A General Synthesis of Pyrroles and Fused Pyrrole Systems from Ketones and Amino Acids

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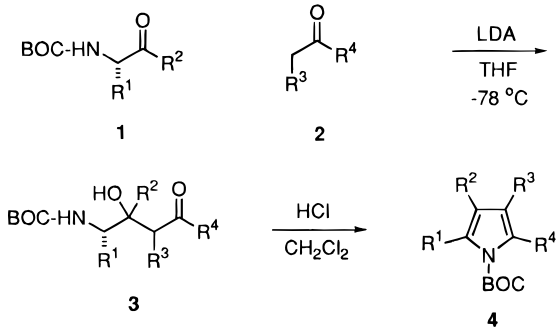
Received February 27, 1996[⊗]

The lithium enolates of ketones react with BOC-α-amino aldehydes and BOC-α-amino ketones to afford aldol intermediates that cyclize under acidic conditions to yield pyrroles. The BOC-amino aldehydes and ketones are readily available from α-amino acids. The method allows incorporation of a wide variety of substituents at any of the five atoms of the pyrrole ring and is also suitable for the preparation of fused pyrrole systems.

The importance of the pyrrole ring system has continued to stimulate a great deal of interest in the development of new methodologies for the synthesis of substituted pyrroles. Several recent reviews on this topic are now available.[1−3] We have been concerned with the potential elaboration of a new pyrrole synthesis in which BOC-α-amino aldehydes (**1**, $R^2 = H$) or ketones (**1**, $R^2 = CH_3$) are reacted with the lithium enolates derived from ketones **2** to afford, after protonation, aldol intermediates **3**, which then cyclize to the desired pyrroles **4** under mild acidic conditions (Scheme 1).[4] Although conceptually related to the familiar Knorr pyrrole synthesis, in which α-oximino ketones are reduced to α-amino ketones and then reacted with *β*-diketones or *β*-keto esters to afford substituted pyrroles,[5] the present method would offer the advantage of employment of BOC-α-amino aldehydes or ketones **1** that are readily available from a wide variety of amino acids. The advantageous application of amino acids as synthons for various heterocyclic systems, including pyrroles, has recently been summarized.[6] In addition, the pyrrole synthesis outlined in Scheme 1 utilizes simple ketones instead of the *β*-diketones or *β*-keto esters that are normally used in the Knorr synthesis, and it avoids the dicarbonyl intermediate **5** and subsequent alternative aldol reactions that lead to Fischer−Fink products **8** and **9** as well as the Knorr product **6** in the Knorr pyrrole synthesis (Scheme 2).[5]

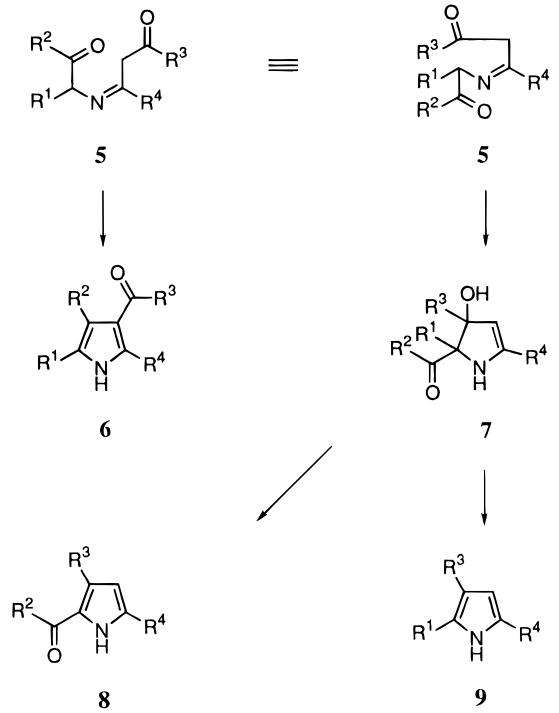
A preliminary paper documented a limited number of examples of the strategy outlined in Scheme 1 for the synthesis of fused pyrrole systems.[4] The present study was undertaken in order to investigate the utility and scope of this new pyrrole synthesis.

Scheme 1



1 2 3 4

Scheme 2



5 5 6 7 8 9

Results and Discussion

The α-amino aldehydes and ketones were prepared from commercially available BOC-amino acids as outlined in Scheme 3.[7−10] Conversion of the starting materials **10** to Weinreb amide intermediates **11** was carried out in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP re-

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⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1996.

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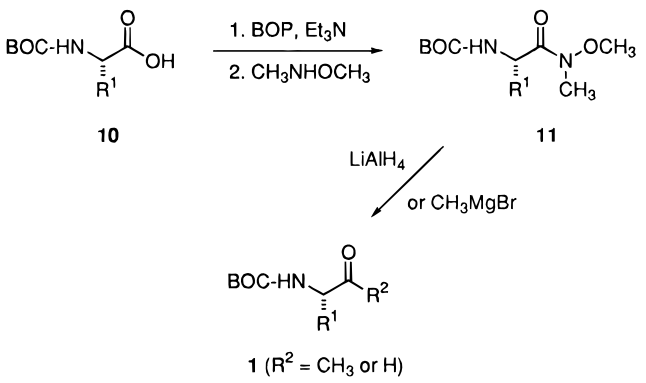
S0022-3263(96)00401-X CCC: $12.00

Scheme 3

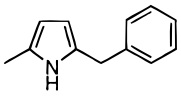


agent) and *N*,*O*-dimethylhydroxylamine. The *N*-methoxy-*N*-methylamides **11** were either reduced with lithium aluminum hydride to BOC-α-amino aldehydes **1** (R^2 = H) or treated with methylmagnesium bromide to afford BOC-α-amino ketones **1** ($R^2 = CH_3$).

Seventeen examples of the conversion of BOC-α-amino aldehydes or ketones **1** to various substituted pyrroles and fused pyrrole systems are listed in Table 1. The reactions were performed by adding the BOC-α-amino aldehydes or ketones **1** to solutions of the lithium enolates of the ketones **2** in THF at −78 °C. The aldol products **3** were obtained as crude diastereomeric mixtures that were cyclized without purification under mild acidic conditions in methylene chloride at room temperature. The products were usually obtained as oils in moderate yields after thin-layer or column chromatography on silica gel.

Examination of the results in Table 1 shows that the method has considerable versatility. Reaction of BOC-L-alaninal **(12)** and BOC-L-phenylalaninal **(15)** with acetone **(13)** gave the corresponding 1,2,5-trisubstituted pyrroles **14**[11] and **16**, respectively. As demonstrated by the reaction of BOC-*S*-trityl-L-cysteinal **(17)** with diethyl ketone **18** to afford pyrrole **19**, the use of a larger ketone **18** (relative to **13**) leads to 1,2,3,5-substituted pyrroles. The reaction of 2-acetyl-5-methylfuran **(21)** with BOC-L-methioninal **(20)** provided the pyrrole **22** having an aromatic substituent. Various fused pyrrole systems **24**, **26**, **27**, **29**, **32**, **33**, **35**, **37**, and **39** were readily obtained when cyclic ketones were reacted with BOC-L-amino aldehydes. Reaction of BOC-α-amino ketones **40** or **42** with ketones **13**, **23**, **44**, or **36** afforded pyrroles **41**, **43**, **45**, and **46** having alkyl groups on the pyrrole carbon derived from the amino acid carboxyl group. The pyrrole synthesis presented here should also accommodate a variety of amino acid protecting groups, leading to different N-1 substituents on the pyrrole. This was investigated in a limited sense with *N*-[(carbobenzyloxy)-carbonyl]-L-leucinal **(28)**, which gave the corresponding *N*-CBZ-2-isobutyl-4,5,6,7-tetrahydroindole **(29)**. It is therefore possible to incorporate substituents at any of the five positions of the pyrrole ring using this method.

The deprotection of the BOC-pyrroles was investigated in a limited number of cases. Treatment of the substituted pyrrole **16** with sodium methoxide in a mixture of methanol and THF, followed by acidification with a 10% solution of acetic acid in methanol, afforded 2-benzyl-5-methylpyrrole **(47)**.[12] Similarly, the BOC group was removed from **32** under the same conditions to give the corresponding pyrrole **48**.



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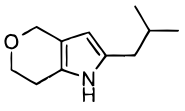

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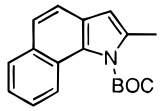

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The possibility of dehydrogenating **39** to a benzindole system was also investigated. Treatment of **39** with DDQ in benzene at room temperature afforded the desired benzindole **49**.

The present pyrrole synthesis, passing through aldol intermediates **3**, bears some resemblance to several syntheses of 3-methylpyrrole **(50)** that have appeared in the literature. The 4-amino acetal **51**, prepared by opening of an epoxide with ammonia, cyclized and dehydrated to 3-methylpyrrole **(50)** when treated with aqueous citric acid (Scheme 4).[13] Similarly, intermediate **52** has been synthesized by conversion of β-ketobutyraldehyde dimethyl acetal to the cyanohydrin and protection of the alcohol as the THP ether, followed by reduction of the nitrile and acetylation of the resulting amine.[14] Compound **52** has also been converted to 3-methylpyrrole **(50)** by treatment with *p*-toluenesulfonic acid in refluxing acetone, followed by hydrolysis of the resulting *N*-acylpyrrole under basic conditions (Scheme 4).[14] However, both of the approaches summarized in Scheme 4 involve multistep procedures and are tedious in comparison to the present approach outlined in Scheme 1. In any case, the fact that pyrroles have been obtained from intermediates such as **51** and **52** under acidic conditions, together with the reported additions of a wide variety of nucleophiles to the aldehyde groups of BOC-amino aldehydes,[15] supports the pathway proposed in Scheme 1. The pathway **1** + **2** → **3** → **4** in Scheme 1, in which CC bond formation precedes CN bond formation, is fundamentally different from the suggested pathway for the Knorr synthesis (Scheme 2), in which CN bond formation, resulting in **5**, precedes CC bond formation.[5]

The overall yields of the substituted pyrroles in Table 1 obtained from BOC-amino aldehydes and ketones were not optimized and ranged from 42% for **24** to 5% for **37** and **46**, which contain an acid-sensitive ketal. Although the yields are far from ideal and do diminish the attractiveness of the approach, it can be pointed out that the yields reported in the Experimental Section are of analytically pure material isolated after chromatography and that they refer to overall yields after two synthetic steps (generation of the aldol **3** as well as its cyclization). On the other hand, the results indicate that the present pyrrole synthesis has considerable versatility, since a variety of substituted pyrroles and fused pyrrole systems have been obtained from readily available starting materials. In addition, the overall route offers the advantage of being relatively short. These considerations suggest that the present synthetic method may offer certain advantages when pyrroles are desired.

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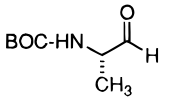
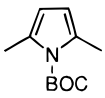
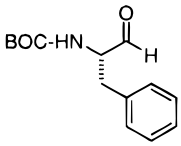
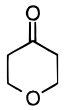
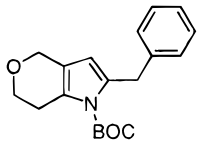
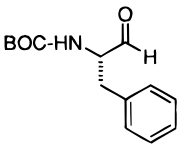
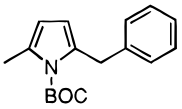
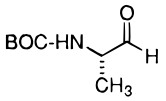
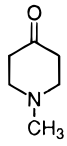
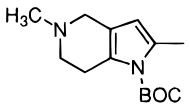
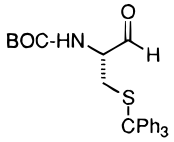
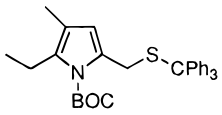
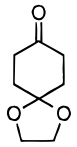
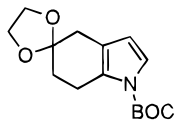
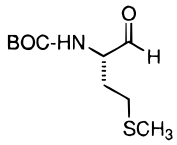
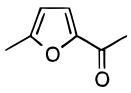
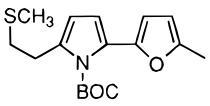
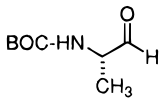
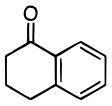
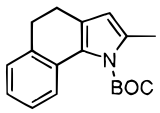
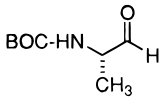
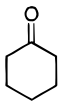
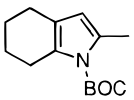
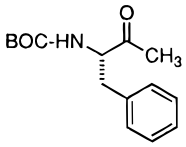
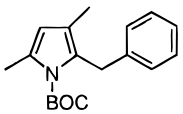
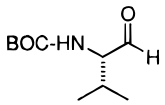
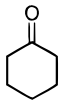
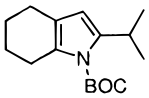
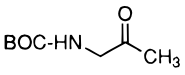
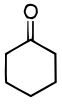
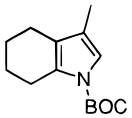
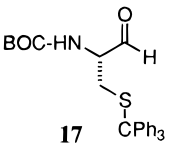
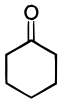
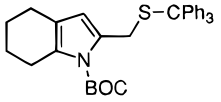
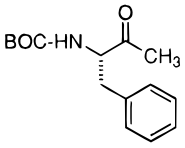
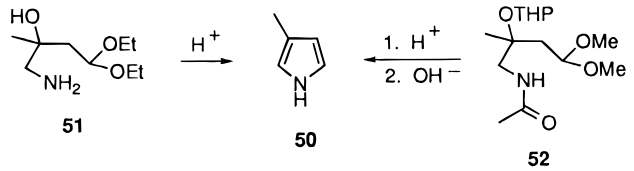
Table 1. Synthesis of Pyrroles and Fused Pyrrole Systems

Amino aldehyde or ketone	Ketone	Pyrrole	Amino aldehyde or ketone	Ketone	Pyrrole
 **12**	 **13**	 **14**	 **15**	 **31**	 **33**
 **15**	 **13**	 **16**	 **12**	 **34**	 **35**
 **17**	 **18**	 **19**	 **15**	 **36**	 **37**
 **20**	 **21**	 **22**	 **12**	 **38**	 **39**
 **12**	 **23**	 **24**	 **40**	 **13**	 **41**
 **25**	 **23**	 **26**	 **42**	 **23**	 **43**
 **17**	 **23**	 **27**	 **40**	**44**	**45**
28	**23**	**29**	**42**	**36**	**46**
30	**31**	**32**			

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were obtained using $CHCl_3$ as the solvent unless otherwise specified. ^1H NMR spectra were obtained using $CDCl_3$ as solvent and TMS as internal standard. ^1H NMR spectra were determined at 200 or 300 MHz as noted. Chemical ionization mass spectra (CIMS) were determined using isobutane as the reagent gas. Microanalyses were performed at the Purdue University Microanalysis Laboratory. THF was distilled from potassium metal and benzophenone under argon to remove moisture and oxygen. Diisopropylamine was dried over calcium hydride and then distilled

Scheme 4



prior to use. All reactions were performed under argon atmosphere. Analytical thin-layer chromatography was carried out on Analtech silica gel GF 1000 μm glass plates. Compounds were visualized with short wavelength UV light, phosphomolybdic acid, or ninhydrin indicator. Silica gel flash chromatography was performed using 230−400 mesh silica gel. With the exception of **42**, the BOC-amino aldehydes and ketones were prepared according to published procedures.[7−10]

Typical Procedure. *N*-(*tert*-Butoxycarbonyl)-2,5-dimethylpyrrole (14). Acetone (0.73 mL, 10 mmol) was added to a stirred solution of freshly prepared LDA (11 mmol) in THF (40 mL) at −78 °C under an Ar atmosphere, and the reaction was allowed to proceed for 1.5 h. *N*-(*tert*-Butoxycarbonyl)-L-alaninal **(12)** (0.9 g, 5 mmol) was dissolved in THF (7 mL) and cooled to −78 °C before it was added dropwise to the reaction mixture. Stirring continued at −78 to +23 °C overnight, and H_2O (25 mL) was added followed by ether (400 mL). The solution was washed with water (4 × 100 mL) and saturated sodium chloride (100 mL) and dried over magnesium sulfate and the solvent evaporated to yield a diastereomeric mixture of aldol products (1.3 g). The aldol products were dissolved in methylene chloride (20 mL), and four drops of concd HCl was added. The yellow solution became orange and was stirred for 1 h at room temperature before methylene chloride (20 mL) was added, the mixture was washed with saturated sodium bicarbonate (3 × 10 mL) and saturated sodium chloride (3 × 10 mL), dried ($MgSO_4$), and the solvent was evaporated. Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (2:1), gave **14**[11] as a colorless oil (0.27 g, 28%): IR (thin film) 2977, 2930, 1738, 1544, 1478, 1455, 1389, 1370, 1334, 1312, 1248, 1174, 1124, 982, 853, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (s, 2 H), 2.38 (s, 6 H), 1.59 (s, 9 H); CIMS *m*/*z* (relative intensity) 196 (MH^+, 100), 140 ($MH^+ - 56$, 49), 96 ($MH^+ - 100$, 6). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.83; H, 9.06; N, 7.36.

***N*-(*tert*-Butoxycarbonyl)-2-benzyl-5-methylpyrrole (16).** Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (2:1), gave the product as a colorless oil in 13% yield: IR (thin film) 2978, 2929, 1739,1536, 1494, 1453, 1388, 1369, 1330, 1313, 1254, 1171, 1121, 851, 787, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.10−7.30 (m, 5 H), 5.82 (dd, 1H, J = 3.0, 1.0 Hz), 5.66 (d,1 H, J = 3.2 Hz), 4.16 (s, 2 H), 2.39 (s, 3 H), 1.44 (s, 9 H); CIMS *m*/*z* (relative intensity) 272 (MH^+, 100), 216 ($MH^+ - 56$, 86), 172 ($MH^+ - 100$, 26). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 74.97; H, 7.89; N, 5.13.

***N*-(*tert*-Butoxycarbonyl)-5-ethyl-4-methyl-2-[(tritylthio)methyl]pyrrole (19).** Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (2:1), gave the product as a colorless oil in 10% yield: IR (thin film) 2976, 2930, 1737, 1532, 1489, 1444, 1380, 1369, 1354, 1326, 1291, 1137, 1099, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24−7.39 (m, 15 H), 5.43 (s, 1 H), 3.58 (s, 2 H), 2.72 (q, 2 H, J = 7.4 Hz), 1.85 (s, 3 H), 1.54 (s, 9 H), 1.26 (t, 3 H, J = 7.3 Hz); CIMS *m*/*z* (relative intensity) 498 (MH^+, 14), 243 ($MH^+ - 255$, 100). Anal. Calcd for $C_{32}H_{35}NO_2S$: C, 77.23; H, 7.09; N, 2.81; S, 6.44. Found: C, 77.51; H, 7.38; N, 2.64; S, 6.77.

***N*-(*tert*-Butoxycarbonyl)-2-(5-methyl-2-furyl)-5-[2-(methylthio)ethyl]pyrrole (22).** Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (1:2), gave the product as an oil in 5% yield: IR (thin film) 2979, 2920, 1742, 1388, 1369, 1313, 1257, 1219, 1150, 1079, 1020, 953, 847, 784 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (dd, 2 H, J = 3.2, 1.3 Hz), 5.99 (d, 1 H, J = 3.3 Hz), 5.97 (dd, 1 H, J = 3.0, 1.1 Hz), 3.11 (t, 2H, J = 7.7 Hz), 2.76 (t, 2 H, J = 7.7 Hz), 2.30 (s, 3 H), 2.13 (s, 3 H), 1.38 (s, 9 H); CIMS *m*/*z* (relative intensity) 322 (MH^+, 100), 278 ($MH^+ - 44$, 35), 266 ($MH^+ - 56$, 30), 222 ($MH^+ - 100$, 90). Anal. Calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36; S, 9.97. Found: C, 63.87; H, 7.41; N, 4.15; S, 9.69.

***N*-(*tert*-Butoxycarbonyl)-2-methyl-4,5,6,7-tetrahydroindole (24).** Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (5:1), gave the product as an oil in 42% yield: IR (thin film) 2930, 2850, 1731, 1547, 1478, 1455, 1360, 1256, 1087, 1002, 854, 794 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71 (s, 1 H), 2.78 (t, 2 H, J = 6 Hz), 2.38 (m, 5 H), 1.71 (m, 4 H), 1.57 (s, 9 H); CIMS *m*/*z* (relative intensity) 236 (MH^+, 45), 180 ($MH^+ - 56$, 100), 136 ($MH^+ - 100$, 17). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.84; H, 9.32; N, 5.71.

***N*-(*tert*-Butoxycarbonyl)-2-isopropyl-4,5,6,7-tetrahydroindole (26).** Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (5:1), gave the product as a colorless oil in 27% yield: IR (thin film) 2967, 2931, 1732, 1370, 1325, 1157, 1129, 1084, 1057, 854 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (s, 1 H), 3.49 (p, 1 H, J = 6.7 Hz), 2.76 (t, 2 H, J = 5.7 Hz), 2.41 (t, 2 H, J = 5.7 Hz), 1.70 (m, 4 H), 1.59 (s, 9 H), 1.21 (d, 6 H, J = 6.7 Hz); CIMS *m*/*z* (relative intensity) 264 (MH^+, 7), 208 ($MH^+ - 56$, 71), 164 ($MH^+ - 100$, 100). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 73.29; H, 9.86; N, 5.16.

***N*-(*tert*-Butoxycarbonyl)-2-[(tritylthio)methyl]-4,5,6,7-tetrahydroindole (27).** Chromatography (SiO_2), eluting with hexane:Et_2O (10:1), gave the product as a colorless oil in 8% yield: IR (thin film) 2930, 2850, 1734, 1539, 1489, 1444, 1366, 1318, 1257, 1137, 1084, 1033, 849, 746, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−7.42 (m, 15 H), 5.41 (s, 1 H), 3.63 (s, 2 H), 2.73 (t, 2 H, J = 5.5 Hz), 2.30 (t, 2 H, J = 5.8 Hz), 1.72 (m, 2 H), 1.60 (m, 2 H), 1.54 (s, 9 H); CIMS *m*/*z* (relative intensity) 510 (MH^+, 30), 243 ($MH^+ - 267$, 100). Anal. Calcd for $C_{33}H_{35}NO_2S$: C, 77.76; H, 6.92; N, 2.75; S, 6.29. Found: C, 78.05; H, 7.17; N, 2.74; S, 6.05.

***N*-[(Carbobenzyloxy)carbonyl]-2-isobutyl-4,5,6,7-tetrahydroindole (29).** Chromatography (SiO_2), eluting with hexane:$CHCl_3$ (3:1), gave the product as an oil in 15% yield: IR (thin film) 2952, 2930, 2850, 1732, 1543, 1389, 1358, 1321, 1298, 1256, 1216, 1164, 1137, 1096, 1071, 982, 911, 829 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.35 (m, 5 H), 5.73 (s, 1 H), 5.30 (s, 2 H), 2.76 (t, 2 H, J = 5.8 Hz), 2.61 (d, 2 H, J = 6.8 Hz), 2.38 (t, 2 H, J = 5.8 Hz), 1.79−1.65 (m, 5 H), 0.84 (d, 6 H, J = 6.6 Hz); CIMS *m*/*z* (relative intensity) 312 (MH^+, 99). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.97; H, 8.07; N, 4.86.

***N*-(*tert*-Butoxycarbonyl)-4,6,7-trihydro-2-isobutylpyrano[4,3-*b*]pyrrole (32).** Preparative thin-layer chromatography (SiO_2), eluting with hexane:EtOAc (3:1), gave the product as a yellow oil in 26% yield: IR (thin film) 2955, 2866, 2846, 1736, 1539, 1462, 1369, 1369, 1328, 1216, 1258, 1138, 1101, 978, 901, 791, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (s, 1 H), 4.55 (t, 2 H, J = 1.8 Hz), 3.88 (t, 2 H, J = 5.5 Hz), 2.87 (t, 2 H, J = 6.0 Hz), 1.59 (s, 9 H), 1.44 (d, 2 H, J = 5.1 Hz), 1.24 (d, 6 H, J = 6.8 Hz); CIMS *m*/*z* (relative intensity) 280 (MH^+, 50), 224 ($MH^+ - 56$, 55), 180 ($MH^+ - 100$, 100). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.59; H, 9.08; N, 5.04.

***N*-(*tert*-Butoxycarbonyl)-2-benzyl-4,6,7-trihydropyrano[4,3-*b*]pyrrole (33).** Chromatography (SiO_2), eluting with $CHCl_3$:hexane (3:2), gave the product as a colorless oil in 25% yield: IR (thin film) 2976, 2845, 1736, 1494, 1453, 1423, 1368, 1325, 1171, 1135, 1099, 976, 900, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.10 (m, 5 H), 5.50 (s, 1 H), 4.51 (s, 2 H), 4.20 (s, 2 H), 3.90 (t, 2 H, J = 5.4 Hz), 2.91 (t, 3 H, J = 5.4 Hz), 1.62 (s, 9 H); CIMS *m*/*z* (relative intensity) 314 (MH^+, 38), 258 ($MH^+ - 56$, 29), 214 ($MH^+ - 100$, 100). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.44; H, 7.73; N, 4.45.

***N*-(*tert*-Butoxycarbonyl)-4,6,7-trihydro-2,5-dimethyl-1*H*-pyrrolo[3,2-*c*]pyridine (35).** Chromatography (SiO_2), eluting with hexane:EtOAc (1:1) containing 1% triethylamine, gave the product as a yellow oil in 17% yield: IR (thin film) 2974, 2936, 2779, 1737, 1386, 1359, 1329, 1315, 1307, 1250, 1159, 1148, 1116, 1083, 1044, 976, 851, 799, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67 (s, 1 H), 3.28 (s, 2 H), 2.89 (t, 2 H, J = 5.7 Hz), 2.63 (t, 2 H, J = 5.8 Hz), 2.41 (s, 3 H), 2.36 (s, 3 H), 1.55 (s, 9 H); CIMS *m*/*z* (relative intensity) 251 (MH^+, 100), 195 ($MH^+ - 56$, 87), 151 ($MH^+ - 100$, 36). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.08; H, 9.07; N, 11.37.

***N*-(*tert*-Butoxycarbonyl)-5-oxotetrahydroindole ethylene ketal (37).** Preparative TLC (SiO_2), eluting with hexane:EtOAc (3:1), gave the product as an oil in 5% yield: IR (thin film) 2974, 1737, 1370, 1314, 1268, 1151, 1097, 1061, 1027, 947, 850, 771, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, 1 H, $J = 3.4$ Hz), 5.96 (d, 1 H, $J = 3.4$ Hz), 4.00 (s, 4 H), 3.01 (t, 2 H, $J = 6.5$ Hz), 2.69 (s, 2 H), 1.94 (t, 2 H, $J = 6.5$ Hz), 1.57 (s, 9 H); CIMS *m/z* (relative intensity) 280 (MH^+, 53), 224 ($MH^+ - 56$, 38), 180 ($MH^+ - 100$, 100). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.14; H, 7.85; N, 5.23.

***N*-(*tert*-Butoxycarbonyl)-4,5-dihydro-2-methyl-1*H*-benz[*g*]indole (39).** Chromatography (SiO_2), eluting with hexane:CH_2Cl_2 (3:1), gave the product as a white solid in 23% yield: mp 80−81 °C; IR (thin film) 2979, 2930, 2990, 2890, 1739, 1516, 1489, 1368, 1344, 1327, 1301, 1153, 1109, 1081, 991, 850, 755, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (s, 1 H), 7.15 (d, 2 H, $J = 3.9$ Hz), 7.05 (m, 1 H), 5.85 (s, 1 H), 2.83 (t, 2 H, $J = 7.3$ Hz), 2.49 (t, 2 H, $J = 7.3$ Hz), 2.41 (s, 3 H), 1.57 (s, 9 H); CIMS *m/z* (relative intensity) 284 (MH^+, 58), 283 (M^+, 94), 228 ($MH^+ - 56$, 100), 184 ($MH^+ - 100$, 26). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.39; H, 7.34; N, 4.85.

***N*-(*tert*-Butoxycarbonyl)-2-benzyl-3,5-dimethylpyrrole (41).** The product was purified by preparative TLC (1000 μm SiO_2). Elution with hexane:chloroform (3:1) afforded the least polar component **41** as a pale yellow oil in 40% yield: IR (thin film) 2977, 2926, 1737,1603, 1546, 1494, 1453,1385, 1351, 1328, 1280, 1257, 1176, 1135, 1077, 851, 799, 770, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 5 H), 5.94 (s, 1 H), 4.34 (s, 2 H), 2.51 (s, 3 H), 2.12 (s, 3 H), 1.47 (s, 9 H); CIMS *m/z* (relative intensity) 286 (MH^+, 100), 230 ($MH^+ - 56$, 17), 186 ($MH^+ - 100$, 49). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 76.09; H, 8.15; N,4.81.

***N*-(*tert*-Butoxycarbonyl)-3-amino-2-propanone (42).** *N*-(*tert*-Butoxycarbonyl)glycine *N*-methoxy-*N*-methylamide (2.2 g, 10 mmol) was dissolved in THF (50 mL), and a 1.0 M solution of methylmagnesium bromide in ether (30 mL, 30 mmol) was added via syringe. After 15 min, the reaction mixture was diluted with ether (300 mL), and a 25% aqueous solution of ammonium chloride (35 mL) was slowly added. The mixture was extracted with saturated sodium bicarbonate solution (3 × 100 mL) and saturated sodium chloride solution (3 × 100 mL), dried ($MgSO_4$), and concentrated to give a pale yellow oil, which after drying *in vacuo* gave a white crystalline solid (1.84 g, 85%): mp 48−49 °C; IR (thin film) 3361, 2978, 1713, 1514, 1504, 1366, 1285, 1250, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.23 (broad), 3.96 (d, 2 H, $J = 4.5$ Hz), 2.11 (s, 3 H), 1.38 (s, 9 H); CIMS *m/z* (relative intensity) 174 (MH^+, 54), 118 ($MH^+ - 56$, 100), 74 ($MH^+ - 100$, 46). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.17; H, 8.91; N, 7.86.

***N*-(*tert*-Butoxycarbonyl)-4,5,6,7-tetrahydro-3-methylindole (43).** The product was purified by flash chromatography (SiO_2). Elution with hexane:chloroform (3:1) afforded the least polar component as a pale yellow oil in 44% yield: IR (thin film) 2933, 2854, 1735, 1390, 1369, 1346, 1332, 1314, 1248, 1162, 1082, 1047, 1016, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 1 H), 2.80 (t, 2 H, $J = 5.5$ Hz), 2.34 (t, 2 H, $J = 5.6$ Hz), 1.93 (s, 3 H), 1.75 (m, 4 H), 1.56 (s, 9 H); CIMS *m/z* (relative intensity) 236 (M^+, 100), 180 ($MH^+ - 56$, 80), 136 ($MH^+ - 100$, 78). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.08; H, 9.21; N, 5.91.

***N*-(*tert*-Butoxycarbonyl)-2-benzyl-3-methylcyclopenta[*b*]pyrrole (45).** Purification of the product was achieved by flash chromatography. Elution with hexane−chloroform (3:1) afforded the least polar component **45** as an off-white glass in 30% yield: mp 77−79 °C; IR (thin film) 2931, 2856, 1735, 1392, 1356, 1337, 1145, 1122, 844, 768, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (m, 5 H), 4.32 (s, 2 H), 2.98 (t, 2 H, $J = 7.1$ Hz), 2.62 (t, 2 H, $J = 7.1$ Hz), 2.43 (p, 2 H, $J = 6.9$ Hz), 2.04 (s, 3 H), 1.49 (s, 9 H); CIMS *m/z* (relative intensity) 312 (MH^+, 100), 256 ($MH^+ - 56$, 31), 212 ($MH^+ - 100$, 28). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.94; H, 8.35; N, 4.38.

***N*-(*tert*-Butoxycarbonyl)-4,5,6,7-tetrahydro-5-oxo-3-methylindole Ethylene Ketal (46).** Purification was achieved by flash chromatography (SiO_2). Elution with hexane−ethyl actetate (4:1) afforded the least polar component **46** as a pale yellow oil in 40% yield: IR (thin film) 2976, 1733, 1391, 1369, 1252, 1162, 1059, 946, 856, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.9 (s, 1 H), 4.03 (s, 4 H), 2.98 (t, 2 H, $J = 6.5$ Hz), 2.58 (s, 2 H), 1.89 (t, 2 H, $J = 6.6$ Hz), 1.53 (s, 9 H); CIMS *m/z* (relative intensity) 294 (MH^+, 100), 238 ($MH^+ - 56$, 98), 194 ($MH^+ - 100$, 69). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.18; H, 8.16; N, 5.09.

1*H*-2-Benzyl-5-methylpyrrole (47). The pyrrole **16** (0.24 g, 0.9 mmol) was stirred in THF (1 mL). A solution of sodium methoxide (0.15 g, 2.7 mmol) in methanol (0.8 mL) was added to the colorless solution. The solution became yellow, and a white precipitate formed. After 2 h, the reaction mixture was diluted with ether (40 mL) and neutralized by dropwise addition of a 10% solution of acetic acid in methanol (10 mL). The organic layer was extracted with brine (3 × 15 mL) and dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting light yellow oil was purified on a preparative TLC plate (1000 μm SiO_2) that had been previously deactivated with 5% triethylamine in hexane. Elution with hexane:$CHCl_3$ (1:1) gave **47**[12] (0.07 g, 46%) as a yellow oil: IR (thin film) 3414, 3365, 3026, 3899, 1591, 1492, 1452, 1420, 1399, 1255, 1173, 1074, 1035, 763, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (s, 1 H, broad), 7.31−7.17 (m, 5 H), 5.82 (t, 1 H, $J = 2.6$ Hz), 5.76 (s, 1 H), 3.88 (s, 2 H), 2.15 (s, 3 H); CIMS *m/z* (relative intensity) 172 (MH^+, 100). Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.99; H, 7.60; N, 8.04.

1*H*-4,6,7-Trihydro-2-isobutylpyrano[4,3-*b*]pyrrole (48). The pyrrole **32** (0.28 g, 1.0 mmol) was stirred in THF (1 mL). A solution of sodium methoxide (0.16 g, 3.0 mmol) in methanol (2.0 mL) was added to the colorless solution. The solution became cloudy. After being stirred overnight, the reaction mixture was diluted with ether (40 mL) and neutralized by dropwise addition of a 10% solution of acetic acid in methanol (10 mL). The organic layer was extracted with brine (3 × 15 mL) and dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting red oil was purified on a preparative TLC plate (1000 μm SiO_2) that had been previously deactivated with 5% triethylamine in hexane. Elution with hexane:EtOAc (3:1) gave the product as a white glass (0.08 g, 45%): IR (thin film) 3308, 2953, 2842, 1462, 1381, 1298, 1214, 1155, 1076, 1059, 961, 928, 864, 845, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (brs, 1 H), 5.62 (d, 1 H, $J = 2.3$ Hz), 4.64 (d, 2 H, $J = 1.3$ Hz), 3.95 (t, 2 H, $J = 5.5$ Hz), 2.66 (t, 2 H, $J = 5.5$ Hz), 2.41 (d, 2 H, $J = 7.1$ Hz), 1.80 (p, 1 H, $J = 6.6$ Hz), 0.93 (d, 6 H, $J = 6.6$ Hz); CIMS *m/z* (relative intensity) 180 (MH^+, 100). Anal. Calcd for $C_{11}H_{17}N0$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.45; H, 9.90; N, 7.90.

***N*-(*tert*-Butoxycarbonyl)-2-methyl-1*H*-benz[*g*]indole (49).** Pyrrole **39** (0.04 g, 0.14 mmol) was dissolved in benzene (10 mL), and DDQ (0.03 g, 0.14 mmol) was added. The reaction mixture was stirred for 40 min at room temperature, and the mixture was filtered. The filtrate was extracted with saturated aqueous sodium bicarbonate (3 × 10 mL) followed by saturated sodium chloride (3 × 10 mL) and dried over magnesium sulfate. Evaporation of solvent gave a dark brown oil which was purified by preparative TLC (1000 μm SiO_2). Elution with hexane:EtOAc (3:1) afforded the least polar component **49** (0.02 g, 48%) as a solid: mp 54−56 °C; IR (thin film) 2979, 1737, 1387, 1369, 1345, 1311, 1258, 1202, 1153, 1113, 1075, 846, 816, 739, 686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, 1 H, $J = 8.1$ Hz), 7.89 (d, 1 H, $J = 8.2$ Hz), 7.61 (d, 1 H, $J = 8.5$ Hz), 7.54 (d, 1 H, $J = 8.5$ Hz), 7.44 (td, 1 H, $J = 8.2$, 1.4 Hz), 7.36 (td, 1 H, $J = 6.9$, 1.4 Hz), 6.40 (s, 1 H), 2.49 (s, 3 H), 1.70 (s, 9H); CIMS *m/z* (relative intensity) 282 (MH^+, 28), 226 ($MH^+ - 56$, 100), 182 ($MH^+ - 100$, 50). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.98; H, 6.87; N, 4.68.

Acknowledgment. This research was made possible by a research grant from the Indiana Elks, as well as NIH Contract NO1-CM-17513.

JO960401Q