Ergoline Synthons. 2.[1] Synthesis of 1,5-Dihydrobenz[*cd*]indol-4(3*H*)-ones and 1,3,4,5-Tetrahydrobenz[*cd*]indol-4-amines

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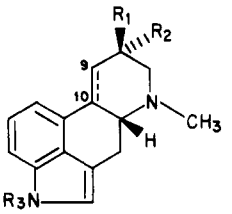
A short (four intermediates) and high-yield (40–50%) synthesis of new tricyclic ergoline synthons 6-H-**5a**, and 6-methoxy-**5b**, substituted 1,5-dihydrobenz[*cd*]indol-4(3*H*)-ones, from 1*H*-indole-4-carboxaldehyde (**6a**) and 5-methoxy-1*H*-indole-4-carboxaldehyde (**6b**), respectively, is described. Sodium cyanoborohydride mediated reductive amination of **5a** and **5b** provides easy access to 1,3,4,5-tetrahydrobenz[*cd*]indol-4-amines, compounds which show specificity for serotonin and dopamine receptors. The new aldehyde **6b** is prepared in several steps from ethyl 5-methoxy-1*H*-indole-2-carboxylate by bromination of the indole 4-position, a reaction whose regiochemistry is a consequence of stereoelectronic control. This synthetic sequence provides a new and practical route to 3,4-bridged indoles which proceeds without the need for protecting groups.

The pharmacological activities of ergot derivatives such as **1** are legion.[1] Recent attempts at side-chain[2] and nuclear modifications[3] and the synthesis of ergot "substructures"[4] have produced pharmacological selectivity in structural relatives of **1**. [1]. During the course of our

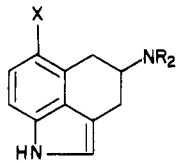


1a, R_1 = $CONEt_2$; R_2 = H; R_3 = H; C_{9-10} = CH=C; LSD

1b, R_1 = CONH–; R_2 = H; R_3 = CH_3; C_{9-10} = CH_2CH; methysergide

1c, R_1 = CH_2NHCO_2Bn, R_2 = H; R_3 = CH_3; C_{9-10} = CH_2CH; metergoline

1d, R_1 = H; R_2 = $NHCONEt_2$; R_3 = H; C_{9-10} = CH=C; lisuride

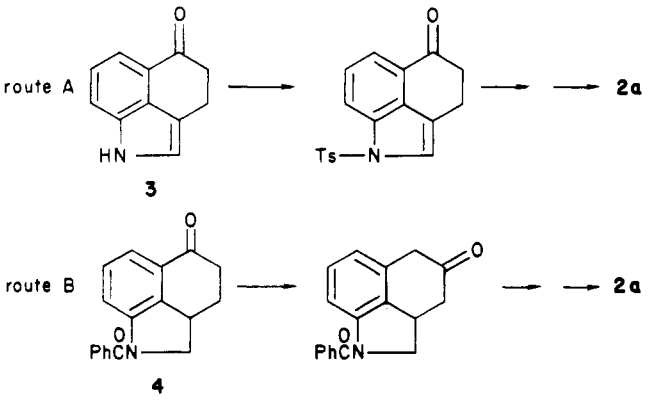


2a, X = H
2b, X = OCH_3

own studies of rigid serotonin congeners we required the tricycle **2b**, a new, ring-oxygenated congener of the known heterocycle **2a**.[4] An electron-rich indole ring[5] and the absence of the ergot D ring were expected to make **2b** selective for serotonin receptor(s).[6]

The biological activity and synthetic challenge provided by the ergot alkaloids has renewed interest in indole chemistry[7] and now elegant new syntheses of lysergic acid,[8a–c] chanoclavine,[8d–f] and paliclavine[8g] complement the classical Kornfeld–Woodward[9] and Uhle[10] strategies for construction of the ergolines. In contrast, we[1,11] and others[12] have employed routes to tricycles **2a** which rely on protected Uhle's ketone derivatives **3** (route A) or the Kornfeld–Woodward ketone **4** (route B), strategies which require formal 1,2-carbonyl transposition and in the case of route B, an oxidative regeneration of the indole ring.[4cd,9,13]

In order to circumvent the protecting-group manipulations and carbonyl transpositions implicit in these lengthy sequences a new approach to **2a,b** was conceived. The new ketones **5a,b** were viewed as versatile synthons for further



elaboration to **2a,b** and the ergots. We became especially intrigued with the preparation and further transformation

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(1) For part 1, see: Meyer, M. D.; Kruse, L. I. *J. Org. Chem.* **1984**, *49*, 3195.

(2) (a) Hökfelt, B.; Nillius, S. J. *Acta Endocrinol. (Copenhagen), Suppl.* **1978**, *216*, 1. (b) Lieberman, A. N.; Liebowitz, M.; Neophytides, A.; Kupersmith, M.; Mehl, S.; Kleinberg, D.; Serby, M.; Goldstein, M. *Lancet* **1979**, *2* (8152), 1129. (c) Lemberger, L.; Crabtree, R. *Science (Washington, DC)* **1979**, *205*, 1151. (d) Lieberman, A. N.; Gopinathan, G.; Estey, E.; Kupersmith, M.; Goodgold, A.; Goldstein, M. *Neurology* **1979**, *29*, 267.

(3) (a) Campaigne, E.; Knapp, D. R. *J. Pharm. Sci.* **1971**, *60*, 809. (b) Bach, N. D.; Hall, D. A.; Kornfeld, E. C. *J. Med. Chem.* **1974**, *17*, 312. (c) Craig, J. C.; Dinner, A.; Mulligan, P. J. *J. Org. Chem.* **1974**, *39*, 1669. (d) Craig, J. C.; Hurt, S. D. *Ibid.* **1979**, *44*, 1108. (e) Craig, J. C.; Hurt, S. D. *Ibid.* **1979**, *44*, 1113. (f) Bach, N. J.; Kornfeld, E. C.; Clemmens, J. A.; Smalstig, E. B.; Fredrickson, R. C. A. *J. Med. Chem.* **1980**, *23*, 492. (g) Cardellini, M.; Cingolani, G. M.; Claudi, F.; Cristalli, G.; Gulini, U.; Martelli, S. *J. Org. Chem.* **1982**, *47*, 688.

(4) (a) Stoll, A.; Petrzilka, T. *Helv. Chim. Acta* **1952**, *35*, 148. (b) Harris, L. S.; Uhle, F. C. *J. Pharmacol. Exp. Ther.* **1960**, *128*, 358. (c) Nichols, D. E.; Robinson, G. S.; Li, G. S.; Cassady, J. M.; Floss, H. G. *Org. Prep. Proced. Int.* **1977**, *9*, 277. (d) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481. (e) Bach, N. J.; Kornfeld, E. C.; Clemens, J. A.; Smalstig, E. B. *Ibid.* **1980**, *23*, 812. (f) Euvard, C.; Ferland, L.; Fortin, M.; Oberlander, C.; Labrie, F.; Boissier, J. R. *Drug Devel. Res.* **1981**, *1*, 151. (g) Nedelec, L.; Pierdet, A.; Fauveau, P.; Euvard, C.; Proulx-Ferland, L.; Dumont, C.; Labrie, F.; Boissier, J. *J. Med. Chem.* **1983**, *26*, 522.

(5) The affinity of indolylalkylamines for serotonin receptor(s) depends crucially upon electron density in the indole ring. Glennon, R. A.; Gessner, P. K. *J. Med. Chem.* **1979**, *22*, 428 and references cited therein.

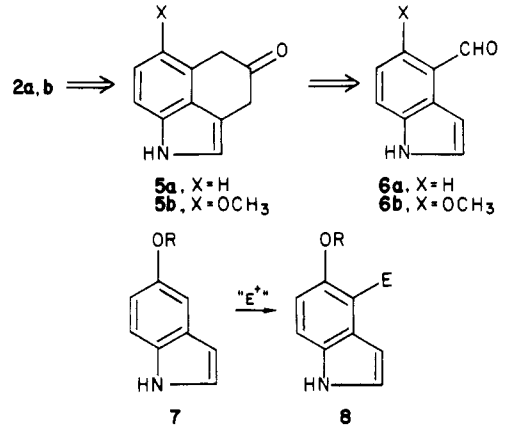
(6) While the preferred side-chain conformation for binding of serotonin to its receptor(s) is subject to some debate, and is being intensively investigated in the authors' laboratory, *published* evidence suggests the rigid conformation found in **2b** may represent an optimum. Glennon, R. A.; Liebowitz, S. M. *J. Med. Chem.* **1982**, *25*, 393 and references cited therein.

(7) For recent reviews, see: (a) Horwell, D. C. *Tetrahedron* **1980**, *36*, 3123. (b) Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267.

0022-3263/84/1949-4761$01.50/0

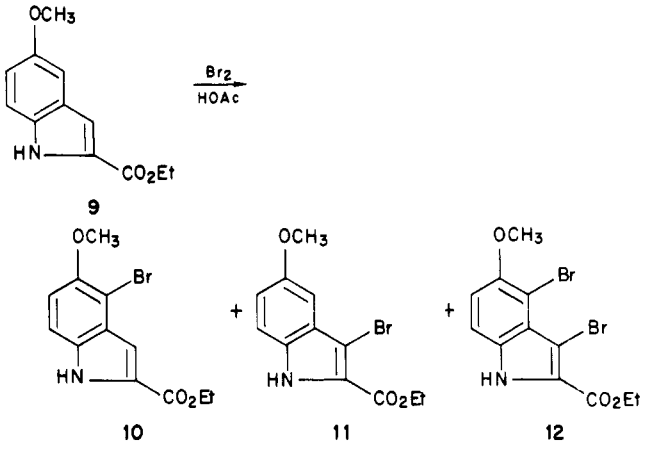
of ergoline synthons **5a,b** since one early attempt at preparing **5a** was unsuccessful and produced only intractable tars.[14] In contrast to this early work, we report here the preparation of ketones **5a,b** and their further elaboration to tricyclic indoles bearing the ergot basic nitrogen.

Retrosynthetic analysis suggested aldehydes **6a,b** as precursors to **5a,b**, a line of reasoning suggested by the recent successful elaboration of indole-4-carboxaldehyde (**6a**) to complex ergolines.[8] As an initial target, however,



the 4,5-disubstituted indolealdehyde **6b** represented a substantial challenge. In contrast to **6a**, which is readily available from simple benzenoid precursors,[15] suitable 1,2,3,4-tetrasubstituted benzenes required as direct precursors of **6b** appeared to lack representation in the literature.[16] Attention was therefore directed toward electrophilic functionalization of a 5-oxygenated indole at C-4, **7** → **8**, a transformation whose regiochemical outcome is a predictable consequence of stereoelectronic control of electrophilic aromatic substitution.[17,18]

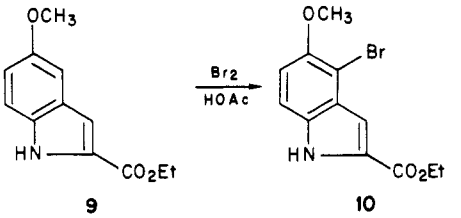
Table I. Reaction of Ethyl 5-Methoxyindole-2-carboxylate with Bromine



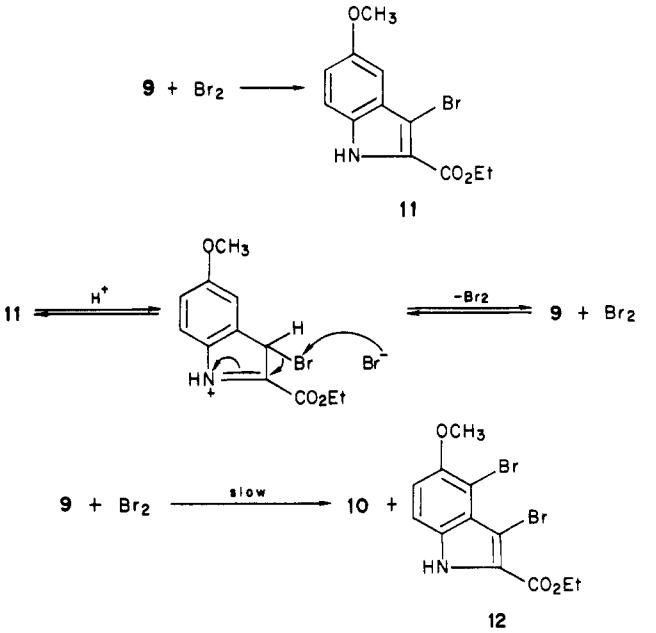
entry	condns[a]	product distribution[b] % 9	10	11	12
A	10-s quench	10	14	71	5
B	30-s quench	9	14	75	2
C	24-h quench	2	92	3	2
D	sodium acetate buffer; 24-h quench	19	3	68	10

[a] A 0.1 M solution of **9** in acetic acid was stirred vigorously while 1.0 equiv of neat bromine was added. [b] Determined by GLPC/MS analysis of the crude reaction product.

Bromoindole **10**, a compound prepared by Julia[18c] from readily available ethyl 5-methoxyindole-2-carboxylate (**9**) by the action of bromine in acetic acid, was an attractive starting material for the preparation of **6b**.



In scaling up this bromination we encountered erratic results and eventually found that the 3-bromo isomer **11** was the major product (70–75%) when the acetic acid solution was quenched in water after 30 sec or less. After



(8) (a) Julia, M.; Le Goffic, F.; Igolen, J.; Baillarge, M. *Tetrahedron Lett.* **1969**, 1569. (b) Oppolzer, W.; Francotte, E.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 478. (c) Rebek, J.; Tai, D. F. *Tetrahedron Lett.* **1983**, *24*, 859. (d) Oppolzer, W.; Grayson, J. I. *Helv. Chim. Acta* **1980**, *63*, 1706. (e) Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265. (f) Natsume, M.; Muratake, H. *Heterocycles* **1981**, *16*, 375. (g) Oppolzer, W.; Grayson, J. I.; Wegmann, H.; Urrea, M. *Tetrahedron* **1983**, *39*, 3695. (h) Kozikowski, A. P.; Chen, Y.-Y. *J. Org. Chem.* **1981**, *46*, 5250.

(9) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.

(10) (a) Uhle, F. C. *J. Am. Chem. Soc.* **1949**, *71*, 761. (b) Uhle, F. C. *Ibid.* **1951**, *73*, 2402.

(11) Kruse, L. I.; Meyer, M. D., unpublished results.

(12) (a) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, H.; Weale, J.; Weyell, D. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 438. (b) Ponticello, G. S.; Baldwin, J. J.; Lumma, P. K.; McClure, D. E. *J. Org. Chem.* **1980**, *45*, 4236 (1980). (c) Baldwin, J. J.; Jones, J. H.; Lundell, G. F. *Eur. Pat. Appl.* 29 581, 1981; *Chem. Abstr.* **1981**, *95*, 150437y.

(13) Cassady, J. M.; Li, G. S.; Spitzner, E. B.; Floss, H. G.; Clemens, J. A. *J. Med. Chem.* **1974**, *17*, 300.

(14) Grob, C. A.; Meier, W.; Renk, E. *Helv. Chim. Acta* **1961**, *44*, 1525.

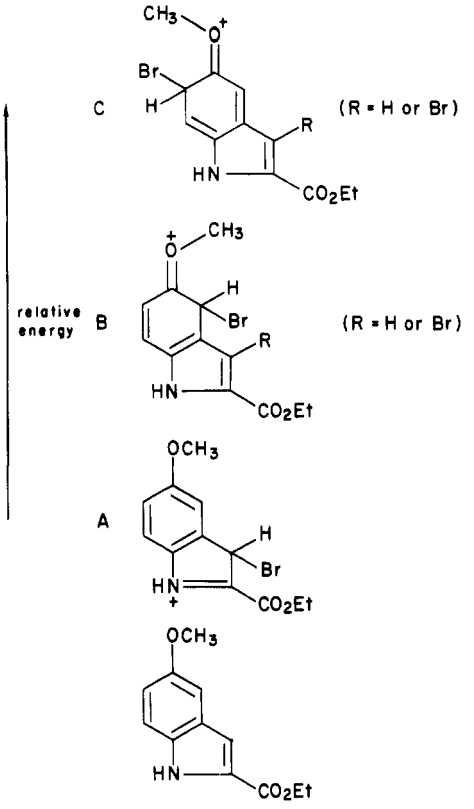
(15) Maehr, H.; Smallheer, J. M. *J. Org. Chem.* **1981**, *46*, 1752 and references cited therein.

(16) 4-Chloro-5-alkoxyindoles have been prepared from benzenoid precursors by two groups, but further elaboration has either not been attempted, or has been found to be unsatisfactory: (a) Robinson, P.; Slaytor, M. *Aust. J. Chem.* **1961**, *14*, 606. (b) Flaugh, M. E.; Crowell, T. A.; Clemens, J. A.; Sawyer, B. D. *J. Med. Chem.* **1979**, *22*, 63.

(17) (a) Kruse, L. I.; Cha, J. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1329. (b) Kruse, L. I.; Cha, J. K. *Ibid.* **1982**, 1333. (c) Kruse, L. I.; Cha, J. K. *Tetrahedron Lett.* **1983**, *24*, 2367.

(18) A few known reactions of 5-oxyindoles exemplify the profound regiochemical consequences of stereoelectronic control during electrophilic aromatic substitutions. (a) 5-(Benzyloxy)gramine nitrates regiospecifically in the 4-position: Gannon, W. F.; Benigni, J. D.; Suzuki, J.; Daly, J. W. *Tetrahedron Lett.* **1967**, 1531. (b) 5-Methoxygramine brominates in the 4-position: Kruse, L. I., unpublished observation. (c) 5-Allyloxyindole undergoes a regiospecific Claisen rearrangement to the 4-position: Julia, M.; Lallemand, J.-Y. *Bull. Soc. Chim. Fr.* **1973**, 2046. (d) 5-Hydroxyindole yields the 4-position Mannich under basic conditions: Troxler, F.; Borman, G.; Seeman, F. *Helv. Chim. Acta* **1968**, *51*, 1203.

Scheme I



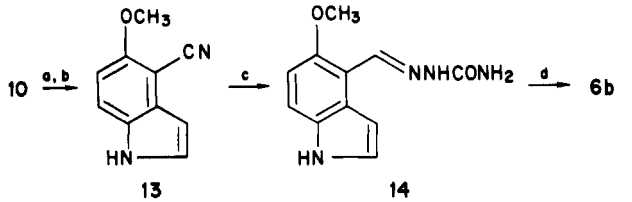
24 h, the 4-bromo compound **10** was obtained (92%) with 2–3% of **11** and the 3,4-dibromo compound **12** (Table I). These results suggest that **11** is the kinetically controlled product, and on subjecting pure **11** to the reaction conditions, or to a solution of LiBr in H_2SO_4/HOAc, conversion to **10** occurred by reversible protonation of **11** and subsequent slower bromination at C-4, events which require both strong acid and bromide ion.[19]

This reaction sequence is precisely that predicted by the stereoelectronic theory of aromatic substitution (Scheme I).[17] Initial rapid (and readily reversible) electrophilic attack by bromine on **9** occurs by a transition state resembling σ-complex A, where maximum aromatic resonance is maintained. A subsequent slower bromination via a transition state with lowered resonance energy which resembles σ-complex B occurs less readily, but with time does lead to **10**. Other transition states resembling σ-complex C where the resonance energy of both aromatic rings is disrupted are sufficiently high in relative energy to be inaccessible under the reaction conditions.

Appropriate adjustment of the reaction conditions made the bromination a convenient preparation of multimolar amounts of **10**. Saponification of **10** and copper cyanide promoted decarboxylation and halogen replacement in refluxing quinoline, or more conveniently in *N,N*-dimethylacetamide, gave nitrile **13** in good overall yield.

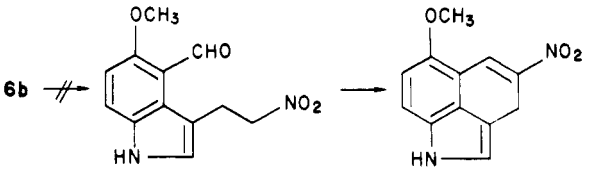
A subsequent conversion of the very hindered and very electron rich nitrile **13** to aldehyde **6b** proved extremely difficult. Reagents known to induce a similar transformation on other cyanoindoles were ineffective in this case. Conditions tried include Raney nickel/sodium hypophosphite,[20] Dibal-H, $LiAlH(OEt)_3$,[21] and $Me_3O^+BF_4^-$/Et_3SiH.[22] Raney alloy[23] in hot aqueous formic acid did produce traces of a product subsequently shown to be **6b**, but intractable polymer was the major product of this reaction—a result which underscores the acid lability of **6b**. Catalytic hydrogenation of **13** and in situ trapping of the intermediate imine with semicarbazide did give the highly crystalline semicarbazone **14** in good yield. Even this apparent success was viewed with some reservation since the simpler semicarbazone of indole-4-carboxaldehyde (**6a**) had already been reported as resistant to hydrolysis.[21] A number of attempts at hydrolysis of **14**, and the semicarbazone of **6a** as a model compound, confirmed the earlier result by producing only low (5–15%) yields of **6b** or **6a**, respectively, which were always accompanied by large amounts of insoluble brown tars. Exploration of the hydrolysis reaction in detail yielded conditions which provided good, reproducible yields of **6b**. Rapid hydrolysis of **14** with a minimum of tar formation resulted upon treatment with distilled pyruvic acid in dilute acetic acid carefully buffered with sodium acetate.[24] Extraction, followed by filtration through silica gel, gave multigram quantities of **6b** (Scheme II).

Scheme II[a]



[a] Conditions: (a) NaOH/EtOH; (b) CuCN/DMAC; (c) H_2/Raney nickel, $NH_2NHCONH_2$·HCl, NaOAc; (d) CH_3COCO_2H, NaOAc/HOAc.

Our attention was next directed toward construction of the carbocyclic bridge of tricycle **5b**. The initial strategy was to prepare nitroalkane **15** and to cyclize **15** to **16**.



Unfortunately, however, all attempts (nitroethylene,[25] $Me_2NH/CH_2O/H^+$,[21] $Me_2NCHCHNO_2/H^+$[26]) to functionalize **6b** at the 3 position proved unsatisfactory. The sensitivity of the aldehyde group in **6b** toward acid was suspected as the cause of this failure, and rather than

(19) Since the rearrangement of an equimolar mixture of dibromoindole **12** and starting material **9** with HBr/HOAc also produces 4-bromoindole **10**, it seems likely **12** may also be on the reaction pathway, although the relative importance of this pathway to the production of **10** cannot be assessed without a detailed kinetic analysis.

(20) Troxler, F.; Harnisch, A.; Bormann, G.; Seemann, F.; Szabo, L. *Helv. Chim. Acta* **1968**, *51*, 1616.

(21) Plieninger, H.; Höbel, M.; Liede, V. *Chem. Ber.* **1963**, *96*, 1618.

(22) Fry, J. L. *J. Chem. Soc., Chem. Commun.* **1974**, 45.

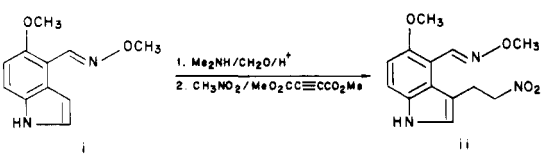
(23) van Es, T.; Staskun, B. *J. Chem. Soc.* **1965**, 5775.

(24) The use of buffer in pyruvic acid/acetic acid deprotection of semicarbazones has occasionally been used. Hershberg, E. B. *J. Org. Chem.* **1948**, *13*, 542. In the present case the acid lability of aldehyde **6b** makes the use of buffer absolutely essential.

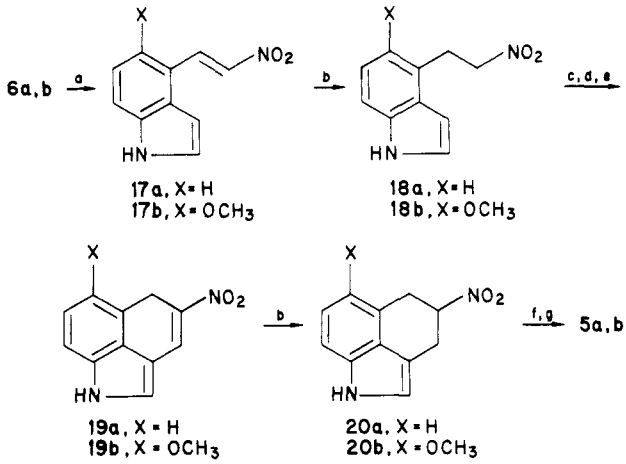
(25) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185.

(26) Büchi, G.; Mak, C.-P. *J. Org. Chem.* **1977**, *42*, 1784.

(27) In accord with this thinking was the observation that **6b** protected as the *O*-methyloxime i was readily elaborated to ii. *O*-Methyloximes are known to be extremely unreactive toward hydrolysis and ii proved no exception. In addition to this failure to hydrolyze, ii was resistant toward direct cyclization to **16**.



Scheme III[a]



[a] Conditions: (a) NH_4OAc/CH_3NO_2; (b) $NaBH_4/CH_3OH$; (c) $POCl_3/DMF$; (d) H_2O/DMF; (e) NEt_3/CH_3OH; (f) $NaOCH_3/CH_3OH$; (g) $TiCl_3/NH_4OAc/H_2O$.

initiate an aldehyde protection–deprotection sequence a slightly different approach was employed.[27]

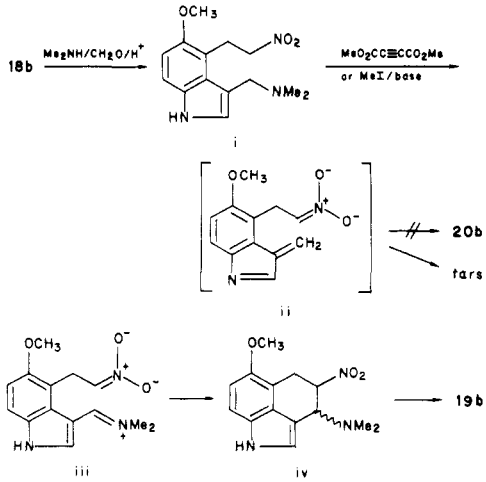
The ammonium acetate catalyzed condensation of **6b** with excess nitromethane[28] produced excellent yields of **17b** as maroon crystals. A number of reducing agents including $NaBH_3CN$[29] failed to effect conjugate reduction of **17b**, but reduction using the alkoxyborohydride generated in situ from excess $NaBH_4$ in methanol gave an excellent yield of **18b**.[30] In an application of the cyclization developed by Natsume for the synthesis of chanoclavine,[8f,31] Vilsmeier formylation of **18b** and in situ cyclization promoted by NEt_3[32] gave tricycle **19b** in excellent yield. Attempts at direct reduction of **19b** to **2b** ($R_2 = H_2$) with $LiAlH_4$ provided only very modest yields of product,

(28) This general procedure is described in ref 21.

(29) Hutchins, R. O.; Rotstein, D.; Natale, N.; Fanelli, J. *J. Org. Chem.* **1976**, *41*, 3328.

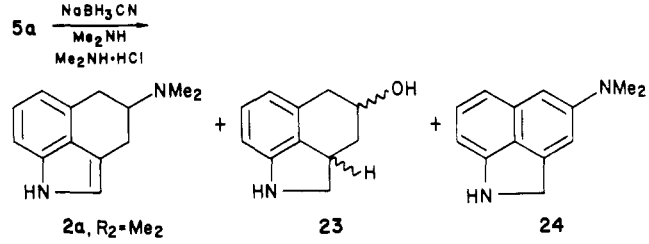
(30) One prior $NaBH_4$ reduction of a nitrovinylindole procedes in only modest (30%) yield (Meyers, A. I.; Sircar, J. C. *J. Org. Chem.* **1967**, *32*, 4134), but a more recent reduction of electron-rich nitrovinylaromatics with $NaBH_4/CH_3OH$ gives good yields of reduction product (McDonald, E.; Martin, R. T. *Tetrahedron Lett.* **1977**, 1317). We have studied in detail the reduction of nitrovinylindoles with $NaBH_4/CH_3OH$ and have shown this reaction to proceed via in situ formation of alkoxyborohydrides (Kruse, L. I.; Hilbert, E. L. *Heterocycles* **1983**, *20*, 1373).

(31) The more direct course of **18b** → i → **20b** was also explored without success. The failure of i to undergo intramolecular cyclization to **20b** is possibly due to inadequate orbital overlap in the *endocyclic* olefin intermediate ii. The success of the Natsume cyclization procedure probably derives from nucleophilic attack on an *exocyclic* iminium species iii → iv.



(32) Triethylamine has consistently given higher yields than other reagents, i.e., NaOH; $NaOCH_3$; NH_4OAc.

Table II. Effect of Conditions on Sodium Cyanoborohydride Reductive Amination of 5a with Dimethylamine[a]

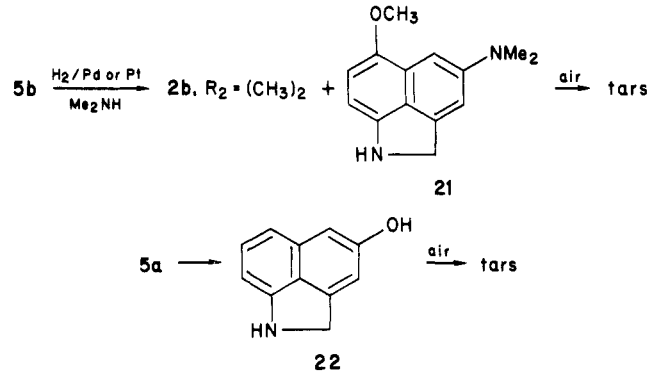


		product distributions,[c] %		
entry	condns[b]	**2a**, R_2 = Me_2	**23**	**24**
A	10:0	29	8	
B	10:2	57[d]		trace
C	10:10	30		15

[a] Ketone (0.58 mmol) was reacted with sodium cyanoborohydride (10 mmol) in methanol (10 mL) containing the indicated amounts of dimethylamine hydrochloride and anhydrous dimethylamine. [b] The ratio is amount of dimethylamine hydrochloride (mmol) and dimethylamine (mmol) used. [c] Determined by GLPC/MS analysis unless otherwise noted. [d] Isolated yield.

while attempted chemical reduction of **19b** with dissolving metals [e.g., Al(Hg); Zn^0; Sn^0; Fe^0] or derived salts gave complex, dark tars rather than ketone **5b**. Once again the mild conjugate reduction with $NaBH_4$ proved useful and nitroalkane **20b** was prepared from **19b** in excellent yield. Subsequent reaction of **20b** as the nitronate anion with McMurry's buffered $TiCl_3$ reagent[33] gave an excellent yield of ketone **5b**. In order to further extend the utility of this synthetic sequence, the parent ketone **5a** was also prepared from aldehyde **6a** in comparable overall yields (Scheme III).

Reductive aminations of ketone **5b** with palladium and platinum catalysts met with only marginal success. While the palladium-catalyzed reductive aminations of **5b** with dimethylamine did produce some **2b** [$R_2 = (CH_3)_2$] as evidenced by NMR and GLPC/MS data, the primary product appeared to be an unstable compound whose structure we have tentatively assigned (NMR, MS) as **21**.



This conclusion is in accord with the suggestion that the related compound **22** led via oxidation to the complex tars observed during the early attempts to prepare **5a**.[14]

It was subsequently discovered that reductive amination of **5a** to **2a** [$R_2 = (CH_3)_2$] proceeded well with sodium cyanoborohydride,[34] and formation of the unstable naphthalene **24** could be almost completely suppressed by employing an optimum ratio of amine hydrochloride to amine (Table II). Interestingly, when free amine was omitted from the reduction (Table II, entry A), the reduced in-

(33) McMurry, J. E.; Melten, J. *J. Org. Chem.* **1973**, *38*, 4367.

(34) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

dole-alcohols **23** (NMR, GLPC/MS) were produced, a result we attribute to the increased acidity of the reaction medium.[35] The optimized conditions developed for the reductive amination of **5a** were successfully applied to **5b** to provide good yields of **2b** [$R_2 = (CH_3)_2$]. In addition to amines prepared from ketones **5a,b**, the nitroalkanes **20a,b** were readily transformed to **2a,b** ($R_2 = H_2$), respectively, by catalytic hydrogenation over platinum oxide.

In summary, the conversion of aldehydes **6a,b** to ketones **5a,b** proceeds in high overall yield, on a multigram scale, without the need for protecting groups. Furthermore, the reductive amination of **5a,b** with dimethylamine suggests these ketones as intermediates of potential utility in the construction of even more complex ergot substructures, particularly so since a regiospecific functionalization of the 5 position of **5a** could in principle lead to a short entry to the ergoline D ring. Lastly, in the context of our original goal of producing a rigid serotonin congener of optimum side-chain conformation, it is interesting to note that **2b** ($R_2 = H_2$) displaces ^{3}[H]-5-HT from rat frontal cortex with an IC_{50} of ~50 nM.[36]

Experimental Section

General Methods. All solvents used in reaction mixtures were dried and/or purified by standard procedures.[37] Thin-layer chromatography was done on Analtech Uniplate 250-μm silica gel plates, Silica Woelm TSC activity III was used for column filtrations, and Baker 40-μm Flash silica gel was used for flash chromatography. Infrared (IR) spectra were recorded on a Perkin-Elmer 727 spectrometer as Nujol mulls calibrated with the 1601-cm^{-1} absorption of polystyrene film. NMR spectra were obtained as $CDCl_3$ solutions, unless otherwise noted, with Varian EM390 and Hitachi Perkin-Elmer R-24 spectrometers, and chemical shifts are reported relative to tetramethylsilane. Ultraviolet (UV) spectra were recorded in absolute ethanol solution with a Perkin-Elmer 559 UV-vis spectrophotometer in the 200–400-nm range. Electron-impact mass spectra were obtained with an Hitachi Perkin-Elmer RMU-6E spectrometer at 70 eV. Gas chromatographic analyses were done on a 4 ft × 2 mm 3% OV17 100–120-mesh Chromasorb HP column at 125–340 °C. GLPC–mass spectra were obtained under similar conditions with a Finnigan 3300/9500 mass spectrometer. Chemical ionization mass spectra were obtained with the same instrument. All melting points are uncorrected and were obtained with a Thomas-Hoover uni-melt or an Electrothermal melting point apparatus. All solutions were dried over anhydrous sodium sulfate and concentrated with a Büchi Rotavapor at ca. 10 torr before pumping at 0.5 torr.

Ethyl 3-Bromo-5-methoxy-1*H*-indole-2-carboxylate (11). A solution of ethyl 5-methoxy-1*H*-indole-2-carboxylate[38] (219 mg, 1.0 mmol) in glacial acetic acid (10 mL) was stirred *vigorously* with a magnetic stirrer during the addition (ca. 5 s) of neat bromine (51 μL, 1.0 mmol). After 30 s water (50 mL) was added, and the mixture was extracted twice with ethyl acetate. The combined organic extracts were washed twice with saturated aqueous sodium carbonate and once with brine, dried, and concentrated. The crude product was purified by flash chromatography[39] using 3:1 hexane–ethyl acetate as eluant and recrystallized twice from ethyl acetate/hexane to give 134 mg (45%) of **11** as colorless needles: mp 155–157 °C; R_f 0.25 with 3:1 hexane–ethyl acetate as eluant; IR 3320, 1680, 1520 cm^{-1}; UV λ_{max} 210 nm (ε 26 100), 300 (20 500); NMR δ 1.42 (t, 3 H, J = 8 Hz), 3.9 (s, 3 H), 4.45 (q, 2 H, J = 8 Hz), 6.95–7.10 (m, 2 H), 7.3 (d, 1 H, J = 9 Hz), 9.2 (br s, 1 H); mass spectrum, m/e 297, 299, 251, 253.

Anal. Calcd for $C_{12}H_{12}BrNO_3$: C, 48.31; H, 4.05; N, 4.69. Found: C, 48.65; H, 4.07; N, 4.73.

Ethyl 3,4-Dibromo-5-methoxy-1*H*-indole-2-carboxylate (12). A solution of ethyl 5-methoxy-1*H*-indole-2-carboxylate (219 mg, 1.0 mmol) in glacial acetic acid (10 mL) was stirred during the addition of bromine (102 μL, 2.0 mmol) and then concentrated. The solid residue was dissolved in ethyl acetate, washed twice with saturated aqueous sodium carbonate and once with brine, dried, and concentrated. The crude product was recrystallized from ethyl acetate/hexane to give **12** (260 mg, 69%) as white needles: mp 165–166 °C; R_f 0.2 with 3:1 hexane–ethyl acetate as eluant; IR 3320, 1680, 1570, 1510 cm^{-1}; UV λ_{max} 234 nm (ε 24 100), 304 (20 600); NMR ($CDCl_3$–acetone-d_6) δ 1.32 (t, 3 H, J = 8 Hz), 3.82 (s, 3 H), 4.32 (q, 2 H, J = 8 Hz), 7.06 (d, 1 H, J = 9 Hz), 7.42 (d, 1 H, J = 9 Hz); mass spectrum, m/e 375, 377, 379, 329, 331, 333.

Anal. Calcd for $C_{12}H_{11}Br_2NO_3$: C, 38.23; H, 2.94; N, 3.71. Found: C, 38.38; H, 2.90; N, 3.78.

Bromination of Ethyl 5-Methoxy-1*H*-indole-2-carboxylate: Product Distribution Study (Table I). A solution of ethyl 5-methoxy-1*H*-indole-2-carboxylate (219 mg, 1.0 mmol) in glacial acetic acid (10 mL) was treated with bromine (51 μL, 1.0 mmol) exactly as for the preparation of **11**. In separate experiments aqueous quenches at 10 s, 30 s, and 24 h, followed by extractive workup and GLPC/mass spectral analysis of the crude mixture, provided product distribution data (Table I). The buffered experiment was done in an analogous fashion, by the inclusion of sodium acetate (90 mg, 1.1 mmol) in the initial solution.

Hydrogen Bromide Catalyzed Rearrangement of 11 to 10. Indole **11** (59.6 mg, 0.2 mmol) was added to 0.1 M hydrogen bromide/acetic acid (2 mL) and the mixture was warmed to effect complete solution and then stirred under argon for 24 h at ambient temperature. Extractive workup as in the Product Distribution Study and GLPC/mass spectral analysis showed the product to consist of **10**, 98.5%; **11**, 0.7%; and **9**, 0.4%. Isolation of **10** by flash chromatography and crystallization provided a sample identical (IR, NMR, mp, mmp) with authentic **10**.

Attempted Rearrangement of 11 to 10 with Sulfuric and Trifluoromethanesulfonic Acids. Treatment of **11** with 0.1 M solutions of H_2SO_4/acetic acid or trifluoromethanesulfonic acid/acetic acid under conditions identical with those used in the hydrogen bromide catalyzed rearrangement of **11** to **10** led only to recovered **11**, as evidenced by TLC and GLPC/mass spectral analyses. A solution of **11** (59.6 mg, 0.2 mmol) in 0.1 M sulfuric acid/acetic acid (2 mL) containing lithium bromide (17 mg, 0.2 mmol) produced after 24 h a product mixture [**10**, 97.1%; **11**, 1.9%; **9**, 0.3%] similar to that observed with hydrogen bromide catalyzed rearrangement.

Hydrogen Bromide Catalyzed Rearrangement of 9 plus 12 to 10. Indole **9** (21.9 mg, 0.10 mmol) and indole **12** (37.7 mg, 0.10 mmol) were dissolved with warming in 0.1 M hydrogen bromide/acetic acid (2.0 mL). After 24 h, the reaction was quenched with 10% aqueous Na_2CO_3 solution (50 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried and concentrated. GLPC/mass spectral analysis showed the product to consist of **10**, 98.5%; **11**, 1.0%; and **9**, 0.5%.

Large-Scale Preparation of Ethyl 4-Bromo-5-methoxy-1*H*-indole-2-carboxylate (10). A mixture of **9** (186 g, 0.85 mol) and glacial acetic acid (4.2 L) was stirred and warmed on a hot plate until only a small amount of indole remained undissolved. The warm solution was stirred vigorously during the dropwise addition (15 min) of bromine (43.4 mL, 135.4 g, 0.85 mol) and then allowed to stand at ambient temperature for 24 h. The resulting dark brown mixture was filtered, and the crystalline product was washed sequentially with acetic acid (2 × 150 mL) and hexane (2 × 200 mL) and then dried at 65 °C to give **10** (180.7 g, 71.3%) as a white crystalline solid: mp 176–178 °C (softens at 166 °C). The crude product was a single spot by TLC (R_f 0.29 with 3:1 hexane–ethyl acetate as eluant) and was found to be 98.9% pure by GLPC/mass spectral analysis. An analytical sample crystallized in two forms from absolute ethanol, as needles, mp 169–170 °C, or prisms, mp 166–167 °C (lit.[18c] mp 179 °C): IR 3350, 1700, 1530 cm^{-1}; UV λ_{max} 224 nm (ε 24 400), 298 (22 000); NMR δ 1.44 (t, 3 H, J = 8 Hz), 3.94 (s, 3 H), 4.45 (q, 2 H, J = 8 Hz), 7.08 (d, 1 H, J = 9 Hz), 7.2–7.5 (m, 2 H), 9.3 (br s, 1 H);

(35) Indoles are readily reduced with sodium cyanoborohydride under acidic conditions: (a) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. (b) Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.* **1978**, *43*, 2733. (c) Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859.

(36) We thank Dr. H. Sarau and Mr. J. Foley for these results. Detailed pharmacological characterization of **2b** will be reported separately.

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(38) Heath-Brown, B.; Philpott, P. G. *J. Chem. Soc.* **1965**, 7185.

(39) Here and subsequently "flash chromatography" means the technique developed by Still: W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2423.

mass spectrum, m/e 299, 297, 251, 253.

Anal. Calcd for $C_{12}H_{12}BrNO_3$: C, 48.31; H, 4.05; N, 4.69. Found: C, 48.46; H, 4.39; N, 4.91.

4-Bromo-5-methoxy-1*H*-indole-2-carboxylic Acid. A 5-L flask was charged with sodium hydroxide (60 g, 1.5 mol) and water (0.5 L), and the contents were stirred until homogeneous. Ethanol (1 L), tetrahydrofuran (0.25 L), and indole **10** (180 g, 0.6 mol) were added, and the mixture was heated at reflux for 1 h and then cooled to ambient temperature. The solution was stirred vigorously as concentrated hydrochloric acid (0.25 L, 3 mol) and water (2.5 L) were added. The resulting thick yellow paste was cooled at 0 °C overnight, and filtered, and the crystalline product was washed with water (3 × 400 mL), sucked as dry as possible, and dried at 60 °C to give the carboxylic acid (161 g, 99.3%): mp 263 °C dec; R_f 0.55 with 2.5% glacial acetic acid–ethyl acetate as eluant. An analytical sample was recrystallized twice from methanol to give light yellow needles: mp 264–265 °C dec; IR 3400–2900, 3360, 1700, 1530 cm^{-1}; UV λ_{max} 222 nm (ϵ 29 200), 294 (15 300); NMR ($CDCl_3$–Me_2SO-d_6) δ 3.86 (s, 3 H), 7.0 (s, 1 H), 7.04 (d, 1 H, J = 9 Hz), 7.42 (d, 1 H, J = 9 Hz); chemical ionization (methane) mass spectrum, m/e 270, 272 ($M + H^+$), 191 ($M + H^+ - Br$).

Anal. Calcd for $C_{10}H_8BrNO_3$: C, 44.47; H, 2.98; N, 5.18. Found: C, 44.32; H, 2.97; N, 5.32.

5-Methoxy-1*H*-indole-4-carbonitrile (13) from Copper(I) Cyanide/Quinoline Treatment of 4-Bromo-5-methoxy-1*H*-indole-2-carboxylic Acid. A 2-L flask was purged with argon and charged with *freshly distilled* quinoline (0.9 L), copper(I) cyanide (159.2 g, 1.78 mol), and 4-bromo-5-methoxy-1*H*-indole-2-carboxylic acid (160 g, 0.593 mol). The mixture was heated (oil bath temperature 240–250 °C) to near reflux for 3 h to give a dark, homogeneous solution. The solution was cooled until crystallization began and then quickly poured into ethyl acetate (2.0 L) with stirring. The mixture was further cooled to ambient temperature, allowed to stand for 3 h, and filtered through Celite. The dark precipitate was washed with ethyl acetate, and the combined organic washes were extracted with a mixture of water (4 L) and concentrated hydrochloric acid (1.25 L). The aqueous phase was extracted with ethyl acetate (3 × 500 mL), and all the combined ethyl acetate phases were washed sequentially with 2 N aqueous hydrochloric acid (5 × 300 mL), water, and brine and then dried and warmed briefly with Darco G-60 before concentration. The crude tan product was purified by bulb-to-bulb distillation [160–190 °C (0.2 torr)] and recrystallization from ethyl acetate/hexane to give **13** (43.9 g, 43%) as beige prisms: mp 129–132 °C; R_f 0.35 with 1:1 ethyl acetate–hexane as eluant. An analytical sample was recrystallized from ethyl acetate as beige prisms: mp 140–142 °C; IR 3400, 2230, 1590, 1500 cm^{-1}; UV λ_{max} 204 nm (ϵ 20 200), 228 (21 900), 316 (11 600); NMR ($CDCl_3$–acetone-d_6) δ 3.95 (s, 3 H), 6.65 (br s, 1 H), 6.87 (d, 1 H, J = 9 Hz), 7.4 (t, 1 H, J = 2 Hz), 7.6 (d, 1 H, J = 9 Hz), 10.2 (br s, 1 H); mass spectrum, m/e 172, 157.

Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.56; H, 4.60; N, 16.39.

Nitrile 13 from Copper(I) Cyanide/*N*,*N*-Dimethylacetamide Treatment of 4-Bromo-5-methoxy-1*H*-indole-2-carboxylic Acid. A 1-L flask was charged with *freshly distilled* *N*,*N*-dimethylacetamide (450 mL), and the solvent was degassed (15 min) with a vigorous stream of argon. 4-Bromo-5-methoxy-1*H*-indole-2-carboxylic acid (75 g, 0.28 mol) and copper(I) cyanide (75 g, 0.84 mole) were added, and the solution was stirred and heated at reflux for 28 h, cooled to ambient temperature, and poured into a mixture of water (500 mL) and ethyl acetate (500 mL). The mixture was filtered through Celite, the precipitate was washed with ethyl acetate (250 mL), and the combined ethyl acetate filtrates were separated from the aqueous layer, washed with water (5 × 250 mL), and brine. The solution was dried and concentrated, and the yellow residue was recrystallized from ethyl acetate/hexane to give **13** (21 g, 44%) as light yellow needles: mp 139–141 °C.

5-Methoxy-1*H*-indole-4-carboxaldehyde Semicarbazone (14). A 450-mL Parr hydrogenation bottle was charged with sodium acetate (12 g, 0.146 mol), semicarbazide hydrochloride (16 g, 0.144 mol), and water (45 mL), and the mixture was heated until homogeneous. A heaping tablespoon of Grace no. 28 Raney nickel was added to the cooled Parr bottle followed by a solution of nitrile **13** (20 g, 0.116 mol) in hot methanol (185 mL). The mixture was hydrogenated at 50 psi until the theoretical uptake of hydrogen was complete (ca. 18–24 h). The mixture was heated to near boiling on a steam bath and filtered hot, and the precipitate was washed with hot dimethylformamide until the catalyst was free of product. The filtrate was concentrated and traces of solvent were removed from the residue by further concentration using a dry ice cold trap to give a solid residue. The residue was triturated with a mixture of ethanol (60 mL) and water (180 mL), filtered, and washed with water to yield **14** (18.89 g, 70%) as tan crystals after drying at 60 °C: mp 219–221 °C dec; R_f 0.64 with 10% methanol–ethyl acetate as eluant. An analytical sample was prepared by triturating the semicarbazone twice with methanol and twice with ether: mp 222–223 °C dec; IR 3460, 3350–2900, 1680, 1590, 1500 cm^{-1}; UV λ_{max} 208 nm (ϵ 21 300), 249 (16 100), 344 (17 300); NMR ($CDCl_3$–Me_2SO-d_6) δ 3.8 (s, 3 H), 6.2 (br s, 2 H), 6.8 (d, 1 H, J = 9 Hz), 6.95 (br s, 1 H), 7.25 (br s, 1 H), 7.35 (d, 1 H, J = 9 Hz), 8.5 (s, 1 H), 10.05 (br s, 1 H); chemical ionization (methane) mass spectrum, m/e 233 ($M + H^+$), 190, 175, 160.

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.77; H, 5.17; N, 23.91.

5-Methoxy-1*H*-indole-4-carboxaldehyde (6b). A mixture of water (0.46 L), glacial acetic acid (0.91 L), freshly distilled pyruvic acid (33.23 g, 0.378 mol), and anhydrous sodium acetate (34.16 g, 0.416 mol) was stirred until homogeneous, then semicarbazone **14** (17.5 g, 0.0754 mol) was added, and the mixture was stirred for 16 h. The resulting dark brown solution was concentrated with a dry ice cold trap (water bath temperature <25 °C), the residue was taken up in ethyl acetate (0.5 L) and filtered, and the filtrate was washed sequentially with water (2 × 250 mL), 5% aqueous sodium carbonate (3 × 250 mL), and brine, dried, and warmed briefly with decolorizing charcoal before concentration. The crude product was dissolved in a little ethyl acetate and applied to a silica gel (250 g) column; elution with 2:1 ethyl acetate–hexane and concentration of the first 1.0 L of eluate provided **6b** (9.8 g, 74.2%) as a light yellow solid: mp 134–136 °C (softens at 125 °C); R_f 0.39 with 1:1 hexane–ethyl acetate as eluant. An analytical sample was crystallized twice from ethyl acetate/hexane to give light yellow prisms: mp 146–147 °C; IR 3400–3300, 1640, 1570 cm^{-1}; UV λ_{max} 204 nm (ϵ 19 300), 220 (13 900), 240 (11 700), 353 (11 600); NMR (acetone-d_6) δ 3.9 (s, 3 H), 7.0 (d, 1 H, J = 9 Hz), 7.3 (br s, 1 H), 7.55 (br s, 1 H), 7.75 (d, 1 H, J = 9 Hz), 10.8 (s, 1 H); mass spectrum, m/e 175.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.51; H, 5.19; N, 7.95.

5-Methoxy-4-(2-nitroethenyl)-1*H*-indole (17b). A solution of aldehyde **6b** (8.61 g, 49.2 mmol) and ammonium acetate (1.5 g) in nitromethane (70 mL) was heated on a steam bath for 3 h and diluted with ethyl acetate (150 mL). The solution was washed twice with water and once with brine, dried, and concentrated. The solid product was recrystallized from ethyl acetate/hexane to give **17b** (8.6 g). The crystallization filtrates were concentrated, purified by flash chromatography using 1:1 hexane–ethyl acetate as eluant, recrystallized from ethyl acetate/hexane, and combined with the first crop of product to give **17b** (9.15 g total, 85%) as maroon prisms: mp 175–176 °C; R_f 0.38 with 1:1 ethyl acetate–hexane as eluant. An analytical sample was recrystallized from ethyl acetate: mp 185–186 °C; IR 3350, 1620, 1570, 1500, 1350, 1310 cm^{-1}; UV λ_{max} 206 nm (ϵ 25 200), 225 (23 000), 264 (8700); NMR ($CDCl_3$–Me_2SO-d_6) δ 4.0 (s, 3 H), 6.65 (br s, 1 H), 6.85 (d, 1 H, J = 9 Hz), 7.33 (t, 1 H, J = 2 Hz), 7.52 (d, 1 H, J = 9 Hz), 8.08 (d, 1 H, J = 14 Hz), 8.65 (d, 1 H, J = 14 Hz); mass spectrum, m/e 218.

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.60; H, 4.68; N, 12.73.

5-Methoxy-4-(2-nitroethyl)-1*H*-indole (18b). A 2-L flask was charged with methanol (0.42 L) and indole **17b** (9.1 g, 41.7 mmol), and the resulting mixture was stirred during the slow (20 min) addition of sodium borohydride (7.0 g, 0.185 mol). During the addition, vigorous hydrogen evolution occurred, and the mixture became warm and finally attained a brown-yellow color. The solution was stirred for 20 min after the addition was completed, glacial acetic acid (ca. 15 mL) was added to pH 6, and the solution was concentrated. The solid residue was partitioned between water and ethyl acetate. The aqueous layer was washed twice with ethyl acetate, and the combined ethyl acetate phases

were washed with water, twice with 10% aqueous sodium carbonate, and brine, then dried, and concentrated. The resulting dark oil was purified by flash chromatography using 40% ethyl acetate–hexane as eluant to give **18b** (8.38 g, 91%) as a light yellow solid: mp 77–79 °C; R_f 0.42 with 40% ethyl acetate–hexane as eluant. An analytical sample crystallized from ethyl acetate/hexane as white prisms: mp 80–81 °C; IR 3420, 1580, 1540, 1380 cm^{-1}; UV λ_{max} 210 nm (ϵ 29 800), 274 (7200), 296 (5400); NMR δ 3.55 (t, 2 H, J = 7 Hz), 3.83 (s, 3 H), 4.63 (t, 2 H, J = 7 Hz), 6.46 (br s, 1 H), 6.8 (d, 1 H, J = 8 Hz), 7.1–7.3 (m, 2 H), 8.1 (br s, 1 H); mass spectrum, m/e 220, 173.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.04; H, 5.50; N, 12.62.

6-Methoxy-4-nitro-1,5-dihydrobenz[*c,d*]indole (19b). DMF (20 mL) was stirred under argon in a 500-mL flask during the addition (2 min) of phosphorous oxychloride (3.45 mL, 37.1 mmol), then the flask was cooled in a cold water bath during the addition (2 min) of indole **18b** (7.15 g, 32.5 mmol). After the addition was completed, the cooling bath was removed, stirring was continued for 15 min at ambient temperature, a mixture of water (6.5 mL, 0.36 mol) and DMF (26 mL) was added, and the resulting solution was stirred for 10 min. A mixture of triethylamine (45.5 mL, 0.33 mol) and methanol (130 mL) was added, the solution was heated at reflux for 30 min, water (75 mL) was added slowly to the hot solution, and the mixture was cooled at 20 °C for 2 h. The mixture was filtered and the precipitate was washed sequentially with water, 2:1 methanol–water (2 × 25 mL), and ether (3 × 50 mL) and then dried at 60 °C to yield **19b** (6.8 g, 91%) as lustrous green-black crystals: mp >350 °C dec; R_f 0.41 with 1:1 ethyl acetate–hexane as eluant. An analytical sample was prepared by filtering crude product (1.0 g) through a silica gel (50 g) column by using an acetone–ethyl acetate gradient as eluant and recrystallizing the concentrated eluant from methanol to give brown-black needles: mp >350 °C dec; IR 3350, 1570, 1460 cm^{-1}; UV λ_{max} 206 nm (ϵ 17 900), 230 (18 100), 264 (6600), 300 (8100); NMR ($CDCl_3$–Me_2SO-d_6) δ 3.8 (s, 3 H), 4.16 (s, 2 H), 6.82 (d, 1 H, J = 9 Hz), 7.14 (d, 1 H, J = 9 Hz), 7.56 (s, 1 H), 8.2 (s, 1 H); mass spectrum, m/e 230, 213, 183, 168.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.40; H, 4.49; N, 11.82.

6-Methoxy-4-nitro-1,3,4,5-tetrahydrobenz[*c,d*]indole (20b). A mixture of nitroolefin **19b** (7.26 g, 31.6 mmol) and methanol (0.5 L) was stirred vigorously in a 2-L flask during the slow (ca. 20 min) addition of sodium borohydride (18.25 g, 0.48 mol). During the addition, vigorous hydrogen evolution occurred, and the mixture became quite warm and finally attained a yellow-brown color. After stirring an additional 10 min, glacial acetic acid (ca. 45 mL) was added to a final pH of 5–6. The solution was concentrated and partitioned between water and ethyl acetate, the aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed sequentially with water, 5% aqueous sodium carbonate, and brine. The solution was dried and concentrated, and the solid residue was purified by flash chromatography using 2:1 hexane–ethyl acetate as eluant to give **20b** (6.5 g, 89%) as a light yellow solid: mp 134–136 °C; R_f 0.44 with 2:1 hexane–ethyl acetate as eluant. An analytical sample was recrystallized from ethyl acetate/hexane as yellow needles: mp 135–136 °C; IR 3400, 1550, 1520 cm^{-1}; UV λ_{max} 208 nm (ϵ 24 300), 224 (26 000), 268 (5900), 298 (5000); NMR δ 3.5–3.7 (m, 4 H), 4.05 (s, 3 H), 4.95–5.3 (m, 1 H), 7.1–7.5 (m, 3 H), 8.2 (br s, 1 H); mass spectrum, m/e 232, 186, 185.

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.93, H, 5.18, N, 11.78.

6-Methoxy-1,5-dihydrobenz[*cd*]indol-4(3*H*)-one (5b). A mixture of indole **20b** (1.16 g, 5 mmol) and methanol (25 mL) was treated with solid sodium methoxide (0.3 g, 5.5 mmol) and stirred under argon until homogeneous. A solution made by mixing 20% aqueous titanium trichloride (17.5 mL) with ammonium acetate (10.5 g) dissolved in water (35 mL) was added, and the resulting dark suspension was stirred for 1 h. The mixture was shaken *vigorously* and decanted with diethyl ether (8 × 50 mL). The diethyl ether extracts were washed sequentially with water (3 × 100 mL), 5% aqueous sodium carbonate (2 × 100 mL), and brine, dried, and concentrated to give **5b** (0.82 g, 81%) as an off-white solid: mp 130–132 °C dec; R_f 0.36 with 2:1 hexane–ethyl acetate as eluant. An analytical sample was prepared by flash chromatography with 2:1 hexane–ethyl acetate as eluant and recrystallization of the concentrated eluate from ethyl acetate/hexane: mp 130–132 °C dec; IR 3400, 1705, 1510 cm^{-1}; UV λ_{max} 220 nm (ϵ 25 700), 268 (5800); NMR δ 3.72 (br s, 4 H), 3.85 (s, 3 H), 6.82 (d, 1 H, J = 9 Hz), 6.86 (s, 1 H), 7.14 (d, 1 H, J = 9 Hz), 7.8 (br s, 1 H); mass spectrum, m/e 201.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.23; H, 5.66; N, 7.10.

4-(2-Nitroethenyl)-1*H*-indole (17a). A mixture of 1*H*-indole-4-carboxaldehyde (3 g, 20.7 mmol), ammonium acetate (0.6 g), and nitromethane (30 mL) was heated at 100 °C on a steam bath for 2 h, then diluted with ethyl acetate (150 mL) and washed twice with water and once with brine, dried, and concentrated. The deep red solid was recrystallized from ethyl acetate to give **17a** (3.36 g, 86%) as two crops of red prisms: mp 156–158 °C; R_f 0.56 with 1:1 hexane–ethyl acetate as eluant. An analytical sample was recrystallized from ethyl acetate: mp 161–163 °C; IR 3350, 1630, 1570, 1340 cm^{-1}; UV λ_{max} 218 nm (ϵ 27 700), 256 (9600); NMR ($CDCl_3$–acetone-d_6) δ 6.8 (br s, 1 H), 7.0–7.7 (m, 4 H), 7.85 (d, 1 H, J = 14 Hz), 8.35 (d, 1 H, J = 14 Hz); mass spectrum, m/e 188, 171, 141, 115.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.88. Found: C, 63.69; H, 4.27; N, 14.69.

4-(2-Nitroethyl)-1*H*-indole (18a). A mixture of indole **17a** (3.19 g, 17 mmol) and methanol (175 mL) in a 500-mL flask was stirred vigorously during the slow (15 min) addition of sodium borohydride (2.04 g, 54 mmol). After the vigorous reaction subsided, the light yellow solution was stirred for 30 min, acidified to pH 6 by the addition of glacial acetic acid, and concentrated. The residue was partitioned between water and ethyl acetate, the aqueous layer was extracted twice with ethyl acetate, and the combined ethyl acetate layers were washed with water and brine. The organic layer was dried and concentrated, and the residue was purified by flash chromatography using 2:1 hexane–ethyl acetate as eluant to give **18a** (2.39 g, 74%) as a yellow oil: R_f 0.48 with 2:1 hexane–ethyl acetate as eluant. An analytical sample was prepared by bulb-to-bulb distillation [bp 160–170 °C (0.3 torr)]: mp 61–62 °C; IR 3420, 1550, 1540 cm^{-1}; UV λ_{max} 218 nm (ϵ 30 300), 274 (6000); NMR δ 3.52 (t, 2 H, J = 7 Hz), 4.68 (t, 2 H, J = 7 Hz), 6.5 (br s, 1 H), 6.8–7.3 (m, 4 H), 8.2 (br s, 1 H); mass spectrum, m/e 190, 143.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.19; H, 5.20; N, 14.52.

4-Nitro-1,5-dihydrobenz[*cd*]indole (19a). DMF (5 mL) was stirred under argon in a 250-mL flask as phosphorous oxychloride (0.89 mL, 9.6 mmol) was added. The solution was stirred for 5 min, and indole **18a** (1.6 g, 8.42 mmol) was added. The resulting yellow paste was stirred 15 min, a mixture of water (1.7 mL, 95 mmol) and DMF (6.75 mL) was added, and the quenched reaction was stirred an additional 10 min before the addition of a mixture of triethylamine (11.8 mL, 85 mmol) and methanol (33 mL). The resulting solution was heated at reflux for 20 min, water (42 mL) was added slowly, the mixture was slowly cooled to ambient temperature, and the crystalline product was isolated by filtration. The precipitate was washed with 2:1 water–methanol (25 mL) and dried at 60 °C to give **19a** (1.54 g, 92%) as brown crystals. The crude product was placed as a solid on the top of a silica gel column (50 g, 3 × 20 cm) and eluted with ethyl acetate. When the eluate became slightly yellow, the next 800 mL was collected and concentrated to give **19a** (1.44 g, 86%) as bronze-red crystals: mp 206–208 °C dec; R_f 0.45 with 1:1 hexane–ethyl acetate as eluant. An analytical sample was recrystallized from methanol as red needles: mp 209–210 °C dec; IR 3350, 1650, 1580, 1475 cm^{-1}; UV λ_{max} 204 nm (ϵ 16 500), 224 (20 300), 260 (6600), 288 (8100); NMR ($CDCl_3$–Me_2SO-d_6) δ 4.35 (s, 2 H), 6.8–7.0 (m, 1 H), 7.2 (apparent d, 2 H, J = 6 Hz), 7.5 (s, 1 H), 8.15 (s, 1 H); mass spectrum, m/e 200, 183, 168, 153.

Anal. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.71; H, 3.95; N, 14.06.

4-Nitro-1,3,4,5-tetrahydro[*cd*]indole (20a). A solution of indole **19a** (1.37 g, 6.85 mmol) in methanol (170 mL) was stirred rapidly in a 500-mL flask during the addition (40 min) of sodium borohydride (4.82 g, 0.128 mol). After the addition was completed, the light yellow solution was stirred an additional 20 min and neutralized to pH 5 by the addition of glacial acetic acid. The solution was concentrated and partitioned between water and ethyl

acetate, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed twice with 5% aqueous sodium carbonate, and once with brine, then dried, and concentrated. The crude product was purified by flash chromatography using 2:1 hexane–ethyl acetate as eluant to give **20a** (1.22 g, 88%) as a yellow solid: mp 134–135 °C; R_f 0.45 with 2:1 hexane–ethyl acetate as eluant. An analytical sample was recrystallized from ethyl acetate/hexane: mp 134–135 °C; IR 3420, 1620, 1540 cm^{-1}; UV λ_{max} 224 nm (ϵ 31900), 280 (5400); NMR ($CDCl_3$–acetone-d_6) δ 3.35–3.7 (m, 4 H), 4.8–5.15 (m, 1 H), 6.7–7.2 (m, 4 H), 9.2 (br s, 1 H); mass spectrum, *m/e* 202, 154, 128.

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.02; H, 5.12; N, 13.77.

1,5-Dihydrobenz[*cd*]indol-4(3*H*)-one (5a). A solution of indole **20a** (1.12 g, 5.54 mmol) in methanol (33 mL) was stirred under argon during the addition of solid sodium methoxide (0.33 g, 6.1 mmol). After 5 min, a solution prepared by mixing aqueous 20% titanium trichloride (19.4 mL) with a solution of ammonium acetate (11.6 g, 0.15 mol) in water (37.8 mL) was added, and the resulting mixture was stirred at ambient temperature for 45 min. The dark colored reaction mixture was shaken *vigorously* and decanted with diethyl ether (8 × 50 mL). The combined diethyl ether extracts were washed sequentially with water (2 × 100 mL), 5% aqueous sodium carbonate (2 × 100 mL), and brine. The solution was dried and concentrated, and the crude product was purified by flash chromatography using 1:1 ethyl acetate–hexane as eluant to give **5a** (0.68 g, 72%) as a white solid: mp 136–138 °C dec; R_f 0.41 with 40% ethyl acetate–hexane as eluant. An analytical sample was recrystallized from ethyl acetate/hexane as white needles: mp 146–147 °C dec; IR 3320, 1700, 1470 cm^{-1}; UV λ_{max} 220 nm (ϵ 32000), 276 (5700); NMR δ 3.76 (s, 2 H), 3.88 (s, 2 H), 6.6–6.95 (br m, 2 H), 7.1–7.3 (m, 2 H), 8.1 (br s, 1 H); mass spectrum, *m/e* 171, 143, 115.

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.37; H, 5.28; N, 7.98.

6-Methoxy-1,3,4,5-tetrahydrobenz[*cd*]indol-4-amine (2b, $R_2 = H_2$) Hemioxalate. Platinum oxide (300 mg) was reduced under 60 psi hydrogen pressure in methanol (30 mL) for 30 min. Compound **20b** (1.0 g, 4.31 mmol) was added, and the resulting solution was hydrogenated under 60 psi hydrogen pressure until hydrogen uptake ceased (ca. 2 h). The mixture was filtered, the filtrate was concentrated, and the residue was dissolved in chloroform and decolorized with activated carbon. The resulting mixture was filtered, and the filtrate was concentrated. The residue was dissolved in absolute ethanol (8 mL), and the solution was stirred and heated to near reflux as a solution of oxalic acid dihydrate (540 mg, 4.31 mmol) in absolute ethanol (5 mL) was added slowly. The mixture was diluted with acetone (10 mL), cooled at 0 °C, and filtered, and the precipitate was washed with acetone (2 × 10 mL), hot methanol (2 × 10 mL), and dried to yield **2b** ($R_2 = H_2$) hemioxalate (0.74 g, 70%): mp 260–265 °C dec; IR 3250, 2900, 1680, 1580 cm^{-1}; UV λ_{max} 221 nm (ϵ 25300), 275 (5760); NMR (D_2O–Me_2SO-d_6) δ 2.8–3.6 (br m, 5 H total), 3.6 (s, 3 H), 6.82 (d, J = 8 Hz, 1 H), 7.05 (s, 1 H), 7.20 (d, J = 8 Hz, 1 H); chemical ionization (methane) mass spectrum, *m/e* (M + 1) 203.

Anal. Calcd for $C_{13}H_{15}N_2O_3$: C, 63.15; H, 6.11; N, 11.33. Found: C, 62.78; H, 6.27; N, 11.08.

***N,N*-Dimethyl-6-methoxy-1,3,4,5-tetrahydrobenz[*cd*]indol-4-amine [2b, $R_2 = (CH_3)_2$] Oxalate.** A solution of anhydrous dimethylamine (0.26 g, 5.76 mmol), dimethylamine hydrochloride (2.45 g, 30.0 mmol), and sodium cyanoborohydride (1.88 g, 30.0 mmol) in methanol (30 mL) was prepared. Ketone **5b** (0.60 g, 3.0 mmol) was added, and the reaction was stirred at ambient temperature for 1 h and poured into 5% aqueous sodium bicarbonate solution (100 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with 5% aqueous hydrochloric acid (3 × 30 mL). The acidic extracts were made basic with 20% aqueous sodium hydroxide and extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with 10% aqueous sodium sulfate, dried, and concentrated to yield crude amine as a light yellow oil (0.66 g). The crude product was purified by flash chromatography using 5% diisopropylamine–ethyl acetate as eluant to yield **2b** [$R_2 = (CH_3)_2$] (0.38 g, 57%) as a colorless oil: NMR δ 2.4 (s, 6 H), 2.5–3.4 (m, 5 H total), 3.8 (s, 3 H), 6.7 (br s, 1 H), 6.8 (d, J = 9 Hz, 1 H), 7.0 (d, J = 9 Hz, 1 H), 8.2 (br s, 1 H). The free base was dissolved in methanol (10 mL) and treated with a solution of oxalic acid (0.156 g, 1.73 mmol) in methanol (5 mL). The crystalline product was collected and dried (25 °C, 0.1 torr) to yield the oxalate salt of **2b** [$R_2 = (CH_3)_2$] (0.44 g): mp 215–217 °C dec; IR (KBr pellet) 3300, 3060, 1510 cm^{-1}; UV λ_{max} 221 nm (ϵ 23600), 276 (5500); chemical ionization (methane) mass spectrum, *m/e* 231.

Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.74; H, 6.41; N, 8.87.

***N,N*-Dimethyl-1,3,4,5-tetrahydrobenz[*cd*]indol-4-amine [2a, $R_2 = (CH_3)_2$].** A solution of anhydrous dimethylamine (0.520 g, 11.6 mmol), dimethylamine hydrochloride (4.90 g, 60.0 mmol), and sodium cyanoborohydride (3.76 g, 60.0 mmol) in methanol (60 mL) was prepared. Ketone **5a** (1.026 g, 6.0 mmol) was added, and the reaction was stirred at ambient temperature under N_2 for 2 h. The reaction was poured into 5% aqueous $NaHCO_3$ solution (250 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with 5% aqueous HCl (3 × 30 mL). The acidic extracts were made basic with 20% aqueous NaOH and then extracted with ethyl acetate (3 × 75 mL). The organic extracts were washed with 10% aqueous Na_2SO_4, dried, and concentrated to yield the crude amine as light brown oil (0.980 g). Purification by flash chromatography using 5% diisopropylamine–ethyl acetate as eluant yielded **2a** (0.55 g, 52%) as a colorless oil which crystallized on standing: NMR δ 2.5 (s, 6 H), 2.5–3.4 (m, 5 H), 6.8–7.3 (m, 4 H), 8.4 (br s, 1 H). The product was triturated with petroleum ether and dried to yield **2a** [$R_2 = (CH_3)_2$] (0.52 g, 49%): mp 102 °C; IR (KBr pellet) 3140, 1610, 1445, 1345 cm^{-1}; UV λ_{max} 222 nm (ϵ 31000), 280 (5800); chemical ionization (methane) mass spectrum, *m/e* 201.

Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.94. Found: C, 77.81; H, 8.19; N, 14.03.

1,3,4,5-Tetrahydrobenz[*cd*]indol-4-amine [2a, $R_2 = H_2$]. Platinum oxide (0.50 g) was reduced under 50 psi of hydrogen pressure in methanol (50 mL) for 30 min. The nitro compound **20a** (1.0 g, 4.95 mmol) in methanol (100 mL) was added, and the resulting mixture was hydrogenated at 50 psi for 3 h. The reaction was filtered, and the filtrate was concentrated under reduced pressure to yield a light yellow oil (0.80 g). The crude product was purified by flash chromatography using 15% diethylamine–ethyl acetate as eluant to yield **2a** as a colorless oil (0.58 g, 68%) which crystallized on standing: mp 119–121 °C; IR (KBr) 3340, 1608, 1450 cm^{-1}; UV λ_{max} 222 nm (ϵ 28400), 280 (5200); NMR δ 1.4 (br s, 2 H), 2.5–3.3 (m, 4 H), 3.3–3.7 (m, 1 H), 6.7–7.2 (m, 4 H), 8.1 (br s, 1 H); chemical ionization mass spectrum, *m/e* 173.

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.72; H, 7.26; N, 16.07.

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Registry No. **2a** ($R_2 = (CH_3)_2$), 73625-11-3; **2a** ($R_2 = H_2$), 77963-70-3; **2b** ($R_2 = H_2$)·$^1/_2C_2H_2O_4$, 92622-92-9; **2b** ($R_2 = (CH_3)_2$)·$C_2H_2O_4$, 92622-94-1; **5a**, 2731-96-6; **5b**, 92622-95-2; **6a**, 1074-86-8; **6b**, 92623-00-2; **9**, 4792-58-9; **10**, 30933-69-8; **10** (acid), 92622-97-4; **11**, 92622-96-3; **12**, 30933-70-1; **13**, 92622-98-5; **14**, 92622-99-6; **17a**, 49839-99-8; **17b**, 87149-47-1; **18a**, 87149-48-2; **18b**, 87149-50-6; **19a**, 92623-03-5; **19b**, 92623-01-3; **20a**, 92623-02-4; **20b**, 92623-04-6; *N,N*-dimethylacetamide, 127-19-5; nitromethane, 75-52-5.