Use of 2,5-Dimethylpyrrole as an Amino-Protecting Group in an Efficient Synthesis of 5-Amino-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]indole

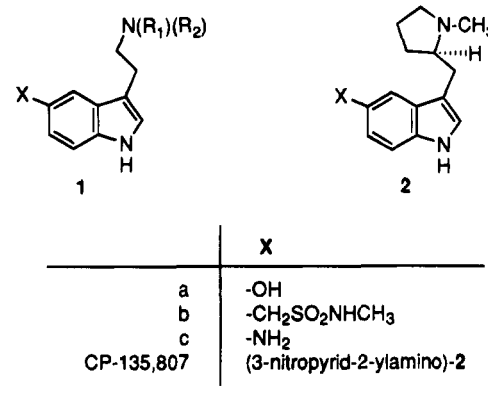
John E. Macor,*[1] Bert L. Chenard, and Ronald J. Post

Department of Medicinal Chemistry, Central Research Division, Pfizer Inc, Groton, Connecticut 06340

Received June 29, 1994

During the course of our investigations[2] into the use of conformationally restricted analogs of the neurotransmitter serotonin (5-HT, **1a** [$R_1 = R_2 = H$], Figure 1) as receptor probes, we became aware of the potential of the 3-(pyrrolidin-2(*R*)-ylmethyl) group in **2** as a replacement for the 3-(2-aminoethyl group) in 5-HT (Figure 1).[2g,2h,2i,3] This group was designed to be a stereogenic, metabolically stable, conformationally restricted replacement for the aminoethyl group of tryptamines.[4] Indoles containing the 3-(pyrrolidin-2(*R*)-ylmethyl) group (**2**) have generally been shown to have equal or improved serotonergic activity when compared to their corresponding tryptamine derivatives, especially at 5-HT_1 receptors.[5] In fact, in a series of conformationally restricted analogs of the antimigraine drug sumatriptan (Imigran, **1b** [$R_1 = R_2 = CH_3$]), the pyrrolidinylmethyl analog **2b** was shown to have 10^4 times greater potency in a measure of antimigraine activity when compared to sumatriptan (**1b** [$R_1 = R_2 = CH_3$]) itself.[3] These results and others have led us to examine a number of 5-substituted-3-(pyrrolidinylmethyl)indoles for their activity at a variety of 5-HT receptors.

Interest in 5-aminoindole analogs of serotonin has been ongoing since the initial discovery of the natural product in 1948. In both patent and primary literature, 5-aminoindoles have been cited as potentially important agents for the modulation of mammalian serotonergic function. Quite recently, we discovered a series of 5-[(3-nitropyrid-2-yl)amino]indoles[2j] which possessed varying degrees of serotonin receptor subtype selectivity. The most potent compound for the 5-HT_{1D} receptor subtype in this series was CP-135,807 [5-[(3-nitropyrid-2-yl)amino]-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]indole] which was directly derived from 5-amino-3-[(*N*-methylpyrrolidin-2(*R*)-yl)-methyl]indole (**2c**). CP-135,807 has been shown to be an orally active, selective 5-HT_{1D} receptor agonist which readily crosses the blood/brain barrier.[6] Such a compound represents an extremely useful tool for understanding the role of the 5-HT_{1D} receptor in mammalian CNS.



	X
a	-OH
b	$-CH_2SO_2NHCH_3$
c	$-NH_2$
CP-135,807	(3-nitropyrid-2-ylamino)-2

Figure 1.

For the original synthesis of CP-135,807, **2c** was synthesized from 5-aminoindole in four steps using dibenzylamino protection/deprotection as the first and fourth steps of the sequence, respectively. The overall yield of the sequence was 34% on small laboratory scale (less than a gram synthesized), but these results did not translate upon larger-scaled syntheses (greater than a gram). The major source of this problem was the capricious nature of the key condensation step between 5-(dibenzylamino)indole and (*R*)-CBZ-proline acid chloride, which on large scale gave varying yields (averaging less than 20% yield) of the desired coupled product. Therefore, the desire to obtain large quantities of CP-135,807 and its immediate precursor (**2c**) for the synthesis of additional analogs prompted us to design a more facile and efficient synthesis of 5-amino-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]indole (**2c**), which we detail in this report.

Our focus for the improvement of the synthesis of **2c** centered on the choice of protecting groups, since we believed the electron rich 5-(dibenzylamino)indole interfered with the crucial condensation step. Key to the necessary amino-protecting group were the following characteristics: (a) nonionizable (i.e. no NH in protecting group); (b) stable to strong base (i.e. alkylmagnesium bromide); (c) stable to strong reducing agents (i.e. LAH); (d) relatively non-nucleophilic (i.e. low reactivity to acid chlorides); and (e) removable under conditions which a 5-aminoindole derivative was stable (i.e. neutral or basic conditions). These requirements obviated the use of the use of carbamates (NH too acidic) and dialkylamino (too electron rich) protecting groups, thus greatly reducing the arsenal of potential protecting groups. Of the remaining possibilities, 2,5-dimethylpyrrole seemed to fit our protecting group description, but the dearth of literature reports[7] on its use was not encouraging.

(1) Present address: Fisons Pharmaceuticals, Divisional Research and Development, 755 Jefferson Rd., Rochester, NY 14623.

(2) (a) Macor, J. E.; Burkhart, C. A.; Heym, J. H.; Ives, J. L.; Lebel, L. A.; Newman, M. E.; Nielsen, J. A.; Ryan, K. Schulz, D. W.; Torgersen, L. K.; Koe, B. K. *J. Med. Chem.*, **1990**, *33*, 2087. (b) Macor, J. E.; Newman, M. E. *Heterocycles* **1990**, *31*, 805. (c) Macor, J. E.; Ryan, K. *Heterocycles* **1990**, *31*, 1497. (d) Macor, J. E.; Newman, M. E. *Tetrahedron Lett.* **1991**, *32*, 3345. (e) Macor, J. E.; Ryan, K.; Newman, M. E. *Tetrahedron* **1992**, *48*, 1039. (f) Macor, J. E.; Fox, C. B.; Johnson, C.; Koe, B. K.; Lebel, L. A.; Zorn, S. H. *J. Med. Chem.* **1992**, *35*, 3625. (g) Macor, J. E.; Blake, J.; Fox, C. A.; Johnson, C.; Koe, B. K.; Lebel, L. A.; Morrone, J. M.; Ryan, K.; Schmidt, A. W.; Schulz, D. W.; Zorn, S. H. *J. Med. Chem.* **1992**, *35*, 4503. (h) Macor, J. E.; Blank, D. H.; Post, R. J.; Ryan, K. *Tetrahedron Lett.* **1992**, *33*, 8011. (i) Macor, J. E.; Blank, D. H.; Post, R. J. *Tetrahedron Lett.* **1994**, *35*, 45. (j) Macor, J. E.; Blank, D. H.; Fox, C. A.; Lebel, L. A.; Newman, M. E.; Post, R. J.; Ryan, K.; Schmidt, A. W.; Schulz, D. W.; Koe, B. K. *J. Med. Chem.* **1994**, *37*, 2509.

(3) Lee, W. S.; Moskowitz, M. A. *Brain Res.* **1993**, *626*, 303.

(4) One of the advantages envisioned by the use of the 3-(pyrrolidin-2(*R*)-ylmethyl) group would be its resistance to the major metabolic pathway of tryptamines, namely oxidation to indole-3-acetic acids via monoamine oxidase (MAO) since α-substituted tryptamines are generally resistant to MAO.

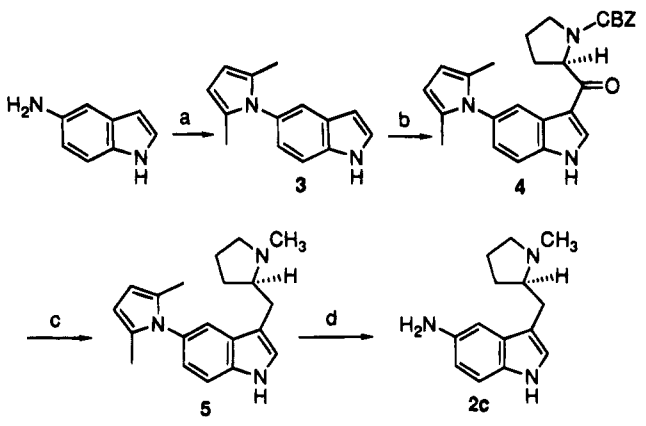
(5) For a review of the pharmacology and clinical implications of 5-HT receptors, see: Glennon, R. A. *Neurosci. Behav. Rev.* **1990**, *14*, 35.

(6) Seymour, P. A.; Macor, J. E. To be presented at the 24th Annual Meeting, Society for Neuroscience, Miami Beach, FL, Nov 13–18, 1994.

(7) (a) Breukelman, S. P.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Chem. Commun.* **1982**, 800. (b) Breukelman, S. P.; Leach, S. E.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Perkins Trans. 1* **1984**, 2801. (c) Chenard, B. L. *J. Org. Chem.* **1984**, *49*, 1224. (d) Kashima, C.; Maruyama, T.; Fujioka, Y.; Harada, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1041. (e) Davis, A. P.; Egan, T. J. *Tetrahedron Lett.* **1992**, *33*, 8125.

0022-3263/94/1959-7496$04.50/0

Scheme 1



However, this little used amino-protecting group proved to be the correct choice, as its use led to the synthesis of multigram quantities (>10 g) of the desired, functionalized 5-aminoindole target **2c**.

Condensation of 5-aminoindole with an excess of acetonylacetone utilizing a Dean–Stark trap for azeotropic water removal led to the 5-pyrrolylindole (**3**) in 66% recrystallized yield on a greater than 100 g lot. The key condensation step of the magnesium salt of **3** (formed by reaction of **3** with ethylmagnesium bromide) with the acid chloride of CBZ-D-proline was consistently efficient (yields between 75 and 85%), readily affording large quantities of the desired 3-ketoindole **4**. As with other acylation reactions of indole magnesium salts, the use of benzene as the reaction solvent afforded maximal C3 regiochemistry and limited N1 reactivity.[8] It should be noted that we have found that these condensation reactions between the indolylmagnesium bromide and a sterically hindered acid chloride such as the one under study are most efficient when 2 equiv of the indolylmagnesium bromide are used with only 1 equiv of the acid chloride. Apparently, with the sterically congested acid chlorides there is an accumulation of the 3-ketoindole **4** during the course of the reaction. The acidic NH proton in this "vinylogous amide" (**4**) is readily and rapidly deprotonated by the starting indole magnesium salt of **3**. This acid/base transfer reaction depletes the indole magnesium salt of **3**, and forms the magnesium salt of **4**, which slowly (compared to the magnesium salt of **3**) reacts with remaining acid chloride to form C3/N1 bis-acylated material. With use of 2 equiv of the magnesium salt of **3**, 1 equiv acts as the equilibrating base between **3** and **4**, while 1 equiv remains for complete reaction with the acid chloride. The use of 2 equiv of the indolylmagnesium bromide leads to a higher yield of **4**, affording a much simpler purification/isolation of the desired ketoindole **4**: direct trituration of the product from the exaction residue yields analytically pure material on large scale.

Direct conversion of CBZ-to-methyl and of the keto-to-methylene is accomplished with a single application of lithium aluminum hydride in refluxing THF affording the desired tertiary amine **5** in high yield.[9] The removal of benzyl alcohol, which arises from the reduction of the CBZ group, necessitated the use of a simple silica gel pad chromatography. However, minimal silica gel and solvent were utilized since the only components needing separation were the relatively nonpolar alcohol and the relatively polar amine **5**.[10]

The reaction of pyrrole with hydroxylamine hydrochloride was first studied in 1889 as a method of synthesizing the dioxime of succindialdehyde.[11] Almost 70 years later, that same reaction was more closely scrutinized and found to be pH dependent, and reaction of pyrroles with hydroxylamine *hemihydrochloride* was found to give the highest yield of the dioxime of the corresponding 1,4-dicarbonyl compound.[12] Reaction of pyrrole **5** with hydroxylamine hydrochloride in refluxing ethanol for 24 h afforded only 44% of the desired 5-aminoindole **2c** on small scale (< 1 g). Rather than prepare hydroxylamine hemihydrochloride, we attempted to raise the reaction pH through the use of a solution of triethylamine in 2-propanol/water as the reaction solvent. Under these conditions (20 equiv of hydroxylamine hydrochloride, 10 equiv of triethylamine), deprotection was rapid (5 h) and high yielding (83%) on large scale in refluxing 2-propanol/water. These conditions offer a novel, high yielding approach to the removal of a 2,5-dimethylpyrrole-protecting group.

In summary, a synthesis of 5-amino-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]indole (**2c**) has been accomplished on large scale with an overall yield of 39%. Crucial to the success of this sequence was the use of a 2,5-dimethylpyrrole as the protecting group for 5-aminoindole derivatives. This protecting group was stable to (unreactive toward): ethylmagnesium bromide, a hindered acid chloride, and lithium aluminum hydride, but easily removed in high yield using unique conditions (hydroxylamine hydrochloride/triethylamine/propanol/water/Δ). These results can be seen as a demonstration of the potential utility of this relatively obscure amine-protecting group in synthesis.

Experimental Section

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Nicolet 510 FT-IR spectrometer. NMR spectra were recorded on either a Bruker AM-300 (300 MHz) or Bruker AM-250 (250 MHz) spectrometer. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. EI mass spectra were obtained on a Kratos Profile instrument, and FAB mass spectra were obtained on a Kratos Concept IS instrument (σ = ±5.0 ppm). Elemental analyses were performed at Schwarzkopf Microanalytical Laboratory in Woodside, NY.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich anhydrous solvents. Chromatography refers to column chromatography per-

(8) Reimers, R. A. Properties and Reactions of Indoles; Houlihan, W. J., Ed.) In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons, Inc.: New York, 1972; Vol. 25, Part 1 pp 133–134.

(9) It should be noted that no racemization of the chiral center in the pyrrolidine ring was seen in 5-methoxy-3-[(*N*-methylpyrrolidin-2-yl)methyl]indole which was synthesized from 5-methoxyindole [ref 2g] using identical reaction conditions described in this manuscript for the formation of **5** from **3**. Therefore, no racemization was assumed in the synthesis of **5**.

(10) Use of a large fritted disc funnel loaded with silica gel allows for a rapid chromatography to be performed on large scale using moderate vacuum to greatly speed the flow of solvent. Collection of fractions in 2 L vacuum flasks makes the purification more like a filtration.

(11) Ciamician, G.; Zanetti, C. U. *Chem. Ber.* **1889**, *22*, 1968.

(12) Findlay, S. P. *J. Org. Chem.* **1956**, *21*, 644.

formed using 32–63 μm silica gel (approximately 50 g of silica gel per gram of material to be chromatographed) and executed under nitrogen pressure (flash chromatography) conditions. Room temperature (rt) refers to 20–25 °C. All optical rotations were recorded using a sodium (589 nm) lamp.

5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-1*H*-indole (3). A mixture of 5-aminoindole (120.0 g, 0.908 mol), acetonylacetone (200.0 mL, 1.70 mol, 1.9 equiv), and toluene (400 mL) was heated at reflux under nitrogen using a Dean–Stark trap for 6 h. The reaction was cooled and then poured through a silica gel filter (approximately 2 kg) followed first by hexanes (4 L) and then by 6% ether in hexanes to afford a pink solid (133.3 g). Recrystallization of this solid in ether/hexanes afforded the title compound (126.1 g, 0.600 mol, 66%) as an off-white, crystalline solid: mp 108.5–109.5 °C; R_f = 0.75 in diethyl ether; IR (KBr) 1632, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (br s, NH), 7.50 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.29 (t, J = 2.8 Hz, 1H), 7.03 (dd, J = 1.9 and 8.5 Hz, 1H), 6.62 (br t, J = 2.1 Hz, 1H), 6.00 (s, 2H), 2.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 135.0, 131.4, 129.5, 128.1, 125.6, 122.4, 120.3, 111.3, 105.0, 103.0, 13.2; FAB LRMS (*m/z*, relative intensity) 212 (17), 211 ($[MH]^+$, 100), 210 (54), 209 (40), 195 (5), 183 (2), 167 (3). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.72; H, 6.75; N, 13.13.

5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-3-[[*N*-(benzyloxycarbonyl)pyrrolidin-2(*R*)-yl]carbonyl]-1*H*-indole (4). To a stirred solution of the *N*-(benzyloxycarbonyl)-D-proline (23.71 g, 95.1 mmol) in anhydrous methylene chloride (240 mL) with a trace of *N*,*N*-dimethylformamide (1 mL) was added oxalyl chloride (12.44 mL, 143 mmol, 1.5 equiv). The resulting effervescing reaction solution was stirred at room temperature under nitrogen for 3 h. The reaction solution was then evaporated under reduced pressure, anhydrous hexanes (100 mL) was added, and the resulting solution was again evaporated under reduced pressure to afford the *N*-(benzyloxycarbonyl)-D-proline acid chloride which was dissolved in anhydrous benzene (100 mL).

Concomitantly, a solution of ethyl magnesium bromide (3.0 M in ether, 67 mL, 201 mmol, 2.1 equiv) was added dropwise to a stirred solution of a 5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1*H*-indole (40.0 g, 190.2 mmol, 2.0 equiv) in benzene (275 mL) at 0 °C under nitrogen. The resulting reaction solution was stirred at 0 °C under nitrogen for 15 min. Then the solution of *N*-(benzyloxycarbonyl)-D-proline acid chloride in benzene from above was then added dropwise with vigorous stirring. The resulting reaction mixture was stirred vigorously at 0 °C under nitrogen for 1 h. Then a saturated solution of sodium hydrogen carbonate (250 mL) and ethyl acetate (300 mL) were added, and this aqueous mixture was stirred at room temperature for 1 h. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Trituration of the extraction residue (60 g) using diethyl ether (500 mL) with vigorous stirring overnight afforded the title compound (32.52 g, 73.7 mmol, 77%) as an off-white solid: mp 155.0–157.0 °C with effervescence; IR (KBr) 1696, 1637, 1621 cm^{-1}. Due to presence of the carbamate in **4**, slow amide inversion on an NMR time scale occurs in the NMR spectra of **4** leading to the presence of two rotomers [approximately 4:3 ratio at room temperature]. Therefore, the ^1H NMR spectrum will be reported separately for the two rotomers: ^1H NMR ($CDCl_3$) (most populated rotomer) δ 10.13 (br s, NH), 8.13 (br s, 1H), 7.76 (d, J = 1.4 Hz, 1H), 7.40–7.25 (m, 4H), 7.06–7.00 (m, 3H), 5.86 (s, 2H), 5.23–5.05 (m, 3H), 3.80–3.59 (m, 2H), 2.40–2.25 (m, 1H), 1.96 (s, 6H), 2.15–1.85 (m, 3H); ^1H NMR ($CDCl_3$) (least populated rotomer) δ 10.13 (br s, NH), 8.26 (br s, 1H), 7.76 (d, J = 1.4 Hz, 1H), 7.40–7.25 (m, 4H), 7.00–6.93 (m, 3H), 5.90 (s, 2H), 5.13–4.95 (m, 3H), 3.80–3.59 (m, 2H), 2.40–2.25 (m, 1H), 2.03 (s, 6H), 2.15–1.85 (m, 3H); high temperature ^1H NMR (DMSO-d_6, 357 K) δ 11.9 (br s, NH), 8.38 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.30–7.10 (br m, 5H), 7.05 (dd, J = 2.1 and 8.5 Hz, 1H), 5.81 (s, 2H), 5.19 (dd, J = 3.7 and 8.5 Hz, 1H), 5.10–4.95 (br m, 2H), 3.56 (t, J = 6.7 Hz, 1H), 2.45–2.31 (m, 1H), 2.02–1.85 (m, 3H), 1.96 (s, 6H); LRMS (*m/z*, relative intensity) 441 (M^+, 30), 265 (19), 160 (36), 91 (100); HRMS calculated for $C_{27}H_{27}N_3O_3$ 441.2046, found 441.2081 (+1.6 σ); $[\alpha]^{25}$ = +101° (methylene chloride, c = 1). Anal. Calcd for $C_{27}H_{27}N_3O_3$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.41; H, 6.02; N, 9.52.

5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]-1*H*-indole (5). To a stirred mixture of lithium aluminum hydride (8.89 g, 0.234 mol, 4.5 equiv) in anhydrous tetrahydrofuran (150 mL) at 0 °C was added dropwise a solution of 5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-[(*N*-(benzyloxycarbonyl)pyrrolidin-2(*R*)-yl)carbonyl]-1*H*-indole (23.00 g, 52.1 mmol) in anhydrous tetrahydrofuran (75 mL). The resulting reaction mixture was heated at reflux under nitrogen for 4 h. The reaction mixture was cooled, and sodium sulfate decahydrate (200 g) was added very carefully portionwise, followed by water (4 mL) and ethyl acetate (100 mL). The resulting mixture was stirred at room temperature under nitrogen for 24 h. The reaction mixture was then filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual oil (25 g) was then passed through a silica gel filter (approximately 500 g) eluting first with ethyl acetate (1 L, to remove benzyl alcohol) and then with ethyl acetate/methanol/triethylamine [8:1:1] to afford the title compound (14.82 g, 48.2 mmol, 93%) as a white amorphous solid: mp 52–58 °C; IR (KBr) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.47 (br s, NH), 7.44 (d, J = 1.9 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 2.2 Hz, 1H), 6.99 (dd, J = 1.9 and 8.5 Hz, 1H), 5.92 (s, 2H), 3.21–3.12 (m, 2H), 2.64 (dd, J = 9.5 and 14.0 Hz, 1H), 2.54–2.44 (m, 1H), 2.44 (s, 3H), 2.28–2.19 (m, 1H), 2.05 (s, 6H), 1.91–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 135.4, 130.7, 129.4, 127.9, 123.6, 122.1, 118.5, 114.3, 111.3, 105.0, 66.7, 57.5, 40.9, 31.5, 30.0, 21.9, 13.2; LRMS (*m/z*, relative intensity) 307 (18), 276 (2), 222 (21), 84 (100); HRMS calcd for $C_{20}H_{25}N_3$ 307.2043, found 307.2028 (−1.0 σ); $[\alpha]^{25}$ = +92° (methylene chloride, c = 1). Anal. Calcd for $C_{20}H_{25}N_3 \cdot 0.5H_2O$: C, 75.92; H, 8.28; N, 13.27. Found: C, 75.88; H, 8.43; N, 13.24.

5-Amino-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]-1*H*-indole (2c). A mixture of the 5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]-1*H*-indole (81.5 g, 0.265 mol), hydroxylamine hydrochloride (368 g, 5.30 mol, 20 equiv), and triethylamine (367 mL, 2.65 mol, 10 equiv) in 2-propanol (800 mL) and water (200 mL) was heated at reflux under nitrogen for 4.5 h. The resulting reaction mixture was cooled in an ice bath, solid sodium hydroxide (212 g, 5.30 mol, 10 equiv) was added, and the resulting reaction mixture was stirred at room temperature under nitrogen for 24 h. The reaction mixture was then filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual oil was passed through a silica gel filter (approx 1 kg) followed by elution with ethyl acetate/methanol/triethylamine [8:1:1] to afford a pale yellow solid (85 g). This solid was dissolved in ethyl acetate (1 L), and this solution was washed with a saturated solution of sodium chloride (3 × 100 mL). The organic layer was dried (Na_2SO_4), and evaporated under reduced pressure to afford the title compound (50.55 g, 0.220 mol, 83%) as a brown amorphous solid: mp 43–47 °C, decomposes 60 °C; R_f = 0.4 in ethyl acetate/methanol/triethylamine [8:1:1]; IR (neat) 1628, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (br s, NH), 7.15 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 2.2 and 8.5 Hz, 1H), 3.45 (br s, NH_2), 3.20–3.10 (m, 2H), 2.61–2.46 (m, 2H), 2.47 (s, 3H), 2.25 (dd, J = 9.2 and 17.2 Hz, 1H), 1.96–1.75 (m, 2H), 1.75–1.55 (m, 2H); ^{13}C NMR (CD_3OD) δ 135.8, 134.3, 129.0, 126.2, 115.5, 113.7, 109.7, 107.7, 58.5, 57.6, 40.1, 31.1, 27.5, 22.3; ^{13}C NMR ($CDCl_3$) δ 138.9, 131.2, 128.5, 122.7, 112.8, 112.7, 111.7, 104.0, 66.7, 57.5, 40.7, 31.5, 29.8, 21.8; LRMS (*m/z*, relative intensity) 229 (M^+, 10), 198 (5), 181 (5), 159 (6), 144 (24), 84 (100); HRMS calcd for $C_{14}H_{19}N_3$ 229.1575, found 229.1593 (+1.6 σ); $[\alpha]^{25}$ = +9° (MeOH, c = 1.0). Anal. Calcd for $C_{14}H_{19}N_3 \cdot 0.25H_2O$: C, 71.91; H, 8.41; N, 17.97. Found: 71.68; H, 8.32; N, 17.85.

The spectral and physical properties of this material were identical with the spectral and physical properties previously reported for 5-amino-3-[(*N*-methylpyrrolidin-2(*R*)-yl)methyl]-1*H*-indole.[2j]