(2*R*,11a*S*)-2-Hydroxy-8-(benzoyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8c). This compound was prepared by the reductive cyclization of **6c** with rat liver microsomes and worked up according to the general pressure: mp 214–216 °C; $[\alpha]^{25}_D$ +471° (*c* = 0.14, CH_3OH); IR (KBr) (cm^{-1}) 3490, 1725, 1685, 1610, 1590; ^1H NMR δ 2.09 (1 H, m), 2.73 (1 H, m), 3.51–3.87 (3 H, m), 3.93 (3 H, s), 4.24 (1 H, m), 4.51 (1 H, m), 6.58–7.42 (7 H, m), 8.81 (1 H, br s). Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 62.78; H, 4.89.

(11a*S*)-8-(Benzoyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8d). This compound was prepared by the reductive cyclization of **6d** with rat liver microsomes and worked up according to the general procedure: mp 197–198 °C; $[\alpha]^{25}_D$ +432° (*c* = 0.21, CH_3OH); IR (KBr) (cm^{-1}) 3130, 1720, 1675, 1615, 1595; ^1H NMR δ 1.98 (1 H, m), 2.69 (1 H, m), 3.47–3.76 (3 H, m), 3.89 (3 H, s), 4.12 (1 H, m), 4.58 (1 H, m), 6.63–7.38 (7 H, m), 8.76 (1 H, br s). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.93; H, 4.43. Found: C, 65.76; H, 4.32.

Preparation of Liver Microsomal Fraction from Rat. General Procedure. Phenobarbital-treated male Wistar rats (body weight 150–200 g), fasted for 1 day before being killed, were used. A 10-volume homogenate in 0.25 M sucrose solution containing KCl (1.15% w/v) was prepared from livers by a standard procedure[17] and as described in our earlier work.[8a]

Microsomes were obtained from the postmitochondrial supernatant fraction (centrifuged at 15000*g*) of the homogenate by centrifugation at 105000*g* for 2 h and resuspended in 0.1 M phosphate buffer (pH 7.4). Protein content of the suspension determined by the method of Lowry et al.[18] was 5.6 mg/mL.

(11a*S*)-Pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-triones (9a–c). These were prepared by the Jones oxidation of 2(*R*)-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones as described in the literature.[7a]

(2*S*,11a*S*)-2-Hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (10a). General Procedure. To a solution of **9a** (500 mg, 2.16 mmol) in 0.1 M phosphate buffer (100 mL, pH 7.4) was added bakers' yeast (*Saccharomyces cerevisiae*, Sigma, Type I; 10 g). Incubation was carried out under aerobic conditions at 37 °C with gentle shaking. Glucose (500 mg × 9 portions) was added at every 6 h. After 3 days, the incubation mixture was extracted thrice with ethyl acetate (100 mL) and on workup the crude product was obtained. This was purified by column chromatography (silica gel, dichloromethane/ethyl acetate/methanol, 6:3:1): mp 238–240 °C; $[\alpha]^{25}_D$ +433° (*c* 0.2, CH_3OH) (378 mg, 75% yield); IR (KBr) (cm^{-1}) 3425, 3240, 1680, 1610, 1435; ^1H NMR δ 2.29 (1 H, ddd, *J* = 14, 9, 5 Hz), 2.79 (1 H, br d, *J* = 14 Hz), 3.75 (2 H, d, *J* = 3 Hz), 4.09 (1 H, d, *J* = 6 Hz), 4.17 (1 H, dd, *J* = 2 Hz), 4.50 (1 H, m), 7.14–7.51 (3 H, m), 7.93 (1 H, dd, *J* = 8, 2 Hz), 10.43 (1 H, br s); ^{13}C NMR 34.06, 55.94, 56.42, 68.99, 121.60, 124.58, 126.78, 130.73, 132.33, 136.17, 165.66, 171.56. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17. Found: C, 62.26; H, 5.31.

(2*S*,11a*S*)-2-Hydroxy-8-(benzyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (10b). This material was obtained by the reduction of **9b** by bakers' yeast according to the general procedure: mp 241–243 °C; $[\alpha]^{25}_D$ +253° (*c* = 0.23, CH_3OH); IR (KBr) (cm^{-1}) 3490, 1685, 1610, 1595; ^1H NMR δ 2.36 (1 H, m), 2.81 (1 H, br d, *J* = 13 Hz), 3.58–3.78 (5 H, m), 3.93 (3 H, s), 4.37 (1 H, dd, *J* = 8, 3 Hz), 4.52 (1 H, m), 7.21–7.86 (6 H, m), 8.18 (1 H, dd, *J* = 8, 2 Hz), 8.91 (1 H, br s). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.20; H, 5.47. Found: C, 65.07; H, 5.53.

(2*S*,11a*S*)-2-Hydroxy-8-(benzoyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (10c). This material was obtained by the reduction of **9c** by bakers' yeast according to the general procedure: mp 251–252 °C; $[\alpha]^{25}_D$ +259° (*c* = 0.26, CH_3OH); IR (KBr) (cm^{-1}) 3505, 1720, 1680, 1610, 1590; ^1H NMR δ 2.39 (1 H, ddd, *J* = 13, 8, 5 Hz), 2.78 (1 H, d, *J* = 13 Hz), 3.56 (1 H, br d, *J* = 11 Hz), 3.79 (2 H, m), 3.97 (3 H, s), 4.38 (1 H, dd, *J* = 8, 3 Hz), 4.51 (1 H, m), 7.21–7.76 (6 H, m), 8.21 (1 H, dd, *J* = 8, 2 Hz), 8.85 (1 H, br s). Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 62.63; H, 4.63.

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A Photochemically Based Synthesis of the Benzannelated Analogue of the CC-1065 A Unit

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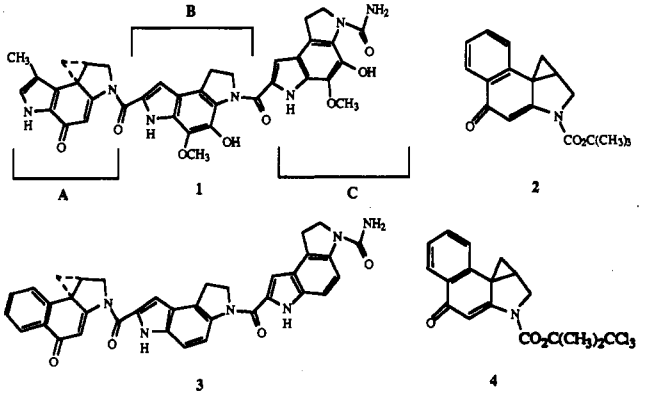
The antibiotic CC-1065 (1) ranks among the most potent antineoplastic agents known, although its in vivo toxicity precludes its use as a practical anticancer agent.[1] For this reason, considerable effort has been directed toward the synthesis of potentially less toxic analogues containing modified B and C units[2] and, to a lesser extent, modified A units.[3]

Several recent communications have described the first reports of a simple derivative (2) of the benzannelated analogue (CBI) of the natural CC-1065 A unit (CPI),[3a] as well as a full A, B, C analogue (3) containing this unit.[3b] Since the cytotoxic potency of these compounds is equal to or better than their CPI analogues, alternate higher yielding routes to the CBI system are desirable objectives in order to facilitate the production of further CBI derivatives for biological studies. As part of our investigations in this area, we now report a photochemically based synthesis of (±)-TCBOC-CBI (4) which provides the target compound in 24% overall yield from *N*-benzylpyrrole-2-carboxaldehyde (5).



The synthesis of 4 began with heterostilbene 7, which was constructed via a Wittig–Horner reaction from al-

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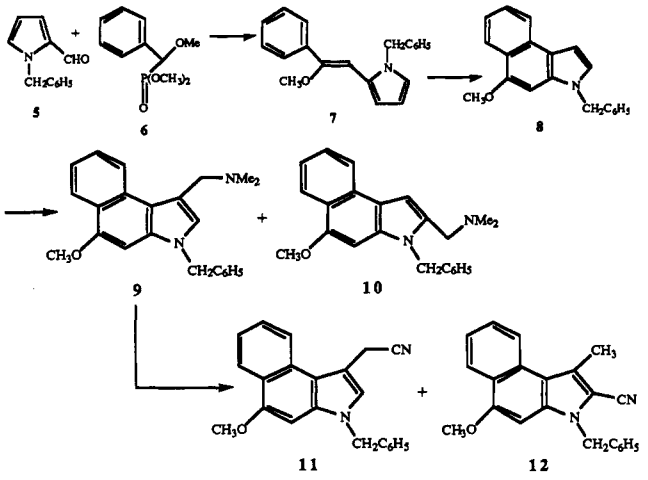
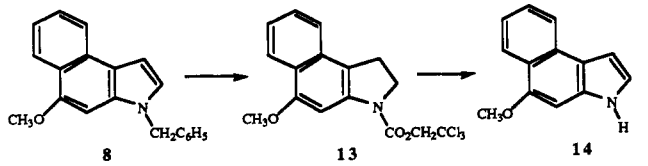
Scheme I



Scheme II

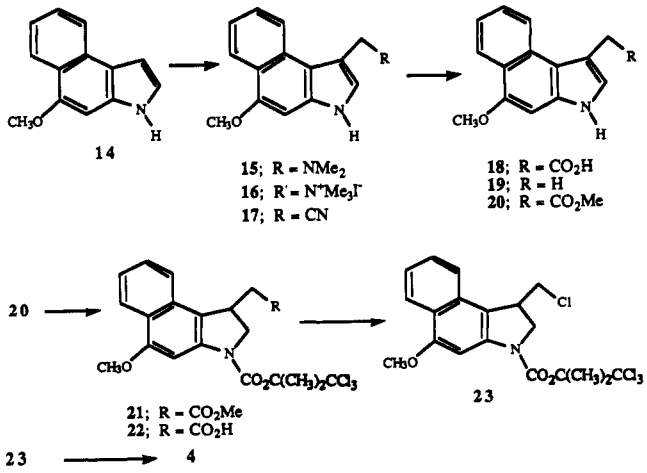


dehyde **5** and phosphonate ester **6** (K^+BuO^-, DMF, 91%). Stilbene **7** was photocyclized using our nonoxidative-dehydrogenation protocol[4] (*p*-NO_2BA Et_3N, Pd/C, CH_3CN, $h\nu$, 98%) which allowed for a clean conversion to the benzindole **8**. When a Mannich reaction (Me_2NH, CH_2O, CH_3CO_2H) was performed with indole **8**, two readily separable products, identified as the α- and β-gramine isomers **10** and **9** were obtained in a 5:3 ratio. Formation of this mixture was attributed to the presence of an alkyl group on the indole nitrogen as well as to the hindrance caused by the proton in the nine position.[5] A large quantity of **9** (β-isomer) was prepared and was converted to its methiodide (CH_3I, benzene, 90%) which was subsequently reacted with sodium cyanide. The cyanide reaction invariably produced the two isomers **11** (35%) and **12** (27%) (Scheme I). The formation of isomers in two consecutive steps made this pathway impractical, and we thus turned our attention to the removal of the benzyl group from indole **8**.

The debenzylation of **8** was readily achieved by a four-step procedure in 81% overall yield. Indole **8** was selectively reduced[6] ($NaCNBH_3$, AcOH, 95%) to the indoline, which was then protected ($ClCO_2CH_2CCl_3$, CH_3CN, 95%) to give the trichlorocarbamate **13**. Carbamate **13** was dehydrogenated (DDQ, benzene, reflux, 95%) and then deprotected[7] (dithienyl ditelluride, $NaBH_4$, 95%) to yield the NH indole **14** in 81% overall yield from its *N*-benzyl derivative **8** (Scheme II).

The Mannich reaction of indole **14** (aqueous dimethylamine and formalin in acetic acid) proceeded normally and yielded only the desired β-isomer **15** (93%). Methylation of **15** with methyl iodide in benzene gave

Scheme III



methiodide **16** (94%), which was converted to nitrile **17** (NaCN, EtOH/DMF, reflux, 60%), which in turn was hydrolyzed to acid **18** (NaOH, EtOH, reflux, 82%) (Scheme III). The acid was subjected to a variety of acidic esterification procedures, which unexpectedly yielded the decarboxylated indole **19** as the major product (>90%). However, when acid **18** was subjected to Kim's nonacidic esterification conditions[8] (CH_3O_2CCl, Et_3N, 0 °C → room temperature), the desired ester **20** was produced in high yield (95%). This ester was then reduced with sodium cyanoborohydride in acetic acid,[6] and the product was immediately protected with TCBOC chloride[9] to give the crystalline carbamate **21** (76% yield from indole ester **20**). Hydrolysis (5% NaOH, MeOH, room temperature, 89%) afforded the free acid **22**, which was then decarboxylatively halogenated using Barton's protocol.[10] Thus, acid **22** was converted to its acid chloride (ClCOCOCl, benzene), which was reacted with the sodium salt of 2-mercaptopyridine *N*-oxide and DMAP in boiling CCl_4 to furnish chloride **23** (81%). This chloride was demethylated and then directly cyclized (Et_3N, CH_3CN) to furnish dienone **4** (90%) as a stable pale tan solid.

Experimental Section

All melting points are uncorrected. All NMR spectra were recorded in $CDCl_3$ unless stated otherwise. The chemical shifts are referenced against TMS as an internal standard (δ = 10). All IR spectra are run as Nujol mulls unless stated otherwise. Elemental analyses (C, H, N) were carried out by Atlantic Microlabs, Norcross, GA. Photolyses were performed using specially designed water-cooled borosilicate immersion wells which were modeled after those available from Ace Glass Co. The light source was a Hanovia 450- or 1200-W, medium-pressure mercury vapor lamp.

α-Methoxybenzyl Phosphonate (6). To a mixture of benzaldehyde dimethyl acetal (100 g, 0.60 mol) and trimethyl phosphite (160 mL, 0.70 mol) in methylene chloride (1000 mL) at −24 °C was added freshly fused zinc chloride (200 g, excess). The mixture was slowly warmed to room temperature and stirred for 72 h. A mechanical stirrer was used to maintain good mixing of this mixture. The filtered organic layer was washed with water (3 × 500 mL), dried (Na_2SO_4), and concentrated to yield **6** as a colorless oil (134.0 g, 88.6%). This was used without further purification (lit.[11] bp 110 °C): ^1H NMR δ 3.39 (s, 3 H, OCH_3), 3.69 (6 H, J = 9.8, 4.6 Hz, $PO(CH_3)_2$), 4.55 (d, 1 H, J = 15.6 Hz, CH), 7.40 (m, 5 H, Ar-H); IR (neat, cm^{-1}) 2960, 2920, 2820, 1480,

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1440, 1250, 1170, 1080, 1060 (b), 1020, 940, 905, 850, 820, 790, 770, 695, 670; MS (EI) *m/e* (relative intensity) 231 (M + 1, 0.4) 230 (m^+, 3.0), 122 (7.8), 121 (100.0), 109 (2.4), 105 (4.9), 94 (27), 93 (4.6), 91 (10.6), 89 (2.1), 79 (3.8), 78 (1.8), 77 (15.2).

***N*-Benzylpyrrole-2-carboxaldehyde (5).** Pyrrole-2-carboxaldehyde (50.8 g, 0.53 mol) was added to benzene (250 mL) and sodium hydroxide (250 mL, 50%). To this suspension were added tetrabutylammonium iodide (2.0 g, cat.) and benzyl bromide (90.6 g, 0.53 mmol) (benzyl chloride could be used in place of the bromide), and the mixture was heated to reflux for 24 h. The cooled solution was separated, and the organic layer was washed with water (3 × 200 mL), dried (Na_2SO_4), and concentrated to yield crude aldehyde **5**. The aldehyde was purified by simple distillation (130 °C, 1.2 Torr; lit.[12] 153 °C, 5 Torr) to yield 89.6 g (90.5%).

***trans*-1-[2-(1-Benzyl-1*H*-pyrrol-2-yl)-1-methoxyethenyl]benzene (7).** To a stirred mixture of aldehyde **5**[12] (30.0 g, 0.16 mol) and phosphonate ester **6** (75.0 g, 0.0732 mol) in dry dimethylformamide (DMF, 500 mL) was added 33.0 g (0.295 mol) of potassium *tert*-butoxide, in 15 equal portions of 2.2 g each over a 6-h period. Progress of the reaction was followed by TLC. After complete disappearance of the starting material (6 h for addition of base and an additional 2 h) the reaction mixture was poured into water (1000 mL) and was extracted with ether (3 × 250 mL). The combined organic extracts were washed with water (2 × 500 mL), dried (Na_2SO_4), and concentrated onto silica (30 g). The adsorbed product was chromatographed (hexane–methylene chloride, 8:1) to afford **7** (42.4 g, 90.5%) as a tan oil, which upon heating and subsequent trituration with pentane yielded the pure product as a white solid (mp 64 °C): ^{1}H NMR δ 3.63 (s, 3 H, OCH_3), 5.17 (s, 2 H, $CH_2C_6H_5$), 5.46 (s, 1 H, 3 H), 5.55 (d, 1 H, *J* = 3.3 Hz, pyrrole-3H), 6.29 (t, 1 H, *J* = 3.2 Hz, pyrrole-4H), 6.59 (t, 1 H, *J* = 3.3 Hz, pyrrole-5H), 7.47–7.01 (m, 10 H, C_6H_5CH, $CH_2C_6H_5$); IR (neat, cm^{-1}) 3090, 3060, 3020, 2960, 1600, 1500, 1480, 1460, 1380, 1340, 1240, 1220, 1160, 1140, 1090, 1040, 1000, 930, 860, 840, 790, 710; MS (EI) *m/e* (relative intensity) 291 (m + 2, 2.6); 290 (m + 1, 19.3), 289 (m^+, 90.8), 198 (6.5), 183 (7.9) 169 (10.0), 168 (28.8), 167 (20.6), 154 (11.4), 105 (35.7), 92 (10.5), 91 (100.0), 77 (12.8), 65 (14.1). Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62. Found: C, 83.05; H, 6.65.

5-Methoxy-3-benzylbenz[*e*]indole (8). A solution of *p*-nitrobenzoic acid (2.05 g, 12.3 mmol), triethylamine (1.25 g, 12.3 mmol), 10% palladium on carbon (350 mg), silica (350 mg), acetonitrile (500 mL), and stilbene **7** (3.50 g, 12.2 mmol) was heated to a gentle reflux, while being purged with nitrogen for 30 min. The reaction mixture was then irradiated, maintaining a slow, constant stream of nitrogen. The reaction proceeded gradually to completion (28 h). The cooled mixture was filtered to remove the palladium on carbon, and the solvent was removed under reduced pressure. The crude product mixture was adsorbed on to silica gel and chromatographed (hexanes–methylene chloride, 6:1) to yield **8** as a white solid upon trituration with pentane (3.43 g, 97.8%; mp 133.5 °C). This solid was crystallized from absolute ethanol: ^{1}H NMR δ 3.94 (s, 3 H, OCH_3), 5.39 (s, 2 H, $CH_2C_6H_5$), 6.74 (s, 1 H, indole-7H), 6.99 (d, 1 H, *J* = 3.1 Hz, indole-2H) 7.4–7.0 (m, 7 H, C_6H_5, indole-3H,10H), 7.56 (st, 1 H, *J* = 5.9, 6.6 Hz, 9 H), 8.23 (dd, 2 H, *J* = 8.1, 6.6 Hz, peri-H's [8, 11]); IR (cm^{-1}) 1600, 1490, 1450, 1370, 1350, 1300, 1270, 1200, 1200, 1150, 1110, 1080, 1030, 990, 960, 840, 830, 805, 770, 750, 710, 6470; MS (EI) *m/e* (relative intensity) 289 (m + 2, 2.4), 288 (m + 1, 18.8), 287 (m^+, 85.9), 273 (6.9), 272 (34.2), 196 (25.8), 153 (163), 126 (9.9), 91 (100.0), 65 (32.7). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96. Found: C, 83.52; H, 5.96.

α- and β-Gramine Derivatives (10, 9). To a chilled solution of dimethylamine (40% aqueous, 4.3 g, 38.3 mmol) and formalin (37% aqueous, 3.1 g, 38.3 mmol) in glacial acetic acid was added 5-methoxy3-benzyl-3*H*-benz[*e*]indole (**8**) (10.0 g, 34.8 mmol) in portions at 0 °C. After being warmed to room temperature and stirred for 4 h, the solution was poured into ice water (500 mL) and basified with 50% NaOH. The crude product was extracted with ether (3 × 100 mL). The ether extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed (methylene chloride–hexane, 1:1) to yield α-gramine **10** (7.1 g, 59.3%, 138 °C) and β-gramine **9** (4.3 g, 35.6%, 123 °C) as shiny white plates. (Both compounds were recrystallized from EtOH, 95%).

α-Gramine 10: ^{1}H NMR δ 2.23 (s, 6 H, $N(CH_3)_2$), 3.47 (s, 2 H, CH_2NMe_2), 3.91 (s, 3 H, OCH_3), 5.61 (s, 2 H, $CH_2C_6H_5$), 6.72 (s, 1 H, benz[*e*]indole-4H), 6.87 (s, 1 H, benz[*e*]indole-1H), 7.24 (dd, 5 H, *J* = 2.4, 3.1 Hz, (C_6H_5), 7.51 (2 H, t, *J* = 7.0 Hz, benz[*e*]indole-7- and -8H), 8.15 (1 H, d, *J* = 8.1 Hz, benz[*e*]-indole-9H), 8.26 (1 H, d, *J* = 8.1 Hz, benz[*e*]indole-6H); IR (cm^{-1}) 1620, 1600, 1540, 1490, 1450, 1390, 1380, 1370, 1220, 1190, 1160, 1120, 1000, 990, 960, 850, 810, 790, 760, 750, 710; MS (EI) *m/e* (relative intensity) 346 (m + 2, 3.4), 345 (m + 1, 20.3), 344 (m^+, 81.4), 301 (21.2), 300 (100.0), 299 (69.9), 298 (13.6 (13.6), 284 (24.3), 92 (90), 91 (98.9), 65 (33.5), 58 (28.4). Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.2; H, 7.02. Found: C, 80.1; H, 7.04.

β-Gramine 9: ^{1}H NMR δ 2.38 [s, 6 H, $N(CH_3)_2$], 3.81 (s, 2 H, CH_2NMe_2), 3.93 (s, 3 H, OCH_3), 5.36 (s, 2 H, $CH_2C_6H_5$), 6.71 (s, 1 H, benz[*e*]indole-4H), 6.99 (s, 1 H, benz[*e*]indole-2H), 7.27 (dd, 5 H, *J* = 2.4, 3.1 Hz C_6H_5), 7.41 (t, 1 H, *J* = 7.0 Hz, benz[*e*]-indole-7H), 7.37 (t, 1 H, *J* = 7.0 Hz, benz[*e*]indole-8H), 8.29 (d, 1 H, *J* = 8.0 Hz, benz[*e*]indole-6H), 8.52 (d, 1 H, *J* = 8.0 H, benz[*e*]indole-9H); IR (Nujol, cm^{-1}) 1620, 1600, 1530, 1520, 1450, 1360, 1320, 1305, 1270, 1250, 1230, 1205, 1170, 1100, 1020, 990, 950, 860, 810, 790, 770, 750, 730, 700, 630; MS (EI) *m/e* (relative intensity) 346 (m + 2, 1.5), 345 (m + 1, 8.5), 344 (m^+, 34.2), 302 (12.5), 301 (62.1), 300 (100.0), 209 (11.7), 194 (8.5), 92 (8.1), 91 (91.7). Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.2; H, 7.02. Found: C, 80.0; H, 7.06.

5-Methoxy-3-benzylbenz[*e*]indole-1-acetonitrile and 1-Methyl-2-cyano-5-methoxy-3-benzylbenz[*e*]indole (11, 12). To gramine **9** (1.39 g, 4.0 mmol) in benzene (25 mL) was added methyl iodide (2.0 mL), and the solution was kept in the dark overnight. The product that precipitated was filtered and dried under vacuum to yield the corresponding methiodide (1.75 g, 89.7%, dec ~180 °C).

A solution of the methiodide (8.48 g, 17.3 mmol), sodium cyanide (1.02 g, 20.8 mmol), and dimethyl formamide (150 mL) was refluxed under nitrogen until no more trimethylamine was evolved (ca. 4 h). The cooled solution was poured into water (300 mL) and then extracted with ether (3 × 100 mL). The ethereal layer was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated, and the residue was chromatographed (hexane–ethyl acetate, 7:1) to yield acetonitrile **11** (2.0 g, 35.3%) and indole **12** (1.5 g, 27.1%) as crystalline white compounds (**11**, mp 158 °C; **12**, mp 172 °C). Both of these compounds were crystallized from ethyl acetate–hexane.

Acetonitrile 11: ^{1}H NMR δ 3.94 (s, 3 H, OCH_3), 4.17 (s, 2 H, CH_2CN), 5.35 (s, 2 H, $CH_2C_6H_5$), 6.72 (s, 1 H, benz[*e*]indole-2H), 7.17 (dd, AB, 6 H, benz[*e*]indole-4H, $CH_2C_6H_5$), 7.44 (t, 1 H, *J* = 7.7 Hz, benz[*e*]indole-7H), 7.60 (t, 1 H, *J* = 7.6 Hz, benz[*e*]-indole-8H), 8.07 (d, 1 H, *J* = 8.1 Hz, benz[*e*]indole-6H), 8.34 (d, 1 H, *J* = 8.3 Hz, benz[*e*]indole-9H); IR (cm^{-1}) 1620, 1600, 1570, 1550, 1500, 1420, 1390, 1370, 1300, 1290, 1270, 1250, 1200, 1160, 1150, 1100, 1050, 1000, 980, 940, 910, 805, 770, 730, 710, 680, 660, 640; MS (EI) *m/e* (relative intensity) 328 (m + 2, 2.7) 327 (m + 1, 17.5), 326 (m^+, 58.2), 279 (18.9), 235 (26.9), 167 (34.5), 150 (11.2), 149 (100.0), 91 (40.2), 71 (16.0), 70 (14.5), 656 (11.4), 57 (27.5), 55 (9.1). Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56. Found: C, 80.88; H, 5.59.

Cyanoindole 12: ^{1}H NMR δ 2.83 (s, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 5.47 (s, 2 H, $CH_2C_6H_5$), 6.62 (s, 1 H, benz[*e*]indole-4H), 7.28, 7.40 (dd, AB, 5 H, *J* = 5.8, 2.2 Hz $CH_2C_6H_5$), 7.48 (t, 1 H, *J* = 7.6 Hz, benz[*e*]indole-7H), 7.64 (t, 1 H, *J* = 7.2 Hz, benz-[*e*]indole-8H), 8.33 (t, 2 H, *J* = 7.1 Hz, benz[*e*]indole-5, 8H); IR (cm^{-1}) 2200, 1620, 1600, 1400, 1300, 1260, 1230, 1190, 1160, 1100, 1070, 1030, 970, 950, 800, 760, 740, 700, 670; MS (EI) *m/e* (relative intensity) 328 (m + 2, 3.5), 327 (m + 1, 25.5), 326 (m^+, 100.0), 311 (7.6), 236 (16.5), 235 (97.8), 220 (18.5), 192 (16.5), 191 (6.8), 139 (7.3), 92 (9.1), 91 (96.8), 65 (17.1). Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56. Found: C, 80.90; H, 5.60.

2,2,2-Trichloroethyl 5-Methoxy-1,2-dihydrobenz[*e*]-indole-3-carboxylate (13). To a solution of 5-methoxy-3-benzylbenz[*e*]indole (**8**) (10.0 g, 34.8 mmol) in glacial acetic acid (100 mL) at 15 °C was added sodium cyanoborohydride in 25 mg portions until no starting material remained by TLC. The solution was poured into water (300 mL) and extracted with ether (3 t 150

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mL). The aqueous layer was basified cautiously with saturated sodium bicarbonate to pH 7.5–8.0 and was extracted with ether. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was chromatographed (hexane–ethyl acetate, 10:1) to give the indoline as a pale yellow solid which crystallized from ethanol–water (9.08 g, 90.2%, mp 57 °C). To a solution of the indoline (10.0 g, 35.9 mmol) in acetonitrile (30 mL) at 0 °C was added trichloroethyl chloroformate (7.0 mL, 39.5 mmol). The mixture was purged with nitrogen (3×), stirred at 0 °C for 45 min, and slowly warmed to room temperature and stirred for an additional hour. The precipitate was filtered, and the filtrate was concentrated and redissolved in acetonitrile (2 mL). This solution was cooled in the freezer for 2 h, and the precipitate was filtered and combined with the first crop to yield ester **13** (9.7 g, 75.0%) as a whitish-yellow solid (mp 195 °C dec) which was crystallized from 95% ethanol: ^{1}H NMR δ 3.39 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 4.04 (s, 3 H, OCH_3), 4.30 (t, 2 H, J = 8.5 Hz, NCH_2), 4.89 (s, 2 H, $CO_2CH_2CCl_3$), 7.61–7.34 (m, 3 H, indole-7,8,9H), 7.71 (s, 1 H, indole-4H), 8.22 (d, 1 H, J = 8.3 Hz, indole-6H); IR (cm^{-1}) 1710, 1640, 1590, 1520, 1480, 1460, 1450, 1430, 1400, 1380, 1320, 1270, 1260, 1240, 1210, 1160, 1150, 1100, 1050, 980, 900, 840, 820, 800, 780, 760, 710, 660, 650, 630, 610; MS (EI) m/e (relative intensity) 377 (m + 2, 31.0), 376 (m + 1, 20.8), 375 (m$^+$, 100.0), 374 (32.7), 373 (99.0), 372 (14.1), 243 (19.3), 199 (13.3), 198 (36.5), 183 (14.7), 182 (12.5), 171 (28.5), 167 (12.9), 128 (22.4), 127 (11.8). Anal. Calcd for $C_{16}H_{14}NO_3Cl_3$: C, 52.29; H, 3.77. Found: C, 52.28; H, 3.84.

5-Methoxybenz[*e*]indole (14). To a solution of indoline-carbamate **13** (10.0 g, 26.69 mmol) in benzene (400 mL) was added dicyanodichloroquinone (DDQ, 6.06 g, 26.6 mmol), and the mixture was refluxed under nitrogen for 12 h. The solution was cooled, washed with 2% NaOH (2 × 200 mL) and water (2 × 200 mL), dried (Na_2SO_4), concentrated, and chromatographed (hexane–methylene chloride, 3:1) to yield the corresponding N-protected indole (7.5 g, 76.2%) as a white crystalline solid after trituration with hexane. A solution of the N-protected indole (7.5 g, 20.12 mmol), anhydrous tetrahydrofuran (150 mL), and 2,2′-dithienyl ditelluride (1.0 g, 2.3 mmol) were warmed to 60–70 °C (external temperature). The red solution was treated with aqueous sodium borohydride ($NaBH_4/H_2O/NaOH$, 5.0 g; 25 mL; 3 drops of 10%) until a yellow color persisted under a nitrogen atmosphere. The solution was cooled, and the tellurolate was oxidized back to the red ditelluride by passing air through the reaction mixture. The volatiles were removed, the resulting oil was triturated with water/hexane mixture (100 mL each), and the resulting solid was filtered. The solid was dissolved in methylene chloride, washed with water (2 × 100 mL), dried (Na_2SO_4), concentrated, and chromatographed (hexane–ethyl acetate, gradient 7:1 to 3:1) to yield indole **14** (3.35 g, 84.4%) as a pale white solid which was crystallized from methanol/water and melted at 104 °C: ^{1}H NMR δ 4.00 (s, 3 H, OCH_3), 6.87 (s, 1 H, indole-4H), 7.03 (dd, 2 H, J = 2.6, 7.7 Hz, indole-1,2H), 7.63–7.32 (m, 2 H, indole-7,8H), 8.19, 8.30 (dd, AB, J = 7.7, 8.7 Hz, indole-6,9H); IR (cm^{-1}) 3350, 1620, 1600, 1480, 1470, 1430, 1380, 1370, 1280, 1200, 1170, 1060, 1150, 1100, 1080, 1030, 990, 970, 900, 870, 840, 820, 780, 770, 740, 680, 670, 640, 630, 610; MS (EI) m/e (relative intensity) 198 (m + 1, 1.8), 197 (21.7), 196 (7.7), 195 (2.5), 182 (4.7), 181 (2.6), 155 (2,7), 154 (29.0), 153 (100.0), 152 (2.2). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62. Found: C, 79.08; H, 5.66.

1-((Dimethylamino)methyl)-5-methoxy-3*H*-benz[*e*]indole (15). To a chilled solution of dimethylamino (40% aqueous, 3.5 mL, 22.2 mmol) and formalin (37% aqueous, 1.8 g, 22.2 mmol) in glacial acetic acid was added 5-methoxy-3*H*-benz[*e*]indole **14** (5.0 gm, 22.1 mmol) in portions at 0 °C. After warming to room temperature and stirring for 4 h, the solution was poured into ice water (500 mL) and basified with 50% NaOH. The resulting viscous paste was extracted with ether (3 × 150 mL), dried (Na_2SO_4), and concentrated. Under high vacuum the material dried to colorless flakes of gramine **15** (6.0 gm, 93.0%), which could be recrystallized from benzene to yield the pure gramine (mp 88 °C): ^{1}H NMR δ 2.23 (s, 6 H, $N(CH_3)_2$), 3.64 (s, 2 H, CH_2NMe_2), 3.99 (s, 3 H, OCH_3), 6.79 (s, 1 H, NHC*H*), 6.84 (s, 1 H, benz[*e*]indole-5H), 7.50 (dd, 2 H, J = 7.47, 8.36 Hz), 8.19 (dd, 2 H, J = 8.36, 7.1 Hz), 8.9 (s, 1 H, NH); IR (cm^{-1}) 34,00, 1620, 1610, 1550, 1390, 1370, 1290, 1250, 1200, 1180, 1130, 1100, 1040, 1020, 1005, 990, 830, 810, 740, 720; MS (EI) m/e (relative intensity) 255 (m + 1, 8.7), 254 (m$^+$, 30.1), 211 (24.4), 210 (100.0), 209 (17.4), 195 (20.1), 167 (12.3), 139 (10.5). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13. Found: C, 75.53; H, 7.06.

1-((Dimethylamino)methyl)-5-methoxy-3*H*-benz[*e*]indole Methiodide (16). To gramine **15** (5.8 g, 22.8 mmol) in benzene (15 mL) was added methyl iodide (4.0 gm, 29.6 mmol, 1.3 equiv) and the solution was placed in the dark overnight. The precipitate was filtered and dried under vacuum to yield methiodide **16** (8.45 g, 93.6%, dec 160 °C): ^{1}H NMR (d_6-DMSO) δ 3.37 (s, 9 H, $N(CH_3)_3$), 4.02 (s, 3 H, OCH_3), 4.72 (s, 2 H, $CH_2N(CH_3)_3$), 7.06 (s, 1 H, NHC*H*), 7.7–7.2 (m, 3 H, benz[*e*]indole-5H,7H,9H), 8.2–8.0 (m, 2 H, benz[*e*]indole-7H,10H), 11.6 (br s, 1 H, NH); IR (cm^{-1}) 3400, 1630, 1620, 1610, 1390, 1260, 1240, 1210, 1160, 1120, 1030, 980, 950, 825, 770, 730. Anal. Calcd for $C_{17}N_{21}N_2OI$: C, 51.53; H, 5.56. Found: C, 51.59; H, 5.44.

5-Methoxy-3*H*-benz[*e*]indole-1-acetonitrile (17). A solution of methiodide **16** (4.69 g, 11.8 mmol), sodium cyanide (0.87 g, 17.7 mmol, 1.5 equiv), dimethylformamide (75 mL), and ethanol (95%, 75 mL) was refluxed under a nitrogen flow until no more trimethylamine (evolved (ca. 3 h). The cooled solution was concentrated, dissolved in water (500 mL), and extracted with ether (3 × 100 mL). The etheral layer was washed with water (2 × 200 mL), dried (Na_2SO_4), and evaporated onto silica (10 g). Chromatography on silica (hexane–ethyl acetate, 4:1) yielded nitrile **17** (1.65 g, 60.0%) as a white solid which was crystallized from ethanol–water (mp 168 °C): ^{1}H NMR δ 3.97 (s, 2 H, CH_2CN), 4.01 (s, 3 H, OCH_3), 6.83 (s, 1 H, benz[*e*]indole-6H), 6.86 (s, 1 H, NHC*H*), 7.5–7.3 (m, 3 H), 8.3–8.0 (m, 2 H); IR (cm^{-1}) 3400, 1630, 1610, 1540, 1390, 1320, 1400, 1280, 1210, 1160, 1150, 1130, 1050 1000, 980, 830, 820, 770; MS (EI) m/e (relative intensity) 237 (m + 1, 10.1), 236 (m$^+$, 78.8), 222 (15.7), 221 (100.0), 193 (9.3), 192 (12.3), 167 (4.2), 166 (11.0), 164 (6.6). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12. Found: C, 76.11; H, 5.14.

5-Methoxy-3*H*-benz[*e*]indole-1-acetic Acid (18). A solution of acetonitrile **17** (0.96 g, 4.07 mmol), ethanol (95%, 20 mL), water (20 mL), and potassium hydroxide (2.0 g) was refluxed until no more ammonia evolved (ca. 12 h). The cooled solution was concentrated, and water (200 mL) was added. The aqueous solution was acidified to pH 2 with 10% H_2SO_4 and extracted with ether. The ethereal layer was dried (Na_2SO_4) and concentrated to yield acetic acid **17** (0.75 g, 72.1%), which crystallized from benzene to yield a colorless solid (mp 180 °C). This compound is not stable for long period of time at room temperature and was stored at 0 °C: ^{1}H NMR (d_6-DMSO) δ 3.76 (s, 2 H, CH_2CO_2H), 3.95 (s, 3 H, OCH_3), 6.59 (s, 1 H, NHC*H*), 6.74 (s, 1 H, benz[*e*]indole-6H), 7.41 (t, 1 H, J = 7.49 Hz), 7.51 (t, 1 H, J = 7.53 Hz), 8.11 (t, 2 H, J = 6.5 Hz), 11.2 (br s, 1 H, NH); IR (cm^{-1}) 3400, 1705, 1650, 1640, 1540, 1450, 1390, 1260, 1200, 1100, 1020, 980, 800, 760, 710; MS (EI) m/e (relative intensity) 211 (m – CO_2, 58.8), 197 (12.1), 94 (12.8), 79 (17.0), 78 (37.6), 77 (16.1), 50 (16.3). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13. Found: C, 70.31; H, 5.05.

5-Methoxy-1-methyl-3*H*-benz[*e*]indole (19). A solution of benz[*e*]indoleacetic acid **18** (2.0 g, 7.8 mmol), camphorsulfonic acid (40 mg), and absolute methanol (50 mL) was stirred at 0 °C. The solution was allowed to slowly warm to room temperature and stirred until no starting material remained by TLC (ca. 12 h). The solvent was removed under reduced pressure, and the crude product was chromatographed on silica (methylene chloride–hexane, 2:1) to yield the skatole **19** (1.5 g, 91.1%), which was crystallized from methanol–water: mp 148 °C; ^{1}H NMR δ 2.49 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 6.65 (s, 1 H), 6.82 (s, 2 H), 7.39 (t, 1 H, J = 7.48 Hz), 7.54 (s, 1 H, J = 7.5 Hz), 7.98 (br s, 1 H), 8.09 (d, 1 H, J = 8.7 Hz), 8.27 (d, 1 H, J = 8.5 Hz); IR (cm^{-1}) 3400, 1630, 1610, 1540, 1360, 1300, 1270, 1200, 1160, 1140, 1190, 1100, 1040, 1020, 990, 970, 950, 930, 840, 750, 640; MS (EI) m/e (relative intensity) 212 (m + 1, 8.8), 255 (55.1), 197 (12.6), 196 (100.0); 168 (8.8), 167 (13.8). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.23; H, 6.60. Found: C, 79.41; H, 6.75.

1-(Carbomethoxymethyl)-5-methoxy-3*H*-benz[*e*]indole (20). To a solution of acetic acid **18** (386.7 mg, 1.44 mmol) in methylene chloride (25 mL) at 0 °C was added methyl chloroformate (143.1 mg, 1.44 mmol) and triethylamine (168.7 mg, 1.66 mmol). The solution was stirred at 0 °C for 30 min and then treated with (dimethylamino)pyridine (37.0 mg, 0.2 equiv). The solution was slowly warmed to room temperature and stirred for an additional 1 h. It was diluted with methylene chloride (100

mL) and was washed with saturated ammonium chloride solution (2 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated, and the residue was chromatographed (methylene chloride–hexane, 3:2) to afford ester **20** (0.386 g, 94.8%). The ester was purified by crystallization from methanol–water (mp 86 °C): ^{1}H NMR δ 3.75 (s, 3 H, CO_2CH_3), 3.87 (s, 2 H, $CH_2CO_2CH_3$), 3.95 (s, 3 H, OCH_3), 6.80 (s, 1 H, benz[e]indole-6H), 7.605–7.37 (m, 3 H), 8.18 (dd, 2 H, J = 8.35, 1.32 Hz), 8.81 (s, 1 H, NH); IR (cm^{-1}) 3400, 1610, 1600, 1550, 1450, 1380, 1300, 1270, 1200, 1160, 1140, 1100, 1040, 1010, 1000, 980, 950, 820, 790, 750, 715, 700, 640, 630; MS (EI) m/e (relative intensity) 269 (m$^+$, 11.7), 196 (41.2), 69 (10.0), 59 (7.0), 58 (100.0), 57 (17.1). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.51; H, 5.64.

2,2,2-Trichloro-1,1-dimethylethyl 1-(Carbomethoxymethyl)-5-methoxy-1,2-dihydrobenz[e]indole-3-carboxylate (21). To a solution of methyl ester **20** (250 mg, 0.54 mmol) in glacial acetic acid (20 mL) at 15 °C was added sodium cyanoborohydride (25-mg portions) until no starting material remained by TLC (1.3 equiv). The crude product was poured into water and basified with saturated aqueous sodium bicarbonate to pH 7.5–8.0. The indole was extracted with ether (3 × 100 mL), dried (Na_2SO_4), and concentrated to a pale yellow oil, which was immediately used without purification. The crude indoline was dissolved in acetonitrile (20 mL), cooled in an ice bath, and treated with triethylamine (103 mg, 0.60 mmol), followed by 2,2,2-trichloro-1,1-dimethylethyl chloroformate (144 mg, 0.60 mmol), and 4-(dimethylamino)pyridine (50 mg). The mixture was kept for 12 h at room temperature under a nitrogen atmosphere. The acetonitrile was removed under reduced pressure, and the resulting oil was poured into water (100 mL) and extracted with ether (3 × 100 mL). The etheral layer was washed with 10% H_2SO_4 (2 × 100 mL), dried (Na_2SO_4), concentrated, and chromatographed (2:1 methylene chloride–hexane) to yield carboxylate **21** (270 mg, 76.1%), which was crystallized from methanol (mp 139–140 °C): ^{1}H NMR δ 2.1 (s, 6 H), 2.55–2.68 (m, 2 H), 3.08 (t, 2 H, J = 5.1 Hz), 3.65 (s, 3 H), 4.0 (s, 3 H, OCH_3), 5.02 (br s, 1 H), 7.5–7.2 (m, 3 H), 8.21 (d, 2 H, J = 7.6 Hz); IR (cm^{-1}) 1750, 1680, 1650, 1590, 1510, 1450, 1430, 1380, 1300, 1250, 1200, 1050, 1000, 950, 900, 880, 670, 640; MS (EI) m/e (relative intensity) 477 (m + 2, 13.8), 476 (m + 1, 10.9), 475 (m$^+$, 46.8), 474 (12.2), 473 (40.6), 401 (10.9), 399 (10.4), 272 (25.0), 271 (100.0), 270 (11.7), 256 (15.1), 241 (12.2), 211 (11.2), 210 (53.9), 199 (16.9), 198 (93.7), 197 (71.4), 196 (18.8), 195 (15.3), 183 (16.9), 182 (43.9), 107 (23.4), 154 (14.1), 128 (14.1), 128 (18.1), 127 (23.6), 125 (16.5), 123 (22.7), 91 (15.5), 89 (25.5), 87 (21.9), 77 (12.2), 59 (16.2), 53 (15.8). Anal. Calcd for $C_{21}H_{22}NO_5Cl_3$: C, 58.28; H, 4.59. Found: C, 58.51; H, 4.49.

2,2,2-Trichloro-1,1-dimethylethyl 5-Methoxy-1-(carboxymethyl)-1,2-dihydrobenz[e]indole-3-carboxylate (22). To a solution of ester **21** (318.3 mg, 0.67 mmol) in methanol (10 mL) was added 20% sodium hydroxide (2 mL). The solution was stirred at room temperature until no starting material was present by TLC (ca. 12 h). The reaction mixture was evaporated to dryness. The resulting salt was dissolved in water (50 mL) and acidified to pH 2 with 10% sulfuric acid. The product was extracted with ether, dried (Na_2SO_4), and concentrated to yield **22** (304.3 mg, 98.5%) as an off-white (greenish tint) solid (mp 179–180 °C): ^{1}H NMR δ 2.00 (s, 6 H, $C(CH_3)_2$), 3.94 (s, 3 H, OHC_3), 4.29–4.65 (m, 5 H), 7.30 (s, 1 H), 7.37–7.53 (m, 2 H), 7.6–8.0 (m, 2 H); IR (cm^{-1}) 3500–2800 (b), 1710, 1640, 1590, 14780, 1370, 1300, 1240, 1160, 1130, 1020, 980, 840, 800, 780, 750, 720; MS (EI) m/e (relative intensity) 463 (m + 2, 11.4), 461 (m$^+$, 27.7), 459 (29.2), 315 (12.1), 257 (85.0), 256 (28.2), 255 (37.1), 240 (10.4), 212 (10.7), 211 (40.5), 210 (48.78), 199 (24.0), 198 (100.0), 197 (62.1), 196 (76.9), 195 (18.8), 183 (21.1), 182 (39.8), 168 (13.3), 167 (37.1), 166 (12.1), 154 (14.6), 140 (10.9), 139 (16.0), 128 (21.4), 127 (28.9), 126 (17.0), 125 (10.9), 124 (22.6), 123 (12.9), 111 (13.6), 109. (19.9), 91 (17.7), 89 (49.3), 87 (14.6), 84 (11.2), 77 (13.3), 53 (49.3). Anal. Calcd for $C_{20}H_{20}NO_5Cl_3$: C, 52.13; H, 4.41. Found: C, 52.23; H, 4.49.

2,2,2-Trichloro-1,1-dimethylethyl 5-Methoxy-1-(chloromethyl)-1,2-dihydrobenz[e]indole-3-carboxylate (23). To a solution of **22** (250 mg, 0.54 mmol), DMF (1 drop), and benzene (25 mL) was added oxalyl chloride (0.52 mL, 0.60 mmol). After stirring for 30 min under a nitrogen atmosphere, the yellow-brown solution of acid chloride was evaporated to dryness at room temperature in vacuo. To the resulting oil was added the sodium salt of 2-mecaptopyridine N-oxide (80.5 mg, 0.6 mmol), 4-(dimethylamino)pyridine (10 mg), and carbon tetrachloride (25 mL). The mixture was evacuated, purged with nitrogen (3X), and heated to reflux for 4 h. The cooled solution was filtered, concentrated, and chromatographed (methylene chloride–hexane, 1:1) to yield chloride **23** as a colorless oil (81.1%): ^{1}H NMR δ 2.04 (s, 6 H), 3.57 (dd, 2 H, J = 9.4, 15.7 Hz), 3.96 (dd, J = 2.3, 10.7 Hz), 4.04 (s, 3 H), 4.91–4.87 (m, 1 H), 7.38 (t, 1 H, J = 7.2 Hz), 7.61 (s and d, 2 H, J = 8.5 Hz), 7.52 (t, 1 H, J = 7.45 Hz), 8.22 (d, 1 H, J = 8.4 Hz); IR (cm^{-1}) 1770, 1740, 1605, 1590, 1550, 1450, 1320, 1280, 1210, 1190, 1160, 1100, 1050, 1020, 920, 900, 820, 800, 750, 730, 710; MS (EI) m/e (relative intensity) 451 (m$^+$, 15.8), 449 (11.6, 293 (26.6), 292 (15.5), 291 (100.0), 246 (10.5), 242 (13.8), 198 (26.6), 197 (14.5), 196 (15.5), 182 (15.5), 171 (12.4), 167 (13.8), 159 (12.0), 128 (11.5), 127 (14.2), 125 (10.5), 123 (15.5), 102 (16.8), 100 (14.2), 89 (14.7), 87 (10.1), 84 (14.2), 72 (10.2). Anal. Calcd for $C_{19}H_{19}NO_3Cl_4$: C, 50.52; H, 4.43. Found: C, 50.61; H, 4.49.

***N*-((2,2,2-Trichloro-1,1-dimethylethoxy)carbonyl)-1,2,10,10α-tetrahydrocyclopropa[1,2-*c*]benz[*e*]indol-5-one (4).** To a solution of chloride **23** (39 mg, 0.086 mmol) in 1,2-dichloroethane (5 mL) was added boron trichloride–dimethylsulfide complex (250 mg, excess) in 5 equal portions. The solution was refluxed until no starting material remained (ca. 4 h). The cooled solution was poured into water (20 mL), and the crude product was extracted with methylene chloride (3 × 25 mL), dried (Na_2SO_4), and concentrated. This crude oil was treated with Et_3N (0.5 mL) in CH_3CN (5 mL), and the reaction mixture was stirred vigorously for 3 h (23 °C) under nitrogen. The solvent was removed under reduced pressure, and the oil was washed with methylene chloride–water, and the methylene chloride layer was dried (Na_2SO_4), evaporated at room temperature, and chromatographed CH_2Cl_2–ether (10:1) to yield **4** as a tan colored solid (mp 131 °C): ^{1}H NMR δ 1.3–1.2 (m, 1 H), 1.65 (br s, 2 H), 1.97 (d, 1 H, J = 6.5 Hz), 2.04 (t, 1 H, J = 7.9 Hz), 2.18 (s, 6 H), 7.39 (s, 1 H), 7.8–7.4 (m, 4 H); MS (EI) m/e (relative intensity) 400.7 (m$^+$, 15.8), 279 (18.4), 278 (16.1), 167 (40.5), 150 (10.8), 149 (100.0), 147 (10.7), 129 (35.5), 113 (11.6), 112 (13.2), 84 (17.2), 83 (19.9), 77 (28.1), 71 (26.9), 70 (23.6), 69 (11.6), 57 (33.8). Anal. Calcd for $C_{18}H_{16}NO_3Cl_3$: C, 53.92; H, 4.02. Found: C, 54.01; H, 4.53.

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A Convenient Method for β-Lactam Formation from β-Amino Acids Using Phenyl Phosphorodichloridate Reagent

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In recent years there has been considerable interest in the development of efficient methods for the construction of appropriately substituted azetidin-2-ones because of the importance of β-lactam antibiotics.[1] Although there are a variety of methods for the construction of the β-lactam ring,[2] one of the most useful approaches is based on dehydration of β-amino acids by means of condensing agents.[3,4] Phosphorus reagents are known to be efficient activating agents for the carboxyl group;[5] however, with the exception

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