,17] It was hoped that oxidation of **9** would provide the desired 1-oxohexahydrocanthin-6-one. Unfortunately, on reaction of **9** with DDQ (see Table I) the necessary blue-colored charge-transfer complex was not observed, and the reaction returned only starting **9**. Similarly, treatment of either **4** or **5** with DDQ, under the analogous conditions, provided no evidence to support formation of the charge transfer complex. The presence of electron-withdrawing groups at position 1, 2, or 3 of the indole prevents the formation of the necessary charge-transfer complex[7,12,17] and limits the approaches to these 1-oxo-substituted systems.

(18) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. Braude, E. A.; Jackman, L. M.; Linstead, R. P. *J. Chem. Soc.* **1954**, 3548. Braude, E. A.; Jackman, L. M.; Linstead, R. P. *J. Chem. Soc.* **1954**, 3564. Jackman, L. M. *Adv. Org. Chem.* **1960**, *2*, 329. Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand. (B)* **1976**, *30*, 853.

Table II. Synthesis of 4-Alkoxy-β-carbolines



entry	substrate	added reagents	reaction conditions	product	% yield
1	18, R = H, R′ = Ph	MeOH, $(MeO)_3CH$, pTSA	3 days, reflux	**19a**, R = H, R″ = CH_3	64
2	18	EtOH, $(EtO)_3CH$, pTSA	3 days, reflux	**19b**, R = H, R″ = C_2H_5	70
3	18		3 days, 75–80 °C	**19c**, R = H, R″ = $CH_2CH{=}CH_2$	38
4	18		3 days, 75–80 °C	**19d**, R = H, R″ = CH_2Ph	36
5	4, R = C_2H_5, R′ = Ph	MeOH, $(CH_3O)_3CH$, pTSA	1 day, reflux	**1a**, R = C_2H_5, R″ = CH_3	42
6	22, R = C_2H_5, R′ = CCl_3	MeOH, $(CH_3O)_3CH$, H_2SO_4	1 day, reflux	**1a**, R = C_2H_5, R″ = CH_3	48

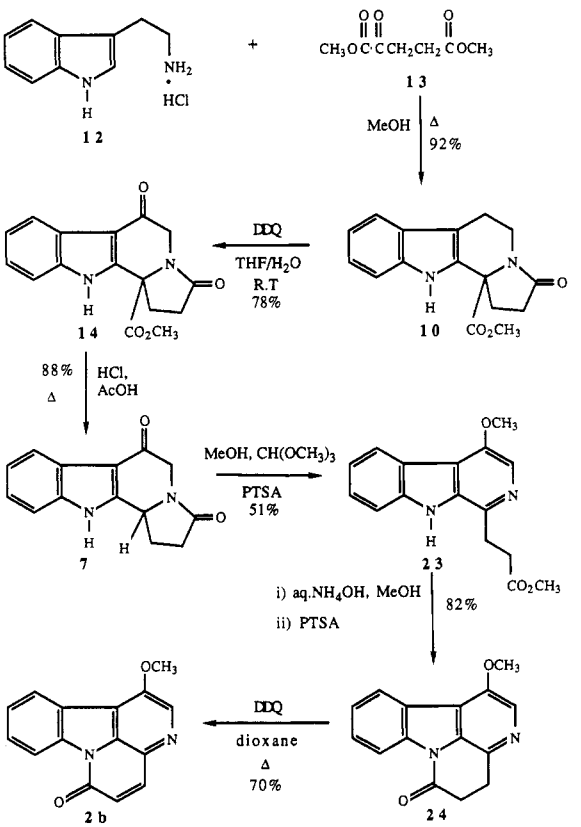
Results and Discussions

With particular regard to the observations detailed above, a retrosynthetic analysis of 1-methoxycanthin-6-one (**2b**) is depicted in Scheme II. It was decided to begin efforts toward the preparation of the 1-substituted (blocked) tetrahydro-β-carboline **10** in order to direct the regiochemistry of the DDQ oxidation toward position 4, rather than to positions 1 and 4 (Scheme I). Hydrolysis of the labile ester function at C-1[21] would provide keto amide **7**, which presumably could be hydrolyzed and oxidized to the phenolic (desmethyl) derivative of **11** (R = H). Formation of the aromatic β-carboline nucleus would prevent facile relactamization to **7** and promote cyclization of **11** to the canthin-6-one skeleton.

In this regard, the dimethyl ester of 2-ketoglutaric acid **13** was reacted with tryptamine hydrochloride **12** in refluxing methanol to provide the desired lactam **10** in 92% yield, as illustrated in Scheme III. During this process a Pictet–Spengler cyclization had occurred and the γ-lactam **10** had formed in a one-pot reaction. The lactam **10** could also be obtained by heating the free base of tryptamine with **13** in refluxing benzene. The highly electrophilic nature of the iminium ion is responsible for the effective cyclization in nonacidic aprotic media.[9,19] The γ-lactam **10** contains the necessary carbon atoms for the synthesis of **2b**; moreover, both the N_b-nitrogen atom and C-1 are protected from interaction with DDQ. In fact, when **10** was stirred with DDQ (≃1:2) in aqueous THF at room temperature, the desired 3-acylindole (4-oxo-THBC) **14** was obtained in good yield. Under the conditions (2 equiv of DDQ, −70 °C) earlier reported by Cain,[17] only the corresponding 4-hydroxy-1,2,3,4-tetrahydro-β-carboline was obtained. It is believed that steric hindrance from the newly generated 4-hydroxyl group and the substituent at C-1 prevent (at low temperature) the formation of the second charge-transfer complex required for the conversion of the 4-hydroxy derivative of **10** into ketone **14**. This is not without precedent (see **15** → **16**, Table I and ref 17 for details).

In order to remove the ester protecting group from C-1 and convert the γ-lactam of **14** into the δ-lactam present in **2b**, ester **14** was heated in HCl/HOAc, according to the procedure of Hobson.[20] This resulted in formation of 3-acylindole **7** in 88% yield; however, none of the δ-lactam

Scheme III

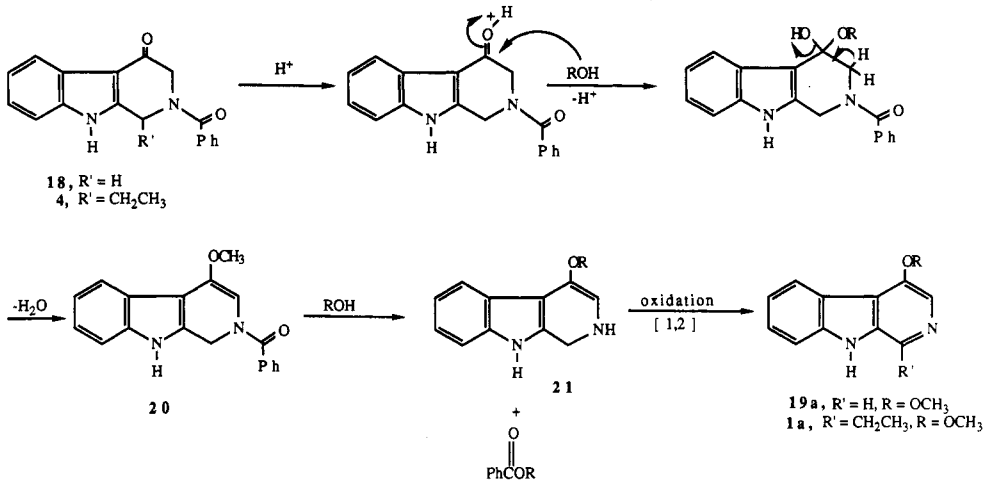


was observed. In agreement with the original plan the ester at C-1 had been easily removed on treatment with acid.[21] The γ-lactam of **7**, however, proved to be resistant to hydrolysis under a variety of conditions.[2a] Moreover, the use of aqueous sodium peroxide,[22] which has been employed for amides found to be reluctant to hydrolysis, led only to decomposition products, many of which reflected the destruction of the indole system.

In order to facilitate cleavage of the γ-lactam to provide the δ-lactam, it was decided to form the enol ether of the 3-acylindole **7**. This would provide a 1,2-dihydro-β-carboline, congeners of which are known to readily undergo oxidation (O_2, air) or disproportionation to provide the

(19) 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.
(20) Hobson, J. D.; Raines, J.; Whiteoak, R. *J. Chem. Soc.* **1963**, 3495.
(21) Hahn, G.; Hansel, A. *Chem. Ber.* **1938**, *71*, 2163. Corsano, S.; Algieri, S. *Ann. Chim. (Italy)* **1960**, *50*, 75.
(22) Vaughan, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187.

Scheme IV



fully aromatic β-carbolines.[19,23] The acylpyridinium species generated in this process would be activated toward hydrolysis; moreover, the propionic acid function at C-1 would be prohibited from recyclization to the γ-lactam (see **11**, Scheme II). To examine this hypothesis 4-oxo-2-benzoyl-1,2,3,4-tetrahydro-β-carboline (**18**) was chosen as a substrate (Table II, entry 1). When **18** was heated with trimethyl orthoformate in methanol in the presence of *p*-toluenesulfonic acid (pTSA), a reasonable yield of 4-methoxy-β-carboline **19a** was realized (Table II, entry 1). Although the yield was only 64%, four steps had occurred in a one-pot reaction (see below). This alkoxylation–oxidation proved to be general for **18** and gave 3-ethoxy-β-carboline (**19b**) in 70% yield when heated in ethanol [pTSA, $(EtO)_3CH$]; however, the yields decreased in the case of the allyloxy (**19c**) (Table II, entry 3) and benzyloxy (**19d**) β-carbolines. This is presumably due to carbocation-mediated side reactions in the cases of the allyl and benzyl alcohols. In the two reactions (Table II, entries 1 and 2) examined closely, methyl and ethyl benzoate were isolated, respectively, which resulted from alcoholysis of the 2-benzoyl group of **18**. The trialkyl orthoformate functions as a water scavenger for reaction of **18** with ethanol, and pTSA in the presence of trimethyl orthoformate gave 4-ethoxy-β-carboline (**19d**), accompanied by only trace amounts (<4%) of the 4-methoxy derivative **19a**. Attempts to execute a similar crossover experiment with allyl alcohol resulted only in isolation of 4-oxo-1,2,3,4-tetrahydro-β-carboline. In addition, 4-oxo-1,2,3,4-tetrahydrocarbazole,[24] when treated under these conditions, did not yield 4-methoxycarbazole or the corresponding enol ether intermediate. The addition of $Cu(OAc)_2$[25] or 5% Pd/C to the reaction mixture as oxidants did not improve the yields. A proposed mechanism for this transformation is outlined for **18** in Scheme IV. Formation of the hemiketal of **18**, followed by loss of water, would generate the desired enol ether **20**. The amide, which is now activated to hydrolysis, could undergo reaction with methanol to provide the 1,2-dihydro-β-carboline **21**. Intermediates of this type are known to undergo oxidation–disproportionation[13,23] to provide β-carbolines in related systems. It is also conceivable that the 1,2-dihydro-β-carboline **20** may initially undergo oxidation–disproportionation to generate an acylpyridinium intermediate, followed by hydrolysis to give **19a**. Experiments designed to determine which of these pathways predominates have been unsuccessful, to date.

Examination of the intermediates in Scheme IV clearly demonstrates that four different steps have taken place in this one-pot reaction. Advantage was taken of this methoxylation–oxidation process to provide an improved synthesis of crenatine (**1a**). When 1-ethyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**4**) was heated in methanol and trimethyl orthoformate in the presence of pTSA (Table II, entry 5), **1a** was obtained in 42% yield; moreover, reaction of the 4-oxo-2-trichloroacetamide derivative **22** (Table II, entry 6) under similar conditions [CH_3OH, $(CH_3O)_3CH$, H_2SO_4] gave **1a** in 48% yield. This constitutes a four-step preparation of crenatine (**1a**) in contrast to the seven-step process previously reported from our laboratory[7] and illustrates that the synthesis of 4-oxo-β-carbolines via the DDQ process[7,12] is shorter and more efficient than the acylation approach (12 steps) reported recently by Murakami et al.[8]

Upon completion of the conversion of 4-oxotetrahydro-β-carboline into 4-alkoxy-β-carbolines (Table II), attention returned to the synthesis of **2b**. The keto lactam **7** (Scheme III) was heated with trimethylorthoformate in methanol in the presence of pTSA to provide a 51% yield of 4-methoxy-1-(3-carbomethoxypropyl)-β-carboline (**23**). The ester group that remained was hydrolyzed with aqueous ammonia in quantitative yield, followed by heating of the residual solid in the presence of pTSA to furnish 1-methoxy-4,5-dihydrocanthin-6-one (**24**) in 82% yield from **23**. This material **24** was subjected to dehydrogenation with DDQ in refluxing dioxane to provide 1-methoxycanthin-6-one (**2b**) in good yield, as illustrated in Scheme III. The IR and proton NMR spectra of **2b** were identical with those reported in the literature.[3a] This seven-step synthesis of **2b** proceeds in an overall yield of 20% starting from tryptamine **12** and dimethyl 2-ketoglutarate **13**.

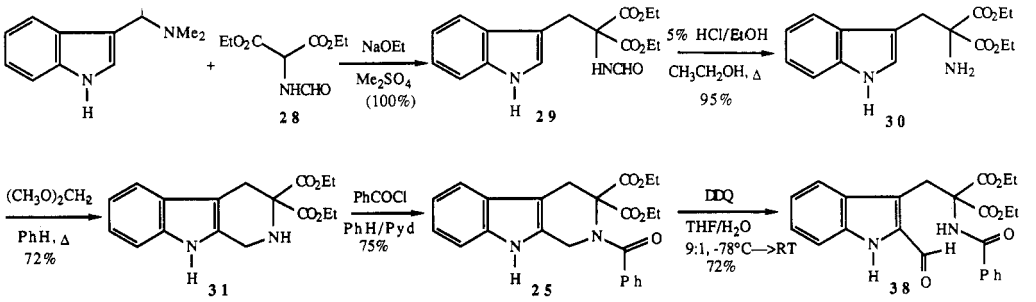
Although the DDQ oxidations discussed above have been designed necessarily to provide 4-oxo-1,2,3,4-tetrahydro-β-carbolines, a study of the geometric and electronic constraints placed on the indole–DDQ charge transfer complex has resulted in the regiospecific preparation of 1-oxotetrahydro-β-carbolines (see Schemes V and VI). The syntheses of the substrates **25** and **26** required for this study are outlined in Schemes V and VI, respectively. The 2-benzoyl-3,3-disubstituted-1,2,3,4-tetrahydro-β-carboline

(23) Fukada, N.; Trudell, M. L.; Johnson, B.; Cook, J. M. *Tetrahedron Lett.* **1985**, *26*, 2139. Also see: Lifer, S. M.S. Thesis, University of Wisconsin—Milwaukee, Milwaukee, WI, 1987.

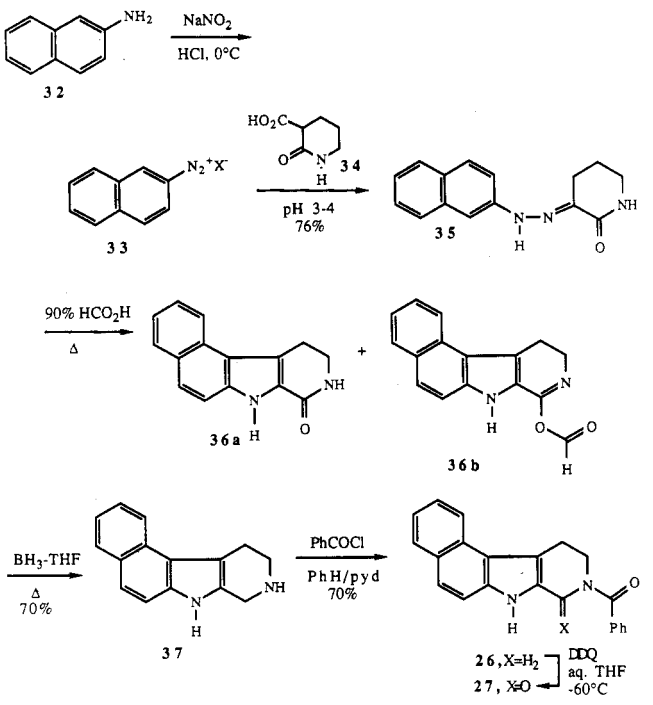
(24) Schultz, C. M.S. Thesis, University of Wisconsin—Milwaukee, Milwaukee, WI, 1987. Mann, F. G.; Wilcox, T. J. *J. Chem. Soc.* **1958**, 1525.

(25) Bell, T. W.; Rothenberger, S. D. *Tetrahedron Lett.* **1987**, *28*, 4817.

Scheme V



Scheme VI

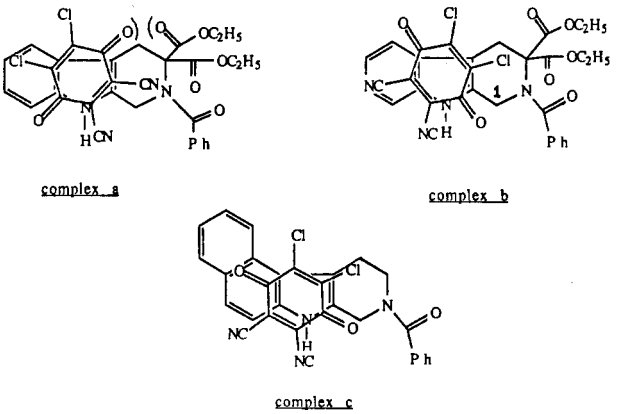


25 was prepared by the sequence outlined in Scheme V. Gramine was reacted with diethyl formamidomalonate (**28**) in the presence of sodium ethoxide to provide the tryptamine derivative **29**, according to the procedure of Albertson et al.[26] The formyl group was removed on hydrolysis to generate the amine **30** in 96% yield, the product of which was subjected to a Pictet–Spengler reaction under aprotic conditions[19] with dimethoxymethane in the presence of trifluoroacetic acid.[27] This process furnished the desired 3,3-disubstituted tetrahydro-β-carboline **31** in 72% yield. The N_b-nitrogen function of **31** was then converted into the amide (see **25**) to prevent its interaction with DDQ.

Synthesis of the 5,6-benzosubstituted tetrahydro-β-carboline **26** was executed according to the protocol illustrated in Scheme VI. A Japp–Klingeman reaction between the 2-naphthyldiazonium salt **33** (from **32**, Scheme VI) and 3-carboxy-2-piperidone (**34**) provided the corresponding hydrazone **35** in 76% yield under conditions described earlier by Abramovitch and Shapiro.[28] Fischer indole cyclization of **35** in 90% formic acid resulted in the formation of the desired 1-oxo-1,2,3,4-tetrahydro-β-carboline **36a** present as the major product, accompanied by the corresponding iminoformate **36b**. This mixture was reduced directly in borane–THF to provide the 5,6-benzosubstituted 1,2,3,4-tetrahydro-β-carboline **37** in 70% yield. The amine **37** was converted into the benzamide derivative **26** analogous to the conversion of **31** into **25** (Scheme V).

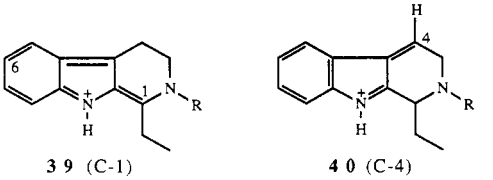
The stage was now set to examine the effect of substitution on the regiochemistry of the DDQ oxidation. When the 3,3-dicarbethoxy-1,2,3,4-tetrahydro-β-carboline **25** was treated with DDQ (THF/H_2O) at low temperature, a 72% yield of the 2-acylindole **38** was obtained. In addition, reaction of the 5,6-benzosubstituted tetrahydro-β-carboline **26**, under the analogous conditions, gave the 1-oxo-substituted derivative **27** to the exclusion of the 4-oxo isomer. It is believed that steric repulsion between the ester groups at C-3 of **25** and DDQ prevent formation of the charge transfer complex which correctly orients the proton at C-4 with the oxidizing agent (see complex a, Figure 2). However, the charge transfer complex can form with a different geometry, as illustrated for complex b, resulting in oxidation at C-1 of the β-carboline to yield **38**.

In the conversion of **26** into **27** (Scheme VI), the interactions that result in the observed regiochemistry (2-acylindole) are electronic rather than steric in nature. It is known that a charge-transfer complex must form between the indole 2–3 double bond and DDQ for oxidation to take place.[12,13,18] Depicted in Figure 3 are the two possible intermediates that lead to oxidation either at C-1 (**39**) or at C-4 (**40**) in tetrahydro-β-carbolines. The structures of these intermediates are in agreement with



complex a complex b complex c

Figure 2.



39 (C-1) **40** (C-4)

Figure 3.

(26) Albertson, N. F.; Archer, S.; Suter, C. M. *J. Am. Chem. Soc.* **1945**, *67*, 36.

(27) Plate, R.; van Hout, R. H. M.; Behm, H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 555. Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177.

(28) Abramovitch, R. A.; Shapiro, D. *J. Chem. Soc.* **1956**, 4589.

the proposed mechanism of this oxidation[12-14] and have been reviewed by Hagen in detail.[2a] Since the planar ring of the 5,6-benzo substituent in **26** is far removed from the site of oxidation, its effect on this process (C-1) results from stabilization of the transition state leading to intermediate **39** (Figure 3) via mesomeric effects. Stabilization of the transition state leading to intermediate **40**, which would result in oxidation at C-4, via the benzo substituent cannot occur to the same degree, consequently oxidation of **26** provides only 1-oxo-THBC **27**. The reactivity of **26** provides evidence for the effect of mesomeric stabilization in the course of this reaction, although secondary orbital effects[29] between **26** and DDQ (see complex c, Figure 2) may play some role in the observed regiochemistry.

In summary, the oxidation of 1,2,3,4-tetrahydro-β-carbolines with DDQ at low temperature continues to be the method of choice for the synthesis of 4-oxo-1,2,3,4-tetrahydro-β-carbolines.[2a,7,12,17] However, the choice of an α-keto ester for the Pictet–Spengler reaction provides a tetrahydro-β-carboline (see for example **10**, Scheme III), which carries a protecting group at position 1 and now permits facile oxidation of these systems at C-4 at room temperature. In addition, the conversion of these 4-oxo-tetrahydro-β-carbolines into 4-methoxy-β-carbolines via the methoxylation–oxidation sequence in yields of 50–70% provides entry into these systems in a four-step, one-pot reaction. This has resulted in a four-step synthesis of crenatine. In addition, the seven-step synthesis of **2b** described herein should provide a route to other oxygenated 1-methoxycanthin-6-one alkaloids with enhanced antileukemic activity[4c,6] (see **2e** for example), as well as entry into a host of 4-methoxy-β-carboline alkaloids, some of which are illustrated in Figure 1. The alkyloxylation–oxidation reaction has been shown to be general (Scheme IV and Table II) and has resulted in the synthesis of 4-methoxy-, 4-ethoxy-, 4-(allyloxy)-, and 4-(benzyloxy)-β-carbolines from **18** (Table II), although the yields in the latter two cases were poor.

Finally, consideration of the electronic effects on the intermediates in the DDQ oxidation has provided a means in which to direct the regiochemistry of the reaction toward position 1 (**26** → **27**), regiospecially, by stabilization of the transition state leading to intermediate **39** (Figure 3). Furthermore, steric parameters can also be manipulated to direct oxidation regiospecially, to position 1 of the 1,2,3,4-tetrahydro-β-carboline (see **25** → **38**). Further work directed toward the synthesis of 4-methoxy-β-carboline alkaloids is under way and will be reported in due course.

Experimental Section

Microanalysis was performed on a F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are reported uncorrected. Proton NMR spectra were recorded on a Varian EM-360 or a Bruker 250-MHz spectrometer, and ^{13}C NMR spectra were recorded on a Varian CFT-20 or a Bruker 250-MHz NMR spectrometer. Infrared spectra were taken on a Beckmann Acculab-1 instrument or a Mattson Polaris R-10400, while mass spectral data were obtained on a Hewlett-Packard 5855 GC–mass spectrometer.

All chemicals were purchased from Aldrich Chemical Co. unless otherwise stated. Analytical TLC plates used were E. Merck Brinkmann UV-active silica gel or alumina on plastic. Silica gel 60b and aluminum oxide for column chromatography were purchased from E. M. Laboratories and J. T. Baker, respectively. The TLC plates were visualized under UV light or developed with spray reagents. Alkaloids were visualized by utilizing Dragendorf's reagent, and the 1,2,3,4-tetrahydro-β-carbolines were visualized by using a saturated solution of ceric ammonium sulfate in 50% sulfuric acid. Drangendorf's reagent was prepared by adding a solution of bismuth subnitrate (8 g) in HNO_3 (70 mL, 30%) and an aqueous solution of potassium iodide (27.2 g, 50 mL) to water (100 mL), followed by filtration.

Methanol was dried over magnesium metal. DMF was distilled from $MgSO_4$, under reduced pressure. Tetrahydrofuran (THF) and dioxane were distilled after drying over sodium with benzophenone added as an oxygen and water scavenger. *tert*-Butyl alcohol was distilled from CaH_2, and anhydrous ethanol was obtained from U.S. Industrial Chemicals. 4-Oxocarbazole was prepared analogous to the method of Mann[24] and 4-oxo-2-benzoyl-1,2,3,4-tetrahydro-β-carboline was synthesized on 25-g scale (56% yield) via the method of Lifer.[23]

Dimethyl 2-Ketoglutarate (13). To an ethereal solution of diazomethane (400 mL, 0.3 mol) at 0 °C was slowly added 2-ketoglutaric acid (9.26 g, 0.063 mol). The reaction mixture was allowed to stir for 4 h, at which time the solution that resulted was colorless. The ether was extracted with $NaHCO_3$ (50 mL, saturated), followed by brine (75 mL, saturated), and then dried (Na_2SO_4). The solvent was removed under pressure to yield **13** as an oil (8.3 g, 76%): IR (neat) 2080, 1735 (br) cm^{-1}; ^1H NMR (CCl_4) δ 2.43 (t, 2 H, J = 5 Hz), 2.92 (t, 2 H, J = 5 Hz), 3.42 (s, 3 H), 3.60 (s, 3 H). The spectra of **13** were identical with those reported in the literature.[30]

Methyl 2,3,6,11-Tetrahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-11b(5*H*)-carboxylate (10). A solution of dimethyl 2-ketoglutarate **13** (7.8 g, 45 mmol) and tryptamine hydrochloride **12** (6.0 g, 30 mmol) in MeOH (300 mL) was heated at reflux for 20 h analogous to conditions reported by Maclaren.[31] The solvent was removed under reduced pressure to yield an oily solid, which was partitioned between EtOAc (300 mL) and aqueous HCl (1 N, 50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic extracts were combined and dried (Na_2CO_3). The solvent was removed under reduced pressure, followed by the addition of ether (50 mL). The precipitate that resulted was filtered to yield **10** (7.84 g, 92%); mp 221 °C; IR (KBr) 3220, 1732, 1683 cm^{-1}; ^1H NMR (250 MHz, Me_2SO-d_6) δ 2.17–2.36 (m, 4 H), 2.52 (m, 2 H), 2.88 (m, 1 H), 3.16 (s, 1 H), 3.77 (s, 3 H), 4.10 (m, 1 H), 7.05 (m, 1 H), 7.16 (m, 2 H), 7.44 (t, 2 H, J = 8.7 Hz), 11.29 (s, 1 H, indole NH); ^{13}C NMR (Me_2SO-d_6) δ 20.23 (t), 29.85 (t), 30.30 (t), 35.65 (t), 52.85 (q), 64.81 (s), 107.16 (s), 111.41 (d), 118.10 (d), 118.63 (d), 121.56 (d), 125.56 (s), 131.28 (s), 136.42 (s), 171.47 (s), 172.27 (s); mass spectrum (CI, CH_4), m/e 285 (M + 1, 100); EI (15 eV) m/e 284 (22), 225 ($-CO_2CH_3$, 100). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.86. Found: C, 67.72; H, 5.68; N, 9.92.

Pictet–Spengler Reaction in Aprotic Media.[19] The pH of an aqueous solution of tryptamine hydrochloride **12** (200 mg, 1.01 mmol) was adjusted to 8 with aqueous Na_2CO_3 (saturated), followed by extraction with $CHCl_3$ (4 × 25 mL). The $CHCl_3$ layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield tryptamine. The tryptamine was dissolved in benzene (30 mL), followed by the addition of dimethyl 2-ketoglutarate **13** (245 mg, 1.52 mmol). The solution that resulted was held at reflux for 60 h; a Dean–Stark trap was employed for water removal. The solvent was removed under reduced pressure, and upon the addition of ether a precipiitate formed to yield **10** (206 mg, 72%), identical in all respects with **10** prepared above: mp 211–214 °C; IR (KBr) 3220, 1732, and 1682 cm^{-1}.

Methyl 2,3,6,11-Tetrahydro-3,6-dioxo-1*H*-indolizino[8,7-*b*]indole-11b(5*H*)-carboxylate (14). The ester **10** (500 mg, 1.75 mmol) and DDQ (3.0 g, 13.3 mmol) were mixed together as powdered solids at −78 °C.[7] A cooled solution (−10 °C) of THF–H_2O (9:1, 50 mL) was added dropwise to the stirring solids. The reaction mixture was allowed to warm to room temperature over a period of 4.5 h. The solvent volume was reduced to 10 mL under reduced pressure, followed by the addition of EtOAc (175

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(31) Maclaren, J. A. *Aust. J. Chem.* **1977**, *30*, 2045.

mL). The organic layer was then washed with aqueous Na_2CO_3 (saturated, 4 × 200 mL) and brine (1 × 100 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield the ketone **14** (403 mg, 78%): mp 228–230 °C; IR (KBr) 1742, 1682 (br) cm^{-1}; ^1H NMR (250 MHz, Me_2SO-d_6) δ 2.46–2.60 (m, 4 H), 3.71 (s, 3 H), 3.86 (d, 1 H, J = 18 Hz), 4.44 (d, 1 H, J = 18 Hz), 7.26 (m, 2 H), 7.53 (d, 1 H, J = 7 Hz), 7.97 (d, 1 H, J = 7 Hz), 12.73 (s, 1 H, indole NH); ^{13}C NMR (Me_2SO-d_6) δ 29.10, 29.47, 47.12, 53.56, 64.52, 109.59, 112.48, 120.53, 122.55, 123.17, 123.80, 136.47, 147.30, 169.79, 172.81, 186.44; mass spectrum (Cl, CH_4), m/e 299 (M + 1, 100), 255 (–CO_2CH_3, 49.7). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.69; N, 9.39. Found: C, 64.76; H, 4.66; N, 9.17.

When **10** (500 mg, 1.75 mmol) was reacted with DDQ (780 mg, 3.5 mmol) under conditions analogous to those detailed above, starting ester **10** and the 4-hydroxy derivative of **10** were isolated. None of the desired ketone **14** was observed by (TLC). Furthermore, reaction of **10** with selenium dioxide (see ref 2a) gave the 4-hydroxy derivative of **10**, accompanied by **10**.

Improved Procedure. Methyl 2,3,6,11-Tetrahydro-3,6-dioxo-1*H*-indolizino[8,7-*b*]indole-11b(5*H*)-carboxylate (14). To a mixture of the two solids [ester **10** (10 g, 37 mmol) and DDQ (10 g)] was added THF–H_2O (250 mL, 9:1) at room temperature with stirring. The reaction slurry was allowed to stir at room temperature for 24 h, and additional quantities of DDQ (10 g) were added at 6- and 12-h intervals. The reaction mixture was then poured into EtOAc (600 mL) and extracted with $NaHCO_3$ (3 × 330 mL, saturated). The EtOAc layer was passed through a wash column of alumina (neutral), and the solvent was removed by evaporation to yield the ketone **14** (8.5 g, 77%), mp 228–230 °C, identical in all respects with **14** reported in the previous experiment.

11,11b-Dihydro-1*H*-indolizino[8,7-*b*]indole-3,6(2*H*,5*H*)-dione (7). A solution of the ester **14** (2.0 g, 6.7 mmol) in acetic acid (10 mL, glacial) and HCl (10 mL, concentrated) was held at reflux for 3 h.[20] The reaction mixture was cooled, and the solvent volume was reduced (5 mL) under reduced pressure, followed by the addition of aqueous $NaHCO_3$ (250 mL, saturated) and EtOAc (150 mL). The EtOAc extracts were combined, and washed with brine (150 mL, saturated), and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield the desired ketone **7** (1.42 g, 88%). An analytical sample was crystallized from CH_3OH: mp 273–274 °C; IR (KBr) 3160, 1660 (br) cm^{-1}; ^1H NMR (250 MHz, Me_2SO-d_6) δ 2.45 (m, 4 H), 3.76 (d, 1 H, J = 18 Hz), 4.41 (d, 1 H, J = 18 Hz), 5.26 (t, 1 H, J = 7.5 Hz), 7.22 (m, 2 H), 7.49 (m, 1 H), 7.95 (m, 1 H), 12.40 (s, 1 H, indole NH); mass spectrum (CI, CH_4), m/e 241 (M + 1, 100). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.03; N, 11.66. Found: C, 69.66; H, 5.07; N, 10.96.

Methyl 4-Methoxy-9*H*-pyrido[3,4-*b*]indole-1-propanoate (23). A solution of the ketone **7** (600 mg, 2.5 mmol) and pTSA (700 mg) in MeOH (100 mL) and trimethyl orthoformate (75 mL) was heated to reflux for 24 h. The reaction was then cooled to room temperature, and the solvent volume was reduced (5 mL) under reduced pressure. The oil which resulted was poured simultaneously onto aqueous HCl (1 N, 200 mL) and EtOAc (200 mL). The layers were separated, and the organic phase was extracted again with cold aqueous HCl (1 N, 2 × 200 mL). The aqueous extracts were combined, and ice was added (75 g). The pH was then adjusted to 10 with aqueous NH_4OH (concentrated). The aqueous portion was then extracted with EtOAc (3 × 150 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide the ester **23** (340 mg, 51%): mp 161–162 °C; IR (KBr) 3365, 1710 cm^{-1}; ^1H NMR (250 MHz, Me_2SO-d_6) δ 2.95 (t, 2 H, J = 7 Hz), 3.36 (t, 2 H, J = 7 Hz), 3.63 (s, 3 H), 4.10 (s, 3 H), 7.23 (m, 1 H), 7.50 (m, 1 H), 7.96 (s, 1 H), 8.42 (d, 1 H, J = 8 Hz), 9.22 (s, 1 H, indole NH); mass spectrum EI (15 eV) m/e 284 (58), 253 (–OCH_3, 7), 225 (–CO_2CH_3, 100). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.58; H, 5.67; N, 9.87. Found: C, 67.58; H, 5.68; N, 9.69.

4,5-Dihydro-1-methoxy-6*H*-indolo[3,2,1-*de*][1,5]-naphthyridin-6-one (24). A solution of the ester **23** (240 mg, 0.85 mmol) in CH_3OH (25 mL) and aqueous NH_4OH (25 mL, 6%) was heated to reflux for 2 h. The solvent was then removed under reduced pressure to afford the acid. The acid was directly converted into the lactam **24** without further purification. The solid was dissolved in a mixture of dioxane (60 mL) and benzene (40 mL), after which pTSA (430 mg) was added. The mixture was heated at reflux for 48 h; a Dean–Stark trap was employed for azeotropic removal of water. The solvent was then removed under reduced pressure, and the residue that resulted was taken up in $CHCl_3$ (500 mL) and washed with aqueous $NaHCO_3$ (100 mL, saturated). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide the lactam **24** (176 mg, 82%): mp 175–176 °C; IR (KBr) 3400, 1700, 1420, 1340 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.16 (t, 2 H, J = 7 Hz), 3.38 (t, 2 H, J = 7 Hz), 4.14 (s, 3 H), 7.4 (m, 2 H), 8.08 (s, 1 H), 8.17 (d, 1 H, J = 8 Hz), 8.45 (d, 1 H, J = 8 Hz); mass spectrum CI (CH_4), m/e 253 (M + 1); high-resolution mass spectrum calcd for $C_{15}H_{12}N_2O_2$ 252.0898, found 252.0908.

4,5-Dihydro-1-methoxy-6*H*-indolo[3,2,1-*de*][1,5]-naphthyridin-6-one (24) via NaH/DMF. To a solution of the ester **23** (20 mg, 0.07 mmol) in dry DMF (2 mL) was added sodium hydride (3 mg, 1.61 mmol). The reaction mixture was stirred at room temperature for 3 h. The mixture was poured onto EtOAc (100 mL) and H_2O (10 mL). The organic phase was separated and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a mixture (1:1) of the ester **23** and the desired δ-lactam **24** as determined by comparison to authentic material by ^1H NMR ($CDCl_3$) and TLC.

1-Methoxycanthin-6-one (2b). To a solution of 4,5-dihydro-1-methoxycanthin-6-one (**24**) (100 mg, 0.4 mmol) in dioxane (30 mL) was added DDQ (700 mg) with stirring. The solution that resulted was heated to reflux for 10 h, followed by addition of $CHCl_3$ (600 mL) to the reaction mixture. The organic solution was extracted with aqueous NH_4OH (3%, 2 × 40 mL) followed by brine (20 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a red solid. The product **2b** was purified by flash chromatography (silica gel; $CHCl_3$–EtOH, 9:1) to yield **2b** (68 mg, 70%): mp 250–253 °C (lit.[3a] mp 256 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 4.20 (s, 3 H), 6.85 (d, 1 H, J = 10 Hz), 7.52 (m, 1 H), 7.67 (m, 1 H), 7.99 (d, 1 H, J = 10 Hz), 8.22 (d, 1 H, J = 8 Hz), 8.49 (s, 1 H), 8.67 (d, 1 H), 8.67 (d, 1 H). The IR and proton NMR spectra were identical with those reported in the literature for **2b**.[3a]

4-Methoxy-β-carboline (19a). A mixture of the ketobenzamide **18** (0.290 g, 1.0 mmol), trimethyl orthoformate (0.106 g, 1.0 mmol), and anhydrous *p*-toluenesulfonic acid (0.244 g, 2.0 mmol) was heated to reflux in methanol. The reaction was monitored by TLC until the starting material was no longer detected (silica gel, 15% methanol–ethyl acetate, eluent). The solvent was removed under reduced pressure, and the residue was partitioned between saturated aqueous sodium carbonate and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was treated with anhydrous ether, and the precipitate was filtered and dried. Methyl benzoate was obtained from the etherial filtrate. The yield of **19a** was 64%: mp 223–225 °C; IR (KBr) 1620, 1580, 1510, 1450, 1330, 1320, 1120, 970, 730 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.15 (s, 3 H), 7.30 (m, 2 H), 7.50 (m, 2 H), 8.10 (s, 1 H), 8.20 (d, 1 H, J = 8.0 Hz), 8.60 (s, 1 H), 11.60 (s, 1 H); mass spectrum (CI, CH_4), m/e 199 (M + 1). Anal. Calcd for $C_{12}H_{10}N_2O \cdot {}^1/_3H_2O$: C, 70.58; H, 5.22; N, 13.72. Found: C, 70.76; H, 5.10; N, 13.72.

4-Ethoxy-β-carboline (19b). The procedure employed with **18** was analogous to that described above, except triethyl orthoformate and ethanol was used in place of their methyl congeners: yield 70%; mp 229–230 °C; IR (KBr) 3120, 3060, 1620, 1580, cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.50 (t, 3 H, J = 6.0 Hz), 4.40 (q, 2 H, J = 6.0 Hz), 7.20 (t, 1 H, J = 6.0 Hz), 7.50 (m, 2 H), 8.10 (d, 1 H, J = 8.0 Hz), 8.50 (s, 1 H), 11.5 (s, 1 H); MS (CI, CH_4) m/e 213 (M + 1). Anal. Calcd for $C_{13}H_{12}N_2O \cdot 0.20H_2O$: C, 72.36; H, 5.75; N, 12.98. Found: C, 72.82; H, 5.72; N, 12.61.

4-(Allyloxy)-β-carboline (19c). The ketobenzamide **18** (6.47 g, 22.3 mmol) was dissolved in allyl alcohol (500 mL), followed by addition of *p*-toluenesulfonic acid (1.0 g) and diallyloxy propane (3.48 g, 22.3 mmol). The mixture was heated to 75 °C for 4 days, while additional pTSA (1.0 g) was added at daily intervals. After 4 days the reaction mixture was cooled and quenched with aqueous Na_2CO_3 (1 N, 500 mL), followed by extraction with ethyl acetate (2 × 500 mL). The combined organic layers were washed with aqueous KOH (1 N, 2 × 500 mL) and brine (2 × 500 mL). The solvent was removed under reduced pressure, and the remaining

allyl alcohol was removed by flash distillation with dry benzene under reduced pressure. The reaction mixture was chromatographed on silica gel ($CHCl_3$ → 4% MeOH/$CHCl_3$), and the product was crystallized from ethyl acetate to yield **19c** (1.90 g, 38%): mp 180–182 °C; ^{1}H NMR (DMSO-d_6) δ 4.96 (d, J = 7 Hz, 2 H), 5.43 (d, J = 10 Hz, 1 H), 5.63 (d, J = 15 Hz, 1 H), 6.28 (m, 1 H), 7.30 (t, J = 8 Hz, 1 H), 7.56 (td, J_1 = 6 Hz, J_2 = 8 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H), 8.14 (s, 1 H), 8.26 (d, J = 6 Hz, 1 H), 8.63 (s, 1 H), 11.87 (s, br, 1 H); high-resolution mass spectrum calcd for $C_{14}H_{12}N_2O$ 224.0949, found 224.0939.

4-(Benzyloxy)-β-carboline (19d). The ketobenzamide **18** was converted into **19d** under analogous conditions to that described above except that benzyl alcohol and bis(benzyloxy)propane were substituted for the allyl analogues. The yield of **19d** was 36%: mp 194–196 °C; ^{1}H NMR (DMSO-d_6) δ 5.50 (s, 2 H), 7.00–7.60 (m, 8 H), 8.10 (d, J = 7 Hz, 1 H), 8.20 (s, 1 H), 8.50 (s, 1 H), 11.60 (s, 1 H); IR (KBr) 3140, 3080, 1620 cm^{-1}; mass spectrum (CI, CH_4), m/e 275 (M + 1). Anal. Calcd for $C_{18}H_{14}N_2O \cdot {}^1/_8H_2O$: C, 78.12; H, 5.15; N, 10.12. Found: C, 78.57; H, 5.15; N, 9.80.

Crenatine (1a). Method A. A solution composed of the ketone **4** (500 mg, 1.4 mmol) in methanol (15 mL), trimethyl orthoformate (3 mL), and an acid catalyst (H_2SO_4, concentrated, 1 drop) was heated at reflux for 24 h with stirring. The solvent was removed under reduced pressure, and the residue that resulted was dissolved in EtOAc (100 mL). The organic layer was washed both with aqueous $NaHCO_3$ (50 mL, saturated) and aqueous dilute HCl (2 N, 3 × 50 mL). The acidic aqueous extracts were combined, and the pH of the solution was adjusted to 8 (Na_2CO_3, solid), followed by extraction with EtOAc (3 × 75 mL). The EtOAc extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide **11** (120 mg, 48%), the spectral properties of which were identical in all respects with those of crenatine (mp 168 °C, lit.[7] mp 174 °C).

Method B. The ketone **22** was reacted under the same conditions as above in the presence of pTSA rather than H_2SO_4 to provide a 42% yield of crenatine (**1a**).

Attempted Reaction of 4-Oxo-1,2,3,4-tetrahydrocarbazole with Methanol and Trimethyl Orthoformate. A sample of 4-keto-1,2,3,4-tetrahydrocarbazole (185 mg, 1 mmol), prepared by the method of Mann,[24] was mixed with trimethyl orthoformate (106 mg, 1 mmol), pTSA (342 mg, 2 mmol), and methanol (20 mL) and heated to reflux for 3 days. No evidence for the formation of an enol ether or the carbazole was found on analysis of the reaction mixture by TLC. Starting material was recovered after workup, as confirmed by proton NMR spectroscopy (250 MHz).

2-Benzoyl-4-oxo-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (18). A 500-mL round-bottom flask was cooled to −60 °C (EtOAc/dry ice) and charged with a mixture of finely powdered amide **17** (5.0 g, 18.1 mmol) and DDQ (7.3 g, 32.2 mmol). A solution of THF/water (50 mL, 9:1, −60 °C) was added in one portion, followed by addition of THF (50 mL, −60 °C). The blue solution that resulted was stirred for 2–3 h and allowed to warm to 0 °C, after which the cooling bath was removed. The solution was allowed to continue warming to room temperature and was stirred for an additional hour at this temperature. (THF purchased from J. T. Baker Chemical Co.)

The reaction mixture was quenched with aqueous KOH (1 N, 300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with aqueous HCl (1 N, 1 × 300 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oil that resulted was crystallized from EtOAc to yield **18** (2.9 g, 56%): mp 229 °C; IR (KBr) 3220, 1670, 1628 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.13 (s, 1.1 H), 4.44 (s, 0.9 H), 4.92 (s, 0.9 H), 5.17 (s, 1.1 H), 7.19 (m, 2 H), 7.49 (m, 6 H), 7.92 (d, 1 H, J = 7.5 Hz), 11.97 (s, 0.4 H), 12.25 (s, 0.6 H); mass spectrum (CI, CH_4), m/e (relative intensity) 319 (M + 29, 18), 291 (M + 1, 100). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.84; N, 9.65. Found: C, 74.59; H, 4.89; N, 9.54.

Reaction of Ketobenzamide 18 with Ethanol in the Presence of Trimethyl Orthoformate. A mixture of the ketobenzamide **18** (0.145 g, 0.5 mmol), trimethyl orthoformate (0.530 g, 5 mmol), and absolute ethanol (30 mL) was held at reflux for 2 days. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and concentrated. The 4-ethoxy-β-carboline (**19b**) (0.037 g), was predicitated from the medium on the addition of ether. The ^{1}H NMR spectrum of this sample contained signals corresponding only to 4-ethoxy-β-carboline (**19b**), but the mass spectrum contained peaks corresponding to both **19b** [212 (M^+), 100%] and 4-methoxy-β-carboline (**19a**) [198 (M^+), 4%], albeit the methoxy congener was present in less than 4% yield. No attempts to maximize the yield of this reaction have been made.

A similar experiment executed with allyl alcohol in place of the ethanol resulted only in the isolation of 4-oxo-1,2,3,4-tetrahydro-β-carboline and in low yield.

Ethyl 2-Formamido-3-(3-indolyl)-2-carbethoxypropionate (29). This compound was prepared according to published procedures.[26] Sodium (0.23 g, 10 mmol) was dissolved in absolute ethanol (30 mL). Gramine (1.74 g, 10 mmol) and ethyl formamidomalonate (**28**) (2.03 g, 10 mmol) were added to this solution followed by the slow addition of dimethyl sulfate (2.52 g). The solution was allowed to stand at room temperature for 4 h, and the white precipitate that formed was poured into water, filtered, and dried. The yield of the title compound **29** was 99%: mp 179–180 °C (lit.[32] mp 179–180 °C); ^{1}H NMR (Me_2SO-d_6) δ 1.13 (t, J = 7 Hz, 6 H), 3.60 (s, 2 H), 4.05 (q, J = 7 Hz, 4 H), 6.8–7.5 (m, 5 H), 7.87 (s, 1 H), 8.33 (br s, 1 H), 10.69 (br s, 1 H); IR (KBr) 3370, 3318, 1745 cm^{-1}; mass spectrum CI (CH_4), m/e 333 (M + 1).

Ethyl 2-Amino-3-(3-indolyl)-2-carbethoxypropionate (30). The indolyl amido ester **29** (1.65 g, 5 mmol) was treated with 5% ethanolic hydrochloride acid (5 mL, 5.5 mL of 38% aqueous HCl in 60 mL of absolute ethanol), and the mixture was heated to reflux. The heating was continued until the reaction was complete by TLC. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to yield the amine **30** (1.44 g, 95%): ^{1}H NMR (Me_2SO-d_6) δ 1.20 (t, J = 7.0 Hz, 6 H), 2.10 (b s, 2 H, NH_2), 3.25 (s, 2 H), 4.10 (q, J = 7.0 Hz, 4 H), 6.90 (t, J = 8.0 Hz, 1 H), 7.00 (t, J = 8.0 Hz, 1 H), 7.10 (s, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H); IR (neat) 3400, 2980, 1730, 1580, 1450, 1200, 1020, 720 cm^{-1}; mass spectrum CI (CH_4), m/e 305 (M + 1). This material was used directly in the next experiment.

3,3-Dicarbethoxy-1,2,3,4-tetrahydro-β-carboline (31). The amino ester **30** (1.4 g, 4.6 mmol) and dimethoxymethane (0.7 g, 9.2 mmol) were heated to reflux in a mixture of benzene (25 mL) and trifluoroacetic acid (1.71 g, 15 mmol). The progress of the reaction was monitored by TLC (5% MeOH–EtOAc), and the spots were visualized with a solution of ceric ammonium sulfate. When the reaction was complete, the solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield an oil, **31** (1.05 g, 72%): ^{1}H NMR (Me_2SO-d_6) δ 1.20 (t, J = 7.0 Hz, 6 H), 3.20 (s, 2 H), 3.80 (s, 2 H), 4.00 (m, 4 H), 7.0 (m, 2 H), 7.2 (d, J = 8.0 Hz, 1 H), 7.4 (d, J = 8.0 Hz, 1 H), 10.5 (s, 1 H); IR (neat) 3400, 2980, 1735, 1675, 1480, 1220 cm^{-1}; mass spectrum CI (CH_4), m/e 317 (M + 1). Anal. Calcd for the hydrochloride salt $C_{17}H_{20}N_2O_4 \cdot HCl$: C, 57.95; H, 5.68; N, 7.95. Found: C, 57.46; H, 6.04; N, 7.86.

2-Benzoyl-3,3-dicarbethoxy-1,2,3,4-tetrahydro-β-carboline (25). The 3,3-disubstituted tetrahydro-β-carboline **31** (3.00 g, 9.5 mmol) was stirred with benzoyl chloride (1.46 g, 10.45 mmol) in a mixture of benzene (45 mL) and pyridine (25 mL) at 0 °C and allowed to warm to room temperature overnight. Water was added, and the benzene layer was separated. The aqueous layer was extracted with benzene, and the combined organic layers were dried (Na_2SO_4). The organic layer was removed under reduced pressure, after which the residue was dissolved in ethyl acetate and left in the refrigerator overnight. On addition of ether to the cooled solution a while solid precipitated. It was filtered and dried to provide **25** (2.99 g) in 75% yield: mp 129 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.10 (t, J = 7.0 Hz, 6 H), 3.40 (s, 2 H), 4.00 (m, 4 H), 4.70 (s, 2 H), 7.00 (m, 2 H), 7.20 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.60 (s, 5 H), 10.50 (s, 1 H); IR (KBr) 3400, 3060, 2980, 1740, 1650 cm^{-1}; mass spectrum CI (CH_4), m/e 421 (M + 1). Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.57; H, 5.71; N, 6.67.

(32) Hengartner, V.; Batcho, A. D.; Blount, T. F.; Leimgruber, W.; Larsheid, M. E.; Schott, J. W. *J. Org. Chem.* **1979**, *44*, 3748.

Found: C, 68.14; H, 5.67; N, 6.58.

Oxidation of Benzamide 25 with DDQ To Provide 38. The benzamide **25** (840 mg, 2 mmol) and DDQ (900 mg, 4 mmol) were admixed and cooled to −78 °C. A solution of THF/H_2O (10 mL, 9:1 ratio) was also cooled to −78 °C, and the cooled THF solution was added to the solid material with stirring. The blue-colored reaction mixture that resulted was allowed to warm to room temperature over a period of 4 h. The solution was quenched with aqueous KOH (1 N), followed by extraction with ethyl acetate (4 × 50 mL). The organic layer was washed with aqueous HCl (0.1 N) and water and dried (K_2CO_3). The organic layer was percolated through a column of neutral alumina, and the solvent was removed under reduced pressure to give the indole aldehyde **38** (626 mg, 72%): mp 168 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.20 (t, J = 6 Hz, 6 H), 4.20 (m and s, 6 H), 7.00–7.70 (m, 9 H), 8.00 (s, 1 H) 9.70 (s, 1 H), 11.80 (s, 1 H); IR (KBr) 3400, 3100, 2980, 1740, 1650, 1200, 860, 740 cm^{-1}; mass spectrum CI (CH_4), m/e 437 (M + 1). Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.05; H, 5.50; N, 6.42. Found: C, 65.86; H, 5.58; N, 6.36.

Piperidine-2,3-dione 2-Naphthylhydrazone (35). The 2-naphthylamine (**32**) (2.86 g, 20 mmol) was dissolved in a mixture of aqueous HCl (concentrated, 5.5 mL) and water (30 mL) after which it was diazotized at 0 °C with sodium nitrite (1.8 g), which had been dissolved in H_2O (5 mL). After being stirred for 30 min, the solution was neutralized with urea and 10% aqueous Na_2CO_3 (25 mL). The solution was then filtered directly into a solution of 2-oxopiperidine-3-carboxylic acid (**34**) (20 mmol), which had been prepared in situ at 30 °C for 3-carbethoxy-2-oxopiperidine (3.4 g, 20 mmol) and KOH (1.2 g) in water (40 mL). The latter solution had been allowed to stand overnight before addition to complete the hydrolysis. The reaction mixture was brought to pH 3–4 at 0 °C on the addition of glacial acetic acid, and the mixture that resulted was stirred for 4 h. The precipitate that formed was stored in a refrigerator overnight, filtered, and dried to provide a red solid **35** (3.93 g, 76%): mp 219–220 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.90 (m, 2 H), 2.70 (t, J = 6.0 Hz, 2 H), 3.20 (m, 2 H), 7.20–7.90 (m, 8 H); mass spectrum CI (CH_4), m/e 255 (M + 1). This material was used directly in the next step.

Fischer Indole Cyclization of Hydrazone 35.[28] The hydrazone **35** (3.0 g, 11.85 mmol) was treated with formic acid (12 mL, 90%) and heated to reflux for 30 min. The reaction mixture was cooled and diluted with water. The precipitate that formed was filtered and dried (2.50 g). Examination of ^{1}H NMR data of the crude product indicated that 1-oxo-β-carboline (**36a**) comprised the majority of the material accompanied by **36b** as a minor product in approximately a 4:1 ratio: ^{1}H NMR (Me_2SO-d_6) for **36a** δ 3.30 (m, 2 H), 3.60 (m, 2 H), 7.50–8.40 (m, 6 H and CONH), 12.20 (s, 1 H); IR (KBr) 1635 cm^{-1}; mass spectrum CI (CH_4), m/e 237 (M + 1); for **36b** ^{1}H NMR (Me_2SO-d_6) δ 3.50 (t, J = 6.0 Hz, 2 H), 4.20 (t, J = 6.0 Hz, 2 H); IR (KBr) 1695 cm^{-1} (formate); mass spectrum CI (CH_4), m/e 265 (M + 1). This material was employed directly in the next step.

5,6-Benzo-1,2,3,4-tetrahydro-β-carboline (37). A mixture of 1-oxo-β-carboline (**36a**) and the iminoformate **36b** (1.18 g) was treated with BH_3–THF (20 mL, 1 M solution), and the solution was heated to reflux for 24 h. The reaction mixture was carefully quenched with methanol, and the solvent was removed under reduced pressure. The residue was treated with aqueous HCl (100 mL, 2 N) and heated to reflux for 3 h. The solution was cooled, neutralized with aqueous NH_4OH (concentrated) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to provide **37** (0.77 g, 70%): mp 132–133 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.30–3.60 (m, 4 H), 4.25 (s, 2 H), 7.30–7.70 (m, 4 H), 7.95 (d, J = 8.0 Hz, 1 H), 8.30 (d, J = 8.0 Hz, 1 H), 11.30 (s, 1 H); IR (KBr) 3200, 2900, 2860, 1370, 780, 730 cm^{-1}; mass spectrum CI (CH_4), m/e 223 (M + 1). Anal. Calcd for $C_{15}H_{14}N_2$·HCl·0.25H_2O: C, 68.57; H, 5.90; N, 10.67. Found: C, 68.65; H, 5.97; N, 10.55.

2-Benzoyl-5,6-benzo-1,2,3,4-tetrahydro-β-carboline (26). The benzo-substituted tetrahydro-β-carboline **37** (1.32 g, 6 mmol) was stirred with benzoyl chloride (10 mmol) in benzene/pyridine at 0 °C, after which the solution was warmed to room temperature and allowed to stand overnight. Water was added to the mixture, and the benzene layer was separated. The aqueous layer was extracted with benzene, and the combined organic layers were dried (Na_2SO_4). The solvent was removed in vacuo to provide an oil. On trituration with ether/hexane and cooling a precipitate resulted: **26** (1.37 g, 70%); mp 236–237 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.20 (s, 2 H), 3.70 (s, 1.3 H), 4.10 (s, 0.7 H), 4.80 (2, 0.7 H), 5.00 (s, 1.3 H), 7.30–7.70 (m, 9 H), 8.00 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 8.0 Hz, 1 H); IR (KBr) 3200, 3080, 1620, 1600, 780, 700 cm^{-1}; mass spectrum CI (CH_4), m/e 327 (M + 1). Anal. Calcd for $C_{22}H_{18}N_2O$·0.25H_2O: C, 79.88; H, 5.60; N, 8.47. Found: C, 79.97; H, 5.71; N, 8.30.

Oxidation of Benzamide 26 with DDQ To Provide 27. The benzamide **26** (0.652 g, 2 mmol) and DDQ (0.908 g, 4 mmol) were admixed and cooled to −78 °C in a round-bottom flask. A mixture of tetrahydrofuran/H_2O (10 mL, 9:1) was cooled to −78 °C in a separate vessel, and this solvent mixture was added slowly to the solid mixture. The reaction slurry was allowed to warm to room temperature and stirred for an additional 3 h. Aqueous potassium hydroxide (1 N, 50 mL) was then added, and the benzamide **27** was extracted with ethyl acetate. The organic layer was washed with aqueous HCl (50 mL, 1 N), followed by brine and dried (Na_2SO_4). The ethyl acetate layer was then passed through a short column of alumina, and the solvent was removed in vacuo to provide **27** (0.240 g, 35%): mp 185 °C (darkens) 214–215 °C (melts); ^{1}H NMR (Me_2SO-d_6) δ 3.50 (t, J = 6.0 Hz, 2 H), 4.20 (t, J = 6.0 Hz, 2 H), 7.0–8.20 (m, 11 H), 12.20 (s, 1 H); IR (KBr) 3400, 1640, 1550, 700 cm^{-1}; mass spectrum CI (CH_4), m/e 341 (M + 1). Anal. Calcd for $C_{22}H_{16}N_2O_2$·0.1EtOAc: C, 77.06; H, 4.82; N, 8.02. Found: C, 77.24; H, 5.03; N, 7.56. No attempt to maximize the yield of this reaction has been made, to date.

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Registry No. **1a**, 26585-14-8; **2b**, 60755-86-4; (±)-**4**, 119694-99-4; (±)-**7**, 117908-37-9; (±)-**10**, 79888-13-4; **12**, 343-94-2; **13**, 13192-04-6; **13** (diacid), 328-50-7; (±)-**14**, 117908-36-8; **17**, 66859-09-4; **18**, 98263-41-3; **19a**, 56666-88-7; **19b**, 119694-97-2; **19c**, 98263-42-4; **19d**, 119694-98-3; **23**, 117908-38-0; **24**, 117908-39-1; **25**, 119695-02-2; **26**, 119695-07-7; **27**, 119695-08-8; **28**, 6326-44-9; **29**, 64258-95-3; **30**, 119695-00-0; **31**, 119695-01-1; **32**, 91-59-8; (±)-**34**, 119695-04-4; **35**, 92852-19-2; **36a**, 6722-13-0; **36b**, 119695-05-5; **37**, 119695-06-6; **38**, 119695-03-3; gramine, 87-52-5.