98064-44-9; **5a**, 129731-39-1; **5b**, 98064-47-2; **5c**, 98064-49-4; **7a**, 87129-38-2; **7b**, 129731-40-4; **7c**, 129731-41-5; **8a**, 129731-42-6; **8b**, 129731-43-7; **8c**, 125573-09-3; **11a**, 129731-44-8; **11b**, 129731-45-9; **11c**, 129731-46-0; H_2C=$CHCH_2OH$, 107-18-6; (*Z*)-H_3CCH=$CHCH_2OH$, 4088-60-2; (*E*)-H_3CCH=$CHCH_2OH$, 504-61-0; H_3C-$CH(OH)CH$=CH_2, 598-32-3; $H_3CCHBrCPBr$, 563-76-8; fluoroacetyl chloride, 359-06-8; sodium fluoroacetate, 62-74-8; phthloyl chloride, 88-95-9.

Supplementary Material Available: IR spectral data for compounds **1a-d**, **2a-d**, **5b,c**, **7a-c**, **8a-c**, and **11a-c** (2 pages). Ordering information is given on any current masthead page.

Carboxyl-Mediated Pictet-Spengler Reaction. Direct Synthesis of 1,2,3,4-Tetrahydro-β-carbolines from Tryptamine-2-carboxylic Acids†

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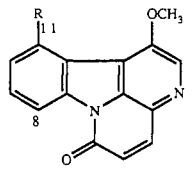
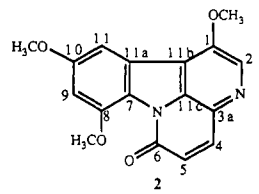
The Pictet-Spengler condensation of various tryptamine-2-carboxylic acids **9a-f** with carbonyl compounds in benzene/dioxane/trifluoroacetic acid (Table I) with simultaneous loss of carbon dioxide afforded directly the corresponding 1,2,3,4-tetrahydro-β-carbolines **14a-j** in good to excellent yields. This reaction greatly enhances the use of the Abramovitch-Shapiro method for the synthesis of highly oxygenated ring A substituted 1,2,3,4-tetrahydro-β-carbolines (THBC). The lactams **14f,g** and **14h** are key intermediates for the synthesis of ring A substituted 1-methoxycanthin-6-one analogues.

In recent years an increasing number of β-carboline alkaloids that contain an oxygen substituent at position 4 have been isolated.[1a,b,2] The 4-methoxy-β-carbolines[1a,b] and canthin-6-ones,[1b,2a] as well as several bisindoles,[3] serve as representative examples. The alkaloids 1-methoxycanthin-6-one (**1a**) 1,11-dimethoxycanthin-6-one (**1b**) and their congeners have been shown to exhibit cytotoxic, antileukemic activity via their inhibitory effects on DNA synthesis in GPK epithelial cells.[2c,4] Oxygenation of the



1a, R=H
1b, R=OCH_3



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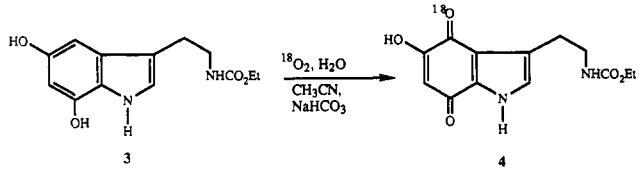
canthin-6-one skeleton either at position 1 (C-4 in the β-carboline numbering system) and/or ring A greatly enhances the cytotoxic, antileukemic activity of these bases. Recently, while studying the mechanism of action of 5,7-dihydroxytryptamine **3** (5,7-DHT), a selective serotonergic neurotoxin, Borchardt[5] proposed two possible modes of autoxidation of 5,7-DHT **3** to the quinone **4** (Scheme I). He demonstrated, experimentally, that a derivative of 5,7-DHT underwent autoxidation in the presence of $^{18}O_2$ to incorporate ^{18}O at the C-4 position of the indole ring system (eq 1). It is possible that the canthin-6-one alkaloids may also undergo autoxidation of ring A in a related fashion in vivo to furnish quinone intermediates which elicit the cytotoxic activity.

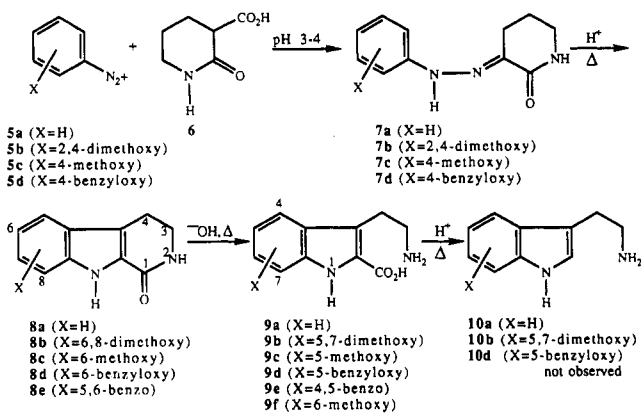
Although **1a** has recently been prepared in our laboratory,[6] current efforts have centered on the synthesis of "unnatural products" such as 1,8,10-trimethoxycanthin-6-one (**2**) to investigate the mode of action in vivo of these unique oxygenated canthin-6-ones.[2c,4] The approach requires a simple route to oxy-substituted tryptamines, the most straightforward of which was reported earlier by Abramovitch and Shapiro.[7] These authors employed a

Scheme I



3 **4**

Scheme II



5a (X=H)
5b (X=2,4-dimethoxy)
5c (X=4-methoxy)
5d (X=4-benzyloxy)

6

7a (X=H)
7b (X=2,4-dimethoxy)
7c (X=4-methoxy)
7d (X=4-benzyloxy)

8a (X=H)
8b (X=6,8-dimethoxy)
8c (X=6-methoxy)
8d (X=6-benzyloxy)
8e (X=5,6-benzo)

9a (X=H)
9b (X=5,7-dimethoxy)
9c (X=5-methoxy)
9d (X=5-benzyloxy)
9e (X=4,5-benzo)
9f (X=6-methoxy)

10a (X=H)
10b (X=5,7-dimethoxy)
10d (X=5-benzyloxy) not observed

† This paper is dedicated to Professor Gilbert Koch on the occasion of his 77th birthday.

(1) (a) For a list of structures of these alkaloids, see: Hagen, T. J. Ph.D. Thesis, University of Wisconsin—Milwaukee, Milwaukee, WI, 1988, p 164. (b) Sung, Y.-i.; Koike, K.; Nikaido, T.; Ohmoto, T.; Sankawa, U. *Chem. Pharm. Bull.* **1984**, *32*, 1872. Ohmoto, T.; Nikaido, T.; Koike, K.; Kohda, K.; Sankawa, U. *Chem. Pharm. Bull.* **1988**, *36*, 4588. Pavanand, K.; Yonganitchit, K.; Webster, H. K.; Dechatiwongse, T.; Nutakul, W.; Jewvachdamrongkul, Y.; Bansiddhi, J. *Phytother. Res.* **1988**, *2*, 33. Arbain, D.; Sargent, M. V. *Aust. J. Chem.* **1987**, *40*, 1527. Ohmoto, T.; Koike, K.; Higuchi, T.; Ikeda, K. *Chem. Pharm. Bull.* **1985**, *33*, 3356. Ohmoto, T.; Tankaka, R.; Nikado, T. *Chem. Pharm. Bull.* **1976**, *24*, 1532. Ohmoto, T.; Koike, K.; Sakamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 390. Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1983**, *31*, 3198. Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1986**, *34*, 2090. Lassak, E. V.; Polonsky, J.; Jacquemin, H. *Phytochemistry* **1977**, *16*, 1126-27. Bowiguignon-Zylber, N.; Polonsky, J. *Chim. Ther.* **1970**, *5*, 396. Joshi, B. S.; Kamat, V. N.; Gawad, D. H. *Heterocycles* **1977**, 193.

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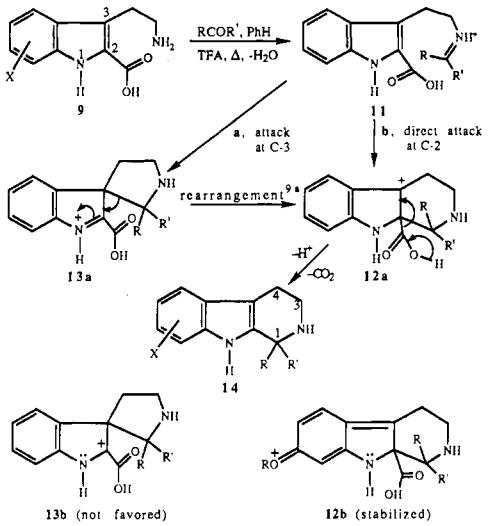
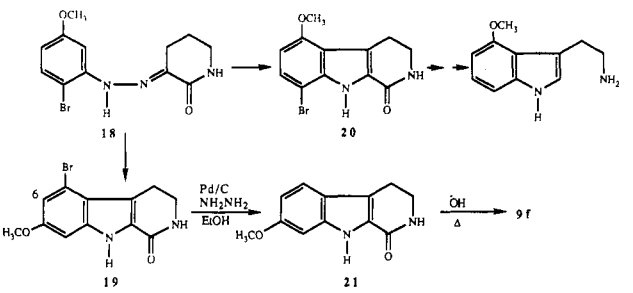
Scheme III



Scheme IV



Japp–Klingemann reaction (**5a** + **6**) followed by the Fischer indole cyclization (**7a** → **8a**) to provide the 1-oxotetrahydro-β-carboline (**8a**). This material on subsequent alkaline hydrolysis followed by decarboxylation of the tryptamine-2-carboxylic acid (**9a**) under acidic conditions leads to substituted tryptamines **10a** (Scheme II). The synthesis of a number of tryptamine-2-carboxylic acids (**9a–e**) has been carried out in this manner. This process suffers, however, because the decarboxylation step sometimes occurs only in moderate yields and occasionally fails completely to provide the desired tryptamine **10**. This is due to the nature of the substituents on the indole ring.[7] For example treatment of **9b** under either acidic conditions or with copper/quinoline[8] failed to provide any of the desired 5,7-dimethoxytryptamine (**10b**). Since the Abramovitch–Shapiro method is perhaps the best route to substituted tryptamine-2-carboxylic acids, the mechanism of the Pictet–Spengler reaction[9a–c] was reviewed in regard to this problem. As outlined in Scheme III, if the tryptamine-2-carboxylic acid **9** could be encouraged to form the Schiff base **11**, and is then heated, this might provide the carbocation **12a** or **13a**. Loss of a proton and the elements of carbon dioxide to regenerate the indole double bond would provide the desired 1,2,3,4-tetrahydro-β-carboline **14**. We report the realization of this objective as detailed below.

Simply heating the substituted tryptamine-2-carboxylic acids **9a–f** with the carbonyl compound in a solution of benzene/dioxane/trifluoroacetic acid at reflux with water removal (Dean–Stark trap[10]) furnished the desired 1,2,3,4-tetrahydro-β-carbolines **14a–j**, respectively. The results of this condensation reaction are summarized in Table I. The process appears to be quite general for simple aldehydes such as benzaldehyde and cyclohexanecarboxaldehyde (entries 1 and 3) yielded the corresponding tetrahydro-β-carbolines **14a** and **14b** while more reactive electrophiles including α-keto acids and α-keto esters (entries 2, 4–11) also yielded tetrahydro-β-carbolines. As illustrated, reaction of diethyl 2-oxomalonate (**15**) with tryptamine-2-carboxylic acid (**9a**) or its 5-benzyloxy derivative **9d** gave the interesting 1,1-disubstituted tetrahydro-β-carbolines **14c** and **14h**, respectively. Moreover, when tryptamine-2-carboxylic acid (**9a**) was heated with α-ketoglutaric acid **16**, loss of carbon dioxide from C-2 of the indole followed by loss of a second mole of CO_2 from C-1 of the tetrahydro-β-carboline[6,7,9b] generated the indolizino[8,7-*b*]indole **14d** in one step. This process is amenable to preparation of a number of ring A substituted congeners of **14d** for biological screening. More importantly, in regard to the present work, when this condensation was carried out between dimethyl 2-oxoglutarate **17** and ring A substituted tryptamine-2-carboxylic acids (see Table I), the 11b-methoxycarbonyl-substituted hexahydro-3-oxoindolizino[8,7-*b*]indoles (**14e**, **14f**, **14g**, and **14j**) were generated. These ester-substituted derivatives of **14d** are key intermediates in an approach to the synthesis of ring A substituted congeners of 1-methoxycanthine-6-one (**1**) in regard to antitumor activity. The parent indolizino[8,7-*b*]indole **14e** had previously been converted into **1** via the use of dichlorodicyanobenzoquinone (DDQ) in aqueous THF as a key step in the process.[6]

Importantly, 5,7-dimethoxytryptamine-2-carboxylic acid (**9b**) and 5-(benzyloxy)tryptamine-2-carboxylic acid (**9d**), both of which were resistant to decarboxylation under a variety of conditions,[7] reacted with α-keto esters with concomitant loss of CO_2 to provide the corresponding tetrahydro-β-carbolines, as illustrated. Moreover, when **9a** was heated under the reaction conditions in the absence of a carbonyl compound no evidence for the formation of tryptamine **10a** was observed.

Mechanistically, the iminium ion **11** can undergo attack at C-3 to provide the spiroindolenine intermediate[9a,b] **13a** or the ion **11** can undergo direct attack at C-2[9c] to provide the carbocation **12a**. The former intermediate is unlikely due to the localization of positive charge adjacent to the

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(5) Sinhababu, A. K.; Borchardt, R. T. *J. Am. Chem. Soc.* **1989**, *111*, 2230.

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(8) Wiley, R.; Smith, N. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 731.

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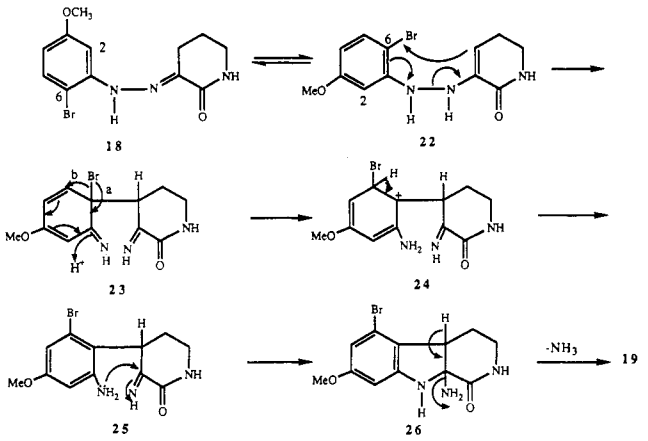
Scheme V



carbonyl group (see resonance structure **13b**, Scheme III).

It is known that 6-alkoxy substituents facilitate attack at C-2[9c] in the Pictet–Spengler reaction. If this were the case then **12b** (Scheme III) might be expected to play a role in stabilization of intermediate **12a** in the condensation reaction described herein. Although results are only preliminary, it is clear that 6-methoxytryptamine-2-carboxylic acid (**9f**) with **17** provides a higher yield of tetrahydro-β-carboline (see **14j**) than either the 5-methoxy analogue **9c** or the parent **9a** did with the same carbonyl compound (see Table I). Further work will be required to determine if this difference (80% vs 60%) is significant.[11]

Most of the tryptamine-2-carboxylic acids employed in this investigation were prepared as outlined in Scheme II.[7] The synthesis of 6-methoxytryptamine-2-carboxylic acid (**9f**) and the 5,7-dimethoxy derivative **9b**, however, deserve comment. Earlier, during the synthesis of 4-methoxytryptamine by the method of Suvorov et al.,[12] it was found that 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carbolines (THBC) were formed in this process. In contrast to the report of Suvorov,[12] when the hydrazone **18** was subjected to the Fischer indole cyclization in our hands, the 5-bromo-7-methoxy-1-oxotetrahydro-β-carboline (**19**) was isolated (20%) directly from the reaction mixture (Scheme IV). Analysis of the mother liquor by 500-MHz ^{1}H NMR spectroscopy indicated it was comprised of a 1:1 mixture (30%) of the expected 5-methoxy-8-bromo THBC **20** and 7-methoxy-1-oxo-THBC **21**. The 5-bromo-7-methoxy-THBC **19** was converted ($Pd/C/NH_2NH_2/EtOH$) into the 7-methoxy-THBC **21**. The structures of **19**, **20**, and **21** were determined by high-resolution proton NMR spectroscopy (see the Experimental Section for details) with emphasis on the ortho and meta coupled protons in **21**.

A possible pathway for the formation of THBCs **19** and **21** in preference to the 5-methoxy derivative **20** is depicted in Scheme V. Cyclization of hydrazine **18** toward carbon atom 2 (Scheme V) would eventually result in **20**; however, cyclization toward the bromine-substituted carbon atom 6 (see **22**) would generate intermediate **23**, as illustrated. Loss of a bromine atom (Br^+) via pathway a from **23** would provide the 7-methoxy-THBC **21** via the necessary steps of the Fischer-indole cyclization.[13] However, if the bromine atom in **23** rearranges as shown (pathway b) or via a bromonium ion the carbocation **24** would be obtained. Loss of a proton from **24** to generate the aromatic ring of **25** followed by the steps (**25** → **26**) outlined in Scheme V would account for the formation of **19**. Fischer indole cyclizations of similar nature have been reported.[13] Hydrolysis of **19** under alkaline conditions provided the desired 6-methoxytryptamine-2-carboxylic acid (**9f**).

Although 5,7-dimethoxytryptamine-2-carboxylic acid (**9b**) was prepared as shown in Scheme II, the conversion of **7b** into **8b** could not be effected under acidic conditions. When **7b** was heated in formic acid, PPA, or HCl/acetic acid, complex mixtures of products resulted. A similar attack toward the *o*-methoxyl-substituted carbon atom, followed by rearrangement during the Fischer indole cyclization of **7b** (see **22** → **23** → **24**, Scheme V) may have occurred. The Fischer indole cyclization, however, was effected under the thermal conditions of Crooks and Robinson[13] (**7b** → **8b**) in 63% yield. The required dimethoxytryptamine-2-carboxylic acid **9b** was obtained by heating **8b** under aqueous alkaline conditions.

In conclusion, an effective method for the direct synthesis of 1,2,3,4-tetrahydro-β-carbolines and hexahydro-3-oxo-indolizino[8,7-*b*]indoles from tryptamine-2-carboxylic acids has been developed. It is no longer necessary to remove the 2-carboxylic acid function prior to the execution of the Pictet–Spengler reaction for the elements of CO_2 are lost during the process of cyclization. This greatly enhances the use of the Abramovitch–Shapiro method[7] for the synthesis of substituted β-carbolines especially in the area of highly oxygenated ring A substituted heterocycles. Moreover, the present method can potentially be extended to other indoles which contain a carboxyl function located at the 2-position. Heterocycles such as indole 2-esters are readily available through the Fischer,[13] Reissert,[14] and Moody[15] routes to indoles. The conversion (for example, via a gramine intermediate) of these indole 2-esters[16] ultimately into tryptamine-2-carboxylic acids would provide yet another way in which to employ these substrates for the synthesis of highly oxygenated ring-A substituted 1,2,3,4-tetrahydro-β-carbolines. Further work to explore the scope of this reaction is in progress as well as applications to the synthesis

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(15) Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1333. Henn, L.; D. Hickey, M. B.; Moody, C. J.; Rees, C. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189.

(16) Kissman, H. M.; Witkop, B. *J. Am. Chem. Soc.* **1953**, *75*, 1967. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. Houlihan, W. J. *Indoles*; Wiley Interscience: New York, 1972; Part One, Chapter II.

of ring A substituted canthine-6-ones[1-4,6] for biological screening.[17]

Experimental Section

Microanalyses were 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 and ^{13}C NMR spectra were recorded on a Bruker 250-MHz spectrometer. Infrared spectra were taken on a Beckman Acculab-1 instrument, a Mattson Polaris R-10400, or a Nicolet Dx, 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. Silica gel 60b for column chromatography was purchased from E. M. Laboratories. The TLC plates were visualized under UV light or developed with spray reagents. The 1,2,3,4-tetrahydro-β-carbolines were visualized by using a standard solution of ceric ammonium sulfate in 50% sulfuric acid.

Tryptamine-2-carboxylic acid (**9a**), 5-methoxytryptamine-2-carboxylic acid (**9c**), and 5-(benzyloxy)tryptamine-2-carboxylic acid (**9d**) were prepared according to the procedure reported by Abramovitch and Shapiro.[7] The spectral data for these compounds and their precursors are provided below. The structures of these molecules were correlated with those reported in ref 7.

2,3-Dioxopiperidine 3-phenylhydrazone (7a): ^1H NMR (Me_2SO-d_6) δ 1.90 (m, 2 H), 2.50 (m, 2 H), 3.20 (m, 2 H), 6.70–8.00 (m, 5 H), 9.45 (s, 1 H); IR (KBr) 3200, 1659, 1610 cm^{-1}; mass spectrum, CI (CH_4) m/e 204 (MH^+, 100).

1,2,3,4-Tetrahydro-1-oxo-β-carboline (8a): ^1H NMR (Me_2SO-d_6) δ 3.00 (t, J = 6.00 Hz, 2 H), 3.60 (m, 2 H), 7.10 (t, J = 8.0 Hz, 1 H), 7.30 (t, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.70 (m, 2 H), 11.50 (s, 1 H); IR (KBr) 3320, 1660 cm^{-1}; mass spectrum, CI (CH_4) m/e 187 (MH^+, 100).

Tryptamine-2-carboxylic acid (9a): mp 235 °C dec (lit.[7] mp 245–246 °C dec); ^1H NMR (Me_2SO-d_6) δ 3.00–3.40 (m, 4 H), 7.00 (t, J = 8.0 Hz, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 11.00 (s, 1 H); IR (KBr) 3540–2590, 3330, 1690 cm^{-1}; mass spectrum, CI (CH_4) m/e 187 ($MH^+ - H_2O$, 100).

2,3-Dioxopiperidine 3-(p-methoxyphenyl)hydrazone (7c): ^1H NMR ($CDCl_3$) δ 1.80 (m, 2 H), 2.40 (m, 2 H), 3.30 (m, 2 H), 3.80 (s, 3 H), 6.80 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H); IR (KBr) 3290, 2960, 2360, 2333, 1637, 1250, 828 cm^{-1}; mass spectrum, CI (CH_4) m/e 234 (MH^+, 10).

6-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (8c): ^1H NMR (Me_2SO-d_6) δ 2.85 (t, J = 6.0 Hz, 2 H), 3.50 (m, 2 H), 3.80 (s, 3 H), 6.80 (dd, J = 8.0 Hz, 1.8 Hz, 1 H), 7.00 (s, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.50 (br s, 1 H), 11.40 (s, 1 H); IR (KBr) 3360, 2205, 1665 cm^{-1}; mass spectrum, CI (CH_4) m/e 217 (MH^+, 100).

5-Methoxytryptamine-2-carboxylic acid (9c): mp 230 °C (lit.[7] mp 238–240 °C; ^1H NMR (Me_2SO-d_6) δ 3.00–3.20 (m, 4 H), 3.70 (s, 3 H), 6.70 (m, 1 H), 7.00 (s, 1 H), 7.20 (d, J = 8.0 Hz, 1 H); IR (KBr) 3600–2180, 3240, 1616, 1545, 1215, 815 cm^{-1}; mass spectrum, CI (CH_4) m/e 217 ($MH^+ - H_2O$, 100).

2,3-Dioxopiperidine 3-[p-(benzyloxy)phenyl]hydrazone (7d): mp 165–168 °C (lit.[7] mp 166–170 °C); ^1H NMR ($CDCl_3$) δ 1.80 (m, 2 H), 2.40 (m, 2 H), 3.30 (m, 2 H), 5.20 (s, 2 H), 7.20–8.00 (m, 9 H); IR (KBr) 3220, 3560–2860, 1660, 1560, 1390 cm^{-1}; mass spectrum, CI (CH_4) m/e 310 (MH^+, 100).

6-(Benzyloxy)-1-oxo-1,2,3,4-tetrahydro-β-carboline (8d): mp 195–197 °C (lit.[7] mp 199–201 °C); ^1H NMR (Me_2SO-d_6) δ 2.90 (m, 2 H), 3.50 (m, 2 H), 5.20 (s, 2 H), 7.00–7.80 (m, 9 H), 11.50 (s, 1 H); IR (KBr) 3225, 1650 cm^{-1}; mass spectrum, CI (CH_4) m/e 293 (MH^+, 100).

5-(Benzyloxy)tryptamine-2-carboxylic acid (9d): mp 240–245 °C dec (lit.[7] mp 243–245 °C); ^1H NMR (Me_2SO-d_6) δ 3.00–3.30 (m, 4 H), 5.10 (s, 2 H), 6.80–7.50 (m, 8 H); IR (KBr) 3215, 3585–2045, 1620, 1540, 1500, 1460 cm^{-1}; mass spectrum, CI (CH_4) m/e 293 ($MH^+ - H_2O$, 100).

Benzo[4,5]tryptamine-2-carboxylic acid (9e): 5,6-Benzo-1-keto-1,2,3,4-tetrahydro-β-carboline (**8e**)[6] (1.70 g) was treated with KOH (3.43 g) in water (37 mL) and heated to reflux for 1 day. The homogeneous solution was filtered, cooled, and neutralized with glacial acetic acid to pH 5. The precipitate **9e** that formed was collected by filtration and dried (2.00 g, 90%): mp 240 °C; ^1H NMR (Me_2SO-d_6) δ 2.90–3.20 (m, 4 H), 7.20–7.70 (m, 4 H), 7.90 (d, J = 8.0 Hz, 1 H), 8.35 (d, J = 8.0 Hz, 1 H), 11.40 (br s, 1 H); ^{13}C NMR (DMSO-d_6/CF_3COOD) δ 26.79, 43.88, 117.00, 122.41, 122.42, 125.35, 126.33, 126.34, 129.28, 129.55, 131.77, 132.16, 132.57, 136.80, 165.84; IR (KBr) 3640–2360, 1550, 1445, 1375 cm^{-1}; mass spectrum, CI (CH_4) m/e 237 ($MH^+ - 18$, 100).

2,3-Piperidinedione 3-(2,4-dimethoxyphenyl)hydrazone (7b): The 3-carbethoxy-2-piperidone **6** (6.3 g, 37 mmol) was stirred with KOH (2.2 g) in water (75 mL) and kept at 30 °C on an oil bath overnight. The 2,4-dimethoxyaniline (6.0 g, 39 mmol) was treated with water (55 mL) and concentrated HCl (10 mL) and cooled to 0 °C. Sodium nitrite (3.3 g) in water (9 mL) was added dropwise to the above solution at 0 °C and stirred for an additional 20 min. Urea was added to decompose the excess nitrous acid, and the diazotized solution was neutralized with 10% aqueous sodium carbonate solution (45–50 mL) to provide **5b**. This solution was filtered into the solution of previously hydrolyzed 3-carbethoxy-2-piperidone (2-piperidone-3-carboxylic acid) at 0 °C. After a few minutes, glacial acetic acid was added to bring the pH of the solution to 3–4. The reaction mixture was stirred at 0 °C for 5–6 h, and the yellow precipitate which resulted was filtered, washed (H_2O), and dried. The mother liquor was placed in the refrigerator overnight, and more hydrazone **7b** was collected by filtration: **7b** (8.46 g, yield 63%); mp 197–198 °C; ^1H NMR (DMSO-d_6) δ 1.82 (m, 2 H), 2.50 (m, 2 H), 3.20 (m, 2 H), 3.68 (s, 3 H), 3.78 (s, 3 H), 6.43–6.56 (m, 2 H), 7.20 (d, J = 7.0 Hz, 1 H), 9.90 (s, 1 H); IR 3310, 2940, 2360, 1539, 1510 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 22.87, 31.05, 42.11, 55.70, 99.03, 104.60, 112.37, 125.16, 127.60, 147.31, 154.75, 164.14; mass spectrum, CI (CH_4) m/e 264 (MH^+, 100). Anal. Calcd for $C_{13}H_{17}N_3O_3 \cdot 0.5H_2O$: C, 57.35; H, 6.61; N, 15.44. Found: C, 56.76; H, 6.33; N, 15.29.

5,7-Dimethoxytryptamine-2-carboxylic Acid (9b). The phenylhydrazone **7b** prepared in the previous experiment (13.0 g, 4.94 mmol) was added to diethylene glycol (250 mL) and heated to reflux for 6 h. The reaction was judged complete by TLC. Most of the diethylene glycol was removed by distillation on a Kugelrohr apparatus. The residue that remained was dissolved in ethyl acetate and washed with water several times to remove the ethylene glycol that remained. The aqueous layer was back extracted with ethyl acetate to recover some of the THBC **8b**. The combined ethyl acetate layers were dried over Na_2SO_4, and the solvents were removed under reduced pressure. The brown oil **8b** that resulted was taken directly onto the next step for hydrolysis. A small amount was crystallized for identification. **8b** (mp 95–97 °C): ^1H NMR ($CDCl_3$) δ 3.10 (t, J = 6.0 Hz, 2 H), 3.70 (m, 2 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 5.80 (br s, 1 H), 6.40 (s, 1 H), 6.50 (s, 1 H), 9.00 (br s, 1 H); mass spectrum, CI (CH_4) m/e 247 (MH^+, 100).

Potassium hydroxide (250 mL, 2 N in H_2O) was added directly to the brown oil, and the mixture was heated to reflux overnight. The reaction mixture became homogeneous. The reaction solution was cooled, filtered, and acidified with glacial acetic acid (pH 4–5) to provide the title compound (**9b**), 9.7 g (60% overall yield from hydrazone): mp 245 °C dec; ^1H NMR (Me_2SO-d_6) δ 2.98 (m, 2 H), 3.25 (m, 2 H), 6.44 (s, 3 H), 6.69 (s, 3 H), 10.59 (br s, 1 H); IR (KBr) 3600–2000 (m), 1520, 1390 cm^{-1}; ^{13}C NMR (DMSO-d_6/CF_3COOD) δ 24.62, 42.73, 57.19, 68.74, 120.05, 125.30, 126.65, 130.37, 130.54, 149.57, 158.17, 166.05; mass spectrum, EI m/e 264,

(17) In keeping with the proposed in vivo origin of the cytotoxic activity of ring A substituted canthine-6-ones, the 6,8-dimethoxy-THBC (i) was recently oxidized with DDQ in aqueous THF to provide benzoquinone (ii). Narayanan, K., Cook, J. M., unpublished results. This is somewhat analogous to the oxidation of **3** by Borchardt[5] to provide **4** (Scheme I). Related oxidations have been reported by the following: (a) Orlemanes, E. O.; Verboom, W.; Schelting, M. W.; Reinhoudt, D. N.; Lelieveld, P.; Fiebig, H. H.; Winterhalter, B. R.; Double, J. A.; Bibby, M. C. *J. Med. Chem.* **1989**, *32*, 1612. (b) Cai, P.; Snyder, J. K. *Tetrahedron Lett.* **1990**, 969. (c) Teuber, H.; Thaler, G. *Chem. Ber.* **1958**, *11*, 2253.

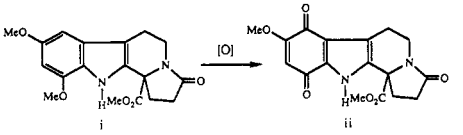
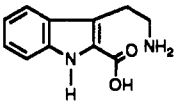
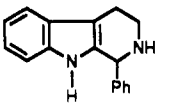
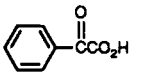
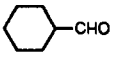
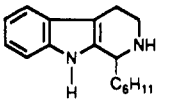
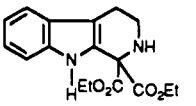
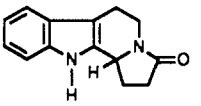
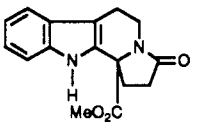
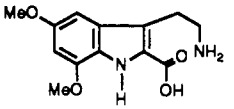
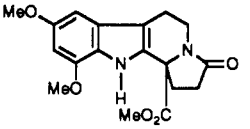
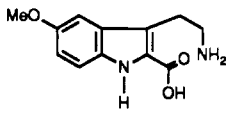
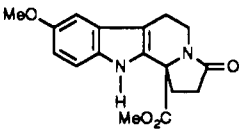
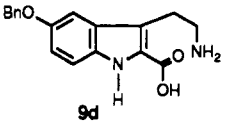
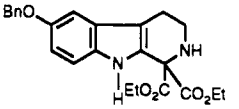
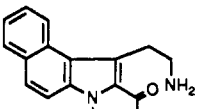
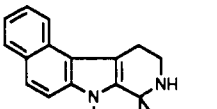
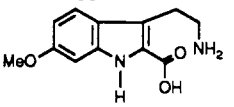
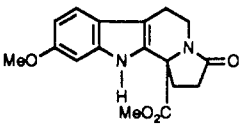


Table I. Synthesis of 1,2,3,4-Tetrahydro-β-carbolines from Tryptamine-2-carboxylic Acids

entry	tryptamine-2-acid	carbonyl component	product (% yield)	
1	 **9a**	PhCHO	 **14a**	(75)
2	**9a**		**14a**	(62)
3	**9a**		 **14b**	(65)
4	**9a**	$EtO_2CC(O)CO_2Et$ **15**	 **14c**	(65)
5	**9a**	$HO_2CC(O)CH_2CH_2CO_2H$ **16**	 **14d**	(58)
6	**9a**	$MeO_2CC(O)CH_2CH_2CO_2Me$ **17**	 **14e**	(55)
7	 **9b**	**17**	 **14f**	(65)
8	 **9c**	**17**	 **14g**	(60)
9	 Bn = benzyl **9d**	**15**	 **14h**	(75)
10	 **9e**	**15**	 **14i**	(60)
11	 **9f**	**17**	 **14j**	(80)

246 (M^+ – 18, 100). Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.59. Found: C, 55.65; H, 5.97.

3-Amino-4-bromoanisole. A 500-mL round-bottom flask fitted with a reflux condenser was charged with 4-bromo-3-nitroanisole (11.6 g, 50 mmol), reduced iron (30 g), 95% ethanol (40 mL), water (10 mL), and aqueous concentrated HCl (0.5 mL). The reaction mixture was heated on a steam bath for 2 h. The residual iron was filtered from the medium and washed with hot ethanol (95%). The filtrate was evaporated under reduced pressure, brought to alkaline pH with concentrated aqueous NH_4OH, and extracted with ether. The ether layer was dried (Na_2SO_4), concentrated, and treated with EtOH/HCl to provide the hydrochloride salt of the title compound (11.90 g, 78%): mp 189–190 °C (lit.[12] mp 186 °C); ^1H NMR (Me_2SO-d_6) δ 3.70 (s, 3 H), 6.50 (dd, J = 8.0, 1.8 Hz, 1 H), 6.90 (d, J = 1.8 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 8.80 (br s, 3 H); IR (KBr) 3150–2650, 2295, 1560, 1490, 870, 815 cm^{-1}; mass spectrum, EI m/e 201, 203 (M^+), Br isotopes (100, 96).

2,3-Piperidinedione 3-(5′-Methoxy-2′-bromophenyl)-hydrazone (18). The title compound was prepared according to the published procedure.[12] The 3-carbethoxy-2-piperidone **6** (7.2 g) was saponified with a solution of KOH (2.52 g) in 84 mL of water overnight at 30 °C. The solution of 2-oxopiperidine-3-carboxylic acid was cooled to 0 °C with stirring, and it was treated with a cold solution of (5-methoxy-2-bromophenyl)diazonium

chloride, prepared by diazotization of 3-amino-4-bromoanisole hydrochloride (10 g, 42 mmol). [The diazo solution was first neutralized with urea (2 scoops) and 10% aqueous Na_2CO_3 (50 mL).] After the solutions were mixed the pH of the mixture was brought to 3–4 by adding a few drops of glacial acetic acid. The reaction mixture was stirred for 5 h at 0–2 °C. The hydrazone **18** was obtained as a yellow precipitate which was filtered, washed (H_2O), and dried in a vacuum desiccator **18** (10.45 g, 80%): mp 175–176 °C (lit.[12] mp 180–182 °C); ^1H NMR (Me_2SO-d_6) δ 1.85 (m, 2 H), 2.65 (m, 2 H), 3.20 (m, 2 H), 3.80 (s, 3 H), 6.50 (dd, J = 8.0, 1.8 Hz, 1 H), 7.10 (d, J = 1.8 Hz, 1 H), 7.45 (d, J = 8.0 Hz, 1 H); IR (KBr) 3300–2600, 1665, 1580 cm^{-1}; mass spectrum, EI m/e 311, 313 (M^+, 100, 95), Br isotopes. Anal. Calcd for $C_{12}H_{14}N_3BrO_2 \cdot 0.5H_2O$: C, 45.00; H, 4.67; N, 13.08. Found: C, 45.38; H, 4.36; N, 12.77.

5-Bromo-7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (19). The 2,3-piperidinedione 3-(5′-methoxy-2′-bromophenyl)-hydrazone (**18**) (5.0 g, 16 mmol) was dissolved in a mixture of acetic acid (24 mL) and concentrated aqueous HCl (12 mL). The solution which resulted was heated under reflux under a stream of nitrogen for 3 h. The reaction mixture turned dark. It was cooled under nitrogen (gas) at 0 °C for 3 h. The pale brown precipitate that formed was filtered, washed (H_2O), and dried. This compound was characterized as 5-bromo-7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (**19**, 0.95 g, 20%): mp 250–252 °C; ^1H NMR (Me_2SO-d_6) δ 2.90 (t, J = 6.0 Hz, 2 H), 3.50 (m, 2 H), 3.80 (s, 3 H), 7.00 (s, 1 H), 7.50 (br s, 1 H), 7.90 (s, 1 H), 11.60 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 19.10, 19.47, 39.87, 54.63, 93.63, 103.28, 116.48, 118.75, 122.32, 125.52, 135.78, 151.44, 160.52, 170.74; IR (KBr) 3240, 1715, 1660 cm^{-1}; mass spectrum, EI m/e 294, 296 (M^+), Br isotopes (100 and 96.8). Anal. Calcd for $C_{12}H_{11}BrN_2O_2 \cdot 0.4HOAc$: C, 49.54; H, 4.06; N, 9.03. Found: C, 49.34; H, 4.15; N, 8.22.

The filtrate obtained above was poured into ice water, and the precipitate that resulted was filtered and dried (1.42 g, in 30%). This material was comprised of a mixture of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (**21**) and 5-methoxy-8-bromo-1-oxo-1,2,3,4-tetrahydro-β-carboline (**20**) as the major products in an approximate ratio of 1:1 (500-MHz ^1H NMR), accompanied by minor amounts of byproducts. **20**: ^1H NMR (Me_2SO-d_6) δ 7.30 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 8.0 Hz, 1 H); compound **21**, δ 6.48 (d, J = 8.0 Hz, 1 H), 6.70 (dd, J = 8.0 and 2.0 Hz), 6.82 (d, J = 2.0 Hz, 1 H). The aliphatic signals in the mixture were too complicated to resolve.

7-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (21). A mixture of 1.6 g of 7-methoxy-5-bromo-1-oxo-1,2,3,4-tetrahydro-β-carboline (**19**) and 10% Pd/C (1.0 g), hydrazine monohydrate (25 mL), and ethanol (50 mL) was heated at reflux until the evolution of N_2 ceased (oil bubbler). The solvent was removed in vacuuo, and the residue was treated with water, filtered, and dried to provide **21** (0.76 g, 65%): mp 198–199 °C (lit.[7] 199–200 °C); ^1H NMR (Me_2SO-d_6) δ 2.95 (t, J = 6.0 Hz, 1 H), 3.50 (m, 1 H), 3.80 (s, 1 H), 6.70–6.90 (m, 2 H), 7.50 (m, 2 H), 11.40 (s, 1 H); ^{13}C NMR (DMSO-d_6/$CDCl_3$) δ 19.89, 40.75, 54.32, 93.57, 110.03, 118.34, 118.54, 119.77, 124.98, 137.61, 157.10, 161.54; IR (KBr) 3210, 1650, 1615 cm^{-1}; mass spectrum, EI m/e 216 (M^+, 100). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 12.96. Found: C, 65.87; H, 5.51; N, 12.73.

6-Methoxytryptamine-2-carboxylic Acid (9f). The 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (**21**) (2.28 g, 10.55 mmol) was treated with KOH (6.50 g) in H_2O (65 mL) and heated to reflux. When the reaction mixture became homogeneous (2–3 h), the reaction was stopped, cooled, filtered, and acidified with glacial acetic acid to pH 4–5. The precipitate which formed was filtered from the medium and dried to give **9f** (2.79 g, 90%): mp 220–222 °C; ^1H NMR (Me_2SO-d_6) δ 3.00–3.30 (m, 4 H), 3.80 (s, 3 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.80 (s, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 10.90 (s, 1 H); ^{13}C NMR (DMSO-d_6/CF_3COOD) δ 24.78, 43.47, 57.35, 121.71, 123.31, 125.67, 167.10; IR (KBr) 3500–2100, 3350, 1630, 1588, 1540, 1430, 1390, 1285 cm^{-1}; mass spectrum, EI m/e 234 (M^+, 24), 216 (M^+ – 18, 33). Anal. Calcd for $C_{12}H_{13}N_2O_3 \cdot CH_3CO_2H$: C, 56.46; H, 5.78; N, 9.52. Found: C, 56.60; H, 5.54; N, 10.31.

General Procedure for the Reaction of Tryptamine-2-carboxylic Acids with Carbonyl Compounds. The tryptamine-2-carboxylic acid **9** (1 mmol) and the carbonyl component (1–1.5 equiv) were taken up in a mixture of benzene/dioxane (2:1, 45 mL), and trifluoroacetic acid (0.5 mL) was added. The reaction mixture was heated to reflux with a Dean–Stark trap to remove water. The reaction progress was monitored by TLC (EtOH/EtOAc, 15:85) with ceric ammonium nitrate in concentrated H_2SO_4 as the visualization reagent. After the reaction was deemed complete (1 day), the solvents were removed under reduced pressure followed by partition of the residue between ethyl acetate and aqueous sodium bicarbonate solution. The tetrahydro-β-carbolines were isolated either as hydrochloride salts or precipitated by ether from the medium. The THBC's were purified in some cases by silica gel column chromatography. All of the compounds in Table I that possess a chiral center are racemic.

1-Phenyl-1,2,3,4-tetrahydro-β-carboline hydrochloride salt (14a): mp 209–210 °C (lit.[18] mp 208 °C); ^1H NMR (Me_2SO-d_6) δ 2.90–3.40 (m, 4 H), 5.90 (br s, 1 H), 7.00–7.52 (m, 9 H), 9.48 (br s, 1 H), 10.34 (br s, 1 H), 10.88 (s, 1 H); IR (KBr) 3415, 3210, 2910, 1460, 760, 690 cm^{-1}; mass spectrum, EI m/e 248 (M^+, 67.4), 218 (100). Anal. Calcd for $C_{17}H_{17}N_2Cl \cdot 0.5H_2O$: C, 69.62; H, 6.14; N, 9.55. Found: C, 69.51; H, 5.85; N, 9.22.

1-Cyclohexyl-1,2,3,4-tetrahydro-β-carboline hydrochloride salt (14b): mp 243–244 °C; ^1H NMR (Me_2SO-d_6) δ 1.00–1.90 (m, 1 H), 2.80–3.50 (m, 4 H), 4.50 (br s, 1 H), 7.00–7.20 (m, 2 H), 7.50 (m, 2H), 8.70 (br s, 1 H), 9.90 (br s, 1 H), 11.0 (s, 1 H); ^{13}C NMR (DMSO-d_6/$CDCl_3$) δ 17.23, 24.63, 24.91, 25.19, 25.30, 29.47, 41.18, 56.77, 105.82, 110.34, 116.73, 118.02, 120.78, 127.31, 135.55; IR (KBr) 3430, 3225, 2930, 1460, 740 cm^{-1}; mass spectrum, EI m/e 254 (M^+, 1.8), 171 (M^+ – 83, 100); HRMS calcd for $C_{17}H_{22}N_2$ 254.1782, found 254.1750. Anal. Calcd for $C_{17}H_{23}N_2Cl \cdot 0.25H_2O$: C, 69.27; H, 7.97; N, 9.50. Found: C, 68.79; H, 7.71; N, 9.36.

1,1-Dicarbethoxy-1,2,3,4-tetrahydro-β-carboline (14c): mp 98–100 °C; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 6.0 Hz, 6 H), 2.80 (t, J = 6.0 Hz, 2 H), 3.20 (t, J = 6.0 Hz, 2 H), 3.50 (br s, 1 H), 4.30 (q, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2 H), 3.50 (br s, 1 H), 4.30 (q, J = 6.0 Hz, 4 H), 7.00–7.70 (m, 4 H), 8.50 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.04, 21.63, 41.04, 62.65, 111.13, 112.10, 118.67, 119.36, 122.53, 126.29, 136.05, 168.80; IR (KBr) 3340, 3247, 2987, 2924, 1743 cm^{-1}; mass spectrum, CI (CH_4) m/e 317 (MH^+, 100); HRMS calcd for $C_{10}H_{20}N_2O_4$ 316.1423, found 316.1409. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.56; H, 6.33; N, 8.86. Found: C, 65.40; H, 6.42; N, 8.64.

2,3,5,6,11,11b-Hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole (14d): mp 245–247 °C; ^1H NMR (Me_2SO-d_6) δ 1.60–3.00 (m, 6 H), 3.50 (m, 1 H), 4.15–4.50 (m, 1 H), 4.75–5.15 (m, 1 H), 6.90–7.50 (m, 4 H), 11.20 (br s, 1 H); IR (KBr) 1660 cm^{-1}; mass spectrum, EI m/e 226 (M^+, 100). The spectral data for **14e** were identical with those obtained from the reaction of tryptamine and α-ketoglutaric acid.[6]

Methyl 2,3,5,6,11,11b-hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-11b-carboxylate (14e): mp 221 °C; ^1H NMR (Me_2SO-d_6) δ 2.17–2.36 (m, 4 H), 2.52 (m, 2 H), 2.88 (m, 1 H), 3.16 (m, 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); mass spectrum, CI (CH_4) m/e 285 (MH^+, 100). The spectral data for **14e** were identical in all respects with those obtained from the reaction of tryptamine and dimethyl 2-oxoglutarate.[6]

Methyl 8-methoxy-2,3,5,6,11,11b-hexahydro-3-oxo-indolizino[8,7-*b*]indole-11b-carboxylate (14g): mp 172–174 °C; ^1H NMR ($CDCl_3$) δ 2.20–2.80 (m, 6 H), 3.20 (m, 1 H), 3.60 (s, 3 H), 3.78 (s, 3 H), 4.60 (m, 1 H), 6.90 (m, 2 H), 7.30 (d, J = 8.0 Hz, 1 H), 8.20 (s, 1 H); IR (KBr) 3200, 3080, 2966, 1743, 1665 cm^{-1}; mass spectrum, CI (CH_4) m/e 257 (MH^+, 100). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.97; H, 5.73; N, 8.92. Found: C, 64.26; H, 5.81; N, 8.24.

Methyl 9-methoxy-2,3,5,6,11,11b-hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-11b-carboxylate (14j): mp 198–200 °C; ^1H NMR ($CDCl_3$) δ 2.15–2.50 (m, 2 H), 2.70 (m, 4 H), 3.10 (m, 1 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 4.30 (m, 1 H), 6.65 (dd, J = 8.0, 1.5 Hz, 1 H), 6.85 (br s, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 11.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.92, 30.49, 32.15, 36.63, 53.05, 55.76, 65.41, 95.30, 109.81, 119.34, 120.83, 129.37, 137.59, 172.40, 172.98; IR (KBr) 3220, 1730, 1680 cm^{-1}; mass spectrum, CI (CH_4) m/e 315 (MH^+, 100). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.97; H, 5.73; N, 8.92. Found: C, 63.49; H, 5.72; N, 8.77. This material was

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identical in all respects with the THBC prepared from 6-methoxytryptamine and dimethyl 2-ketoglutarate.

Methyl 8,10-dimethoxy-2,3,5,6,11,11b-hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-11b-carboxylate (14f): mp 220–221 °C; ^{1}H NMR ($CDCl_3$) δ 2.18–2.80 (m, 6 H), 3.20 (m, 1 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.91 (s, 3 H), 4.51 (m, 1 H), 6.36 (s, 1 H), 6.49 (s, 1 H), 8.27 (s, 1 H); IR (KBr) 3325, 3178, 2952, 1743, 1694, 1658 cm^{-1}; mass spectrumm, CI (CH_4) *m/e* 345 (MH^+, 100). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.79; H, 5.86; N, 8.14. Found: C, 61.83; H, 5.86; N, 7.73.

1,1-Dicarbethoxy-5,6-benzo-1,2,3,4-tetrahydro-β-carboline (14i): mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 6.0 Hz, 6 H), 3.20–3.40 (m, 4 H), 4.40 (q, J = 6.0 Hz, 4 H), 7.30–7.60 (m, 4 H), 7.90 (d, J = 8.0 Hz, 1 H), 8.20 (d, J = 8.0 Hz, 1 H), 9.00 (s, 1 H); IR (KBr) 3410, 3044, 2967, 2925, 1743 cm^{-1}; mass spectrum, CI (CH_4) *m/e* 367 (MH^+, 100). Anal. Calcd for $C_{15}H_{15}N_2Cl\cdot0.25H_2O$ (hydrochloride salt): C, 68.57; H, 5.90; N, 10.67. Found: C, 68.65; H, 5.97; N, 10.55.

1,1-Dicarbethoxy-6-(benzyloxy)-1,2,3,4-tetrahydro-β-carboline (14h): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 6.0 Hz, 6 H), 2.70 (t, J = 5.0 Hz, 2 H), 3.20 (t, J = 5.0 Hz, 2 H), 4.25 (q, J = 6.0 Hz, 4 H), 5.00 (s, 2 H), 6.90–7.60 (m, 8 H), 8.50 (br s, 1 H); IR (neat) 3445, 3550, 3070, 3035, 2980, 1735 cm^{-1}; mass spectrum, CI (CH_4) *m/e* 423 (MH^+, 100). Anal. Calcd for $C_{24}H_{26}H_2O_5$: C, 68.25; H, 6.16. Found: C, 67.98; H, 6.57.

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Registry No. **5a** amine, 62-53-3; **5b** amine, 2735-04-8; **5c** amine, 104-94-9; **5d** amine, 6373-46-2; (±)-**6**, 119695-04-4; **7a**, 57073-81-1; **7b**, 94850-49-4; **7c**, 104742-98-5; **7d**, 101783-07-7; **8a**, 17952-82-8; **8b**, 94850-36-9; **8c**, 17952-87-3; **8d**, 51086-22-7; **8e**, 6722-13-0; **9a**, 5956-86-5; **9b**, 94850-43-8; **9c**, 52648-13-2; **9d**, 54987-14-3; **9e**, 109336-82-5; **9f**, 20731-72-0; (±)-**14a**·HCl, 129968-01-0; (±)-14b·HCl, 129968-03-2; **14c**, 129968-04-3; (±)-**14d**, 115757-58-9; (±)-**14e**, 79888-13-4; (±)-**14f**, 129968-07-6; (±)-**14g**, 129968-05-4; **14h**, 129968-09-8; **14i**, 129968-08-7; **14i**·HCl, 129968-10-1; (±)-**14j**, 129968-06-5; **15**, 609-09-6; **16**, 328-50-7; **17**, 13192-04-6; **18**, 91720-57-9; **19**, 129968-02-1; **20**, 26579-67-9; **21**, 26579-69-1; PhCHO, 100-52-7; $PhCOCO_2H$, 611-73-4; $C_6H_{11}CHO$, 2043-61-0; 4-bromo-3-nitroanisole, 5344-78-5; 3-amino-4-bromoanisole hydrochloride, 129968-11-2.

Supplementary Material Available: Proton and carbon NMR spectra for intermediates **7b**, **9e,f**, **14b,c**, and **19** (17 pages). Ordering information is given on any current masthead page.

The Addition of γ-(Trimethylsilyl)allylboronates to Imines

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The addition of γ-(trimethylsilyl)allylboronates to imines is described and compared with the addition of simple allylboronates to imines. The addition of γ-(trimethylsilyl)allylboronates to imines is found to be more efficient than the addition of simple allylboronates to imines. The stereoselectivity is dependant upon the nature of the imine; imines derived from aromatic aldehydes give anti products and imines derived from aliphatic aldehydes give syn products. Proof of stereochemistry was established by conversion of the anti and syn derivatives to their respective *Z*- and *E*-dienes by a methylation/E-2 elimination process. With α-alkoxy aldehydes the reaction proceeds with excellent selectivity giving the product of Felkin–Ahn addition.

Although a large body of information now exists on the addition of allylboronates to aldehydes and ketones,[2-4] little work on the related additions of allylboronates or allylboranes to the isoelectronic imines[5] and their derivatives[6-8] has been reported in the literature. In our initial work in this area, we explored the additions of ethylene glycol and pinacol allylboronates **1** and **2** to sulfenimines **3** (eq 1) and found that the reactivity of sulfenimines is greatly reduced in comparison with aldehydes and ketones.[8] That the steric bulk of the boronate ester had a profound effect on the reactivity was evident when a 10-fold increase in rate was observed in the reaction of the ethylene glycol boronate **2** over the pinacol boronate **1**. The *Z*–*E* isomerization and the relative rates of reaction for each isomer must also

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