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The Synthesis of Pyrano[3,2-e]indoles and Pyrano[2,3-f]indoles as Rotationally Restricted Phenolic Analogs of the Neurotransmitter Serotonin

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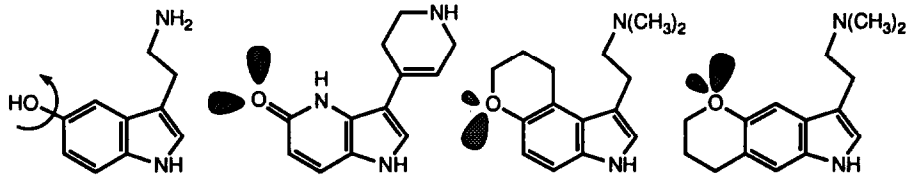
Abstract: The synthesis of two rotationally restricted phenolic analogs (**1a** and **1b**) of the neurotransmitter serotonin have been accomplished. The syntheses of 8,9-dihydropyrano[3,2-e]indole (**13a**) and 7,8-dihydropyrano[2,3-f]indole (**13b**), which formed the template for these targets, are outlined. These novel fused-indoles represent rotationally restricted phenolic analogs of 5-hydroxyindole. The reaction sequence of Claisen rearrangement, olefin hydroxylation, and intramolecular Mitsunobu reaction was used to form the fused-dihydropyran rings.

Introduction: When a natural product of pharmacological interest binds to a number of similar receptors or enzymes, the synthesis of conformationally and/or rotationally restrained "unnatural" analogs can often give insight into the specific recognition requirements of the individual receptors or enzymes. This understanding can then be used to design novel pharmaceutical agents for selective treatment of diseases related to dysfunction of a specific receptor or enzyme. The synthesis of these "unnatural products" [i.e. rationally designed analogs of the natural product which incorporate increased specificity of biological activity] often requires development of novel organic synthetic methodology, and in this paper we would like to describe one such study.

The neurotransmitter serotonin (5-HT) has been a subject of intense study since its discovery in the central nervous system in 1953.[1] More than six distinct receptors have been identified which are serotonin specific,[2] and it is not surprising that serotonin has been linked to feeding, sexual, and social behaviors.[3] However, an understanding of the physiological function of the individual 5-HT receptors has been hampered by the lack of receptor specific ligands.[2] Therefore, over the past few years, we have studied the synthesis and resulting pharmacology of conformationally and rotationally restricted analogs of serotonin.[4] Since 5-methoxytryptamine (the methyl ether of serotonin) is as potent as serotonin itself at 5-HT_1 receptors,[5] it has generally been assumed that the C5-hydroxyl group of serotonin functions as a hydrogen bond acceptor within 5-HT_1 receptors. Accordingly, most of our efforts have been directed towards the synthesis of rotationally restricted phenolic analogs of the C5-hydroxyl group of the serotonin molecule to explore the directionality requirements of this hypothesized hydrogen bond accepting interaction within individual serotonin receptor subtypes. This research has given rise to CP-93,129 [3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one], which has been shown to be entirely selective for the 5-HT_{1B} subtype of serotonin receptors.[4a, 6] Since the C5-oxygen in CP-93,129 was "frozen" in the amide tautomer, the rotation of the C=O was restricted. The inhibited C=O bond rotation of the amide forced hydrogen bond accepting interactions to occur in a directional manner defined by the amide oxygen lone pairs of electrons. Therefore, the pyrrolo[3,2-b]pyridone portion of this molecule represents a rotationally restricted phenolic replacement for the 5-hydroxyindole portion of serotonin, and the specificity of this compound has been attributed to the planar amide character in the pyridone.[4a] Accordingly, any hydrogen bond accepting

interaction between the C5-oxygen lone pairs in CP-93,129 and the receptor must be directional, occurring in the plane of the aromatic ring. This directionality of oxygen lone pairs appeared to favor exclusive binding to the 5-HT_{1B} receptor subtype.

With the success of this approach in hand, we sought to examine other rotationally restricted phenolic analogs of the 5-hydroxyindole portion of serotonin which possessed oxygen lone pair orientations which differed from the planar directionality of the lone pairs found at the C5-oxygen in CP-93,129. This line of reasoning led us to examine 8,9-dihydropyrano[3,2-e]indole[7] and 7,8-dihydropyrano[2,3-f]indole as novel rotationally restricted phenolic analogs of the 5-hydroxyindole portion of serotonin.[8]



Serotonin (5-HT) **CP-93,129** **1a** **1b**

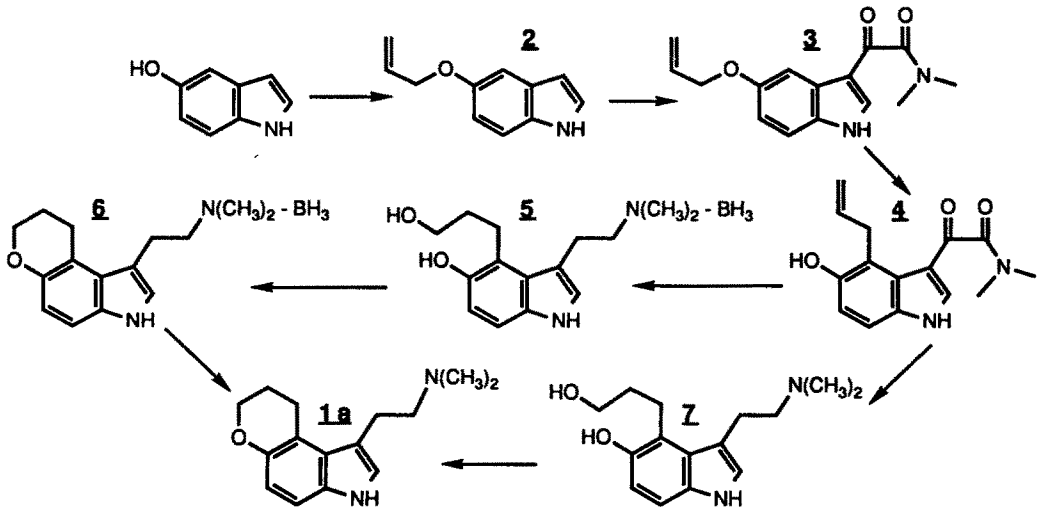
Reports on pyrano[3,2-e]indoles and pyrano[2,3-f]indoles have been scarce. Recently, the pyrano[3,2-e]indole heterocycle was identified in a small group of natural products derived from the root bark of *Murraya euchrestifolia*, a tree of Taiwanese origin,[9] and an 8,9-dihydropyrano[3,2-e]indole skeleton was contained as a hemiaminal in a study of Mannich base methodology[10] and as a ketal in a natural product.[11] However, a synthesis of 8,9-dihydropyrano[3,2-e]indoles and 7,8-dihydropyrano[2,3-f]indoles has not yet been described in the literature. Therefore, in this paper we will describe an approach to these heterocycles as intermediates in the synthesis of two "unnatural products" (**1a** and **1b**) which are rotationally restricted phenolic analogs of the natural product and neurotransmitter serotonin.

Results and Discussion: There has been only limited use of the Claisen rearrangement in the functionalization of indole derivatives.[12] In 1973, Julia and co-workers synthesized 5-(2-propenyloxy)indole and observed its regiospecific [3.3] sigmatropic shift to form 5-hydroxy-4-(2-propenyl)indole in good yield,[12a] and recently, Cannon and Roufos have optimized the yield of that reaction.[12b] Therefore, we saw this approach as the means with which to functionalize C4 (and possibly C6) of an appropriate indole derivative. With an allyl substituent at C4, olefin hydroxylation followed by intramolecular cyclization of the C5-hydroxy with the C4 tethered alcohol should yield the desired dihydropyrano[3,2-e]indole heterocycle. Therefore, Scheme 1 shows our first synthesis of 5-(2-dimethylaminoethyl)-8,9-dihydropyrano[3,2-e]indole (**1a**) using this approach.[7]

A simple deprotonation/alkylation procedure using 5-hydroxyindole led to a 9:1 mixture (determined by ^1H NMR) of the desired 5-(2-propenyloxy)indole (**2**) and 1-(2-propenyloxy)indole, respectively (87% total yield). While this reaction was analogous to the formation of **2** by Julia and co-workers,[12a] they did not report this N-alkylated by-product, which we found impossible to separate from **2**. Accordingly, this 9:1 mixture of C5-oxygen versus N1 alkylation products was used directly in the next step with no adverse effects. While the C5-(2-propenyloxy) functionality was requisite for the desired Claisen rearrangement, it also served to protect the C5-hydroxyl group in the proceeding functionalization of C3 of the indole. Accordingly, treatment of **2** (as the 9:1 mixture of C3:N1 alkylation products) with a slight excess of

oxalyl chloride and 40% by weight phthalimide in anhydrous ether formed the indole-3-glyoxamic acid chloride *in situ*; treatment of the resulting bright yellow mixture with dimethylamine led to the disappearance of the color and the formation of the desired 5-(2-propenyloxy)indole-3-glyoxamide (**3**, 77%). Heating **3** in refluxing bromobenzene (156 °C) for eight hours afforded the Claisen rearranged product (**4**, 51% yield, 76% conversion), which often precipitated directly from the reaction solution in analytically pure form.[13] Some returned starting material was noted in the filtrate from this reaction (and could be recovered), but none of the alternative Claisen product [i.e. 5-hydroxy-6-(2-propenyl)indole] was detected, indicating an apparent absolute degree of regiospecificity in this Claisen rearrangement. This was consistent with the work of Julia,[12a] and Claisen rearrangements usually exhibit a high degree of regiospecificity.[14] Heating this rearrangement reaction longer did not appreciably increase the yield of **4**, but it would consume all of **3**.

Scheme 1



Hydroboration of the olefin could not be accomplished using 9-BBN in our hands, and therefore, borane in THF was used. A large excess of this reagent was needed, however, since concomitant complete reduction of the glyoxamide functionality occurred.[15] The yield of the tryptamine-borane complex (**5**, 31%) from this hydroboration/di-reduction reaction was only moderate, but the extent of the chemical transformation in this step ameliorated this somewhat. Additionally, a small amount of the free tryptamine (**7**, 7%) was also isolated from this reaction. As outlined below, this material could directly be cyclized to our desired target. Since **5** was much less polar than the corresponding amine (**7**), its purification was less tedious. Therefore, **5** was directly subjected to an intramolecular Mitsunobu reaction[16] (Ph_3P, DEAD) forming the dihydropyrano[3,2-e]indole ring (**6**, 64%) still as the tryptamine-borane complex. Destruction of the borane complex in **6** was accomplished using cesium fluoride in refluxing ethanol overnight to afford our desired rotationally restricted phenolic analog of serotonin, the dihydropyrano[3,2-e]indole derivative (**1a**, 71%, 5% overall yield from 5-hydroxyindole).

An alternative, improved synthesis of **1a** (Scheme 1) directly subjected the crude hydroboration/di-reduction reaction mixture to the borane complex destruction conditions (CsF, EtOH) to afford the 5-hydroxy-4-(3-hydroxypropyl)indole derivative (**7**, 37% from **4**). An analogous intramolecular Mitsunobu reaction then afforded the desired "unnatural" serotonin analog (**1a**, 81%, 10% overall yield from 5-hydroxyindole). It should be noted that these intramolecular cyclization reactions of **5** and **7** are rare examples of Mitsunobu reactions involving 5-hydroxyindole derivatives. The shortened approach to **1a** from **4** using **7** afforded the desired target in almost double the overall yield (10%) when compared to our original approach (5%) which used the borane-tryptamine complex through two steps of the synthesis. The most efficient route (i.e. via **7**) is the preferable approach to **1a**.

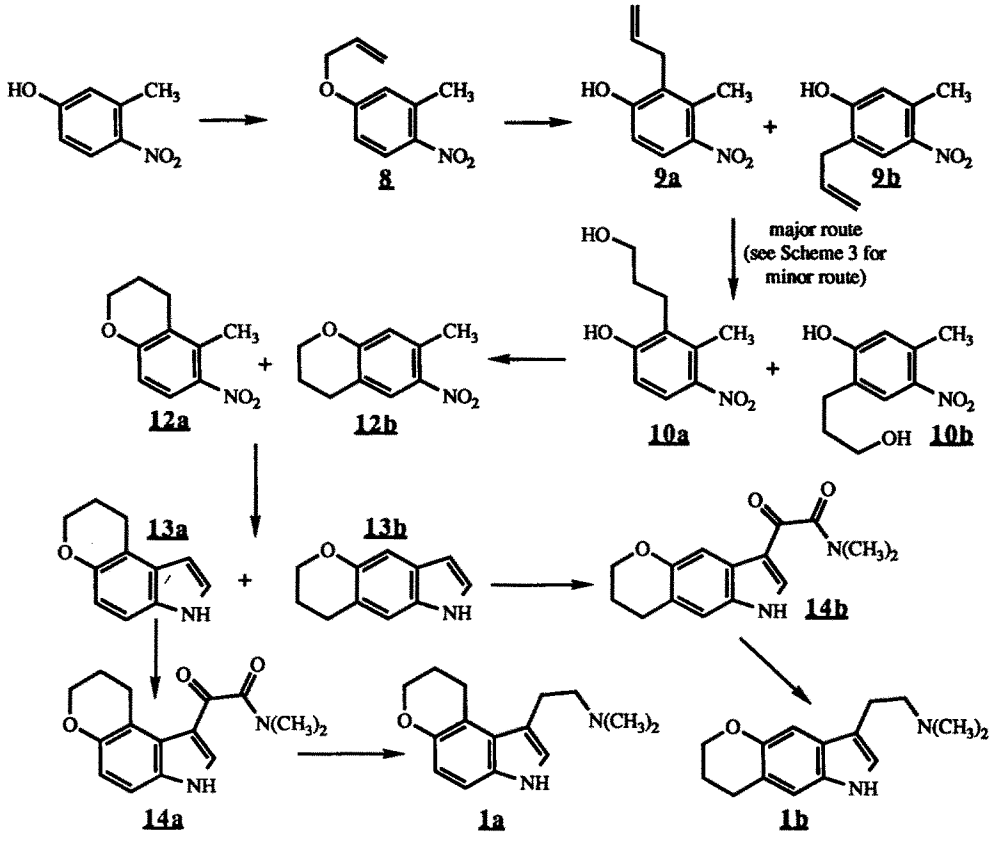
While this novel use of an indole Claisen reaction and intramolecular Mitsunobu reaction afforded access to the dihydropyrano[3,2-e]indole derivative (**1a**), the regiospecificity of the Claisen reaction denied the formation of our other desired rotationally restricted phenolic analog of 5-hydroxyindole, the dihydropyrano[2,3-f]indole derivative (**1b**). Additionally, the synthesis of **1a** lacked generality with respect to the synthesis of other dihydropyrano[3,2-e]indole derivatives. Therefore, we sought a more general approach to dihydropyrano[3,2-e]indoles and dihydropyrano[2,3-f]indoles which would allow for the formation and isolation of the parent heterocycles. The approach is outlined in Scheme 2. Alkylation of 3-methyl-4-nitrophenol with allyl iodide was straightforward to form the Claisen rearrangement precursor (**8**, 99%). The [3.3] sigmatropic shift of the allyl group in **8** required a higher reaction temperature than the analogous reaction using **3**, and consequently, a greater degree of product decomposition was seen. Variations of reaction temperature and reaction time were tried, and the conditions which allowed for the multigram (> 10 g) preparation of the desired Claisen products (**9a** and **9b**) involved the use of refluxing 1,2-dichlorobenzene (180 °C) for six hours. This afforded a 41% yield (58% conversion) of a 2:1 mixture[17] of **9a** to **9b**. Recovery of the 1,2-dichlorobenzene solution with returned **8** via a simple silica gel filtration allowed for a second reaction to be run which afforded additional **9a** and **9b** (53% overall for the two runs). If the rearrangement reaction is run longer than six hours at 180 °C, the decomposition of existing product begins to exceed the formation of new product, and lower yields are achieved. If the reaction is run at a significantly lower temperature, the formation of product is unreasonably slow. The products **9a** and **9b** were inseparable by all TLC systems tested, and therefore, the mixture was carried forward as a whole.

Standard hydroboration of the 2:1 mixture of **9a** and **9b** using borane in THF afforded the desired primary (terminal) alcohols (**10a** and **10b**, 2:1 respectively, 73%) along with a small amount of the secondary (internal) alcohols (**11a** and **11b**, 2:1 respectively, 11%) (Scheme 3). While separation of the primary alcohols (**10a** and **10b**) from the less polar secondary alcohols (**11a** and **11b**) could be achieved by flash chromatography, separation of the individual regiomers in each case (i.e. **10a** from **10b** and **11a** from **11b**) could not be achieved for either **10** or **11**. In both cases, the 2:1 ratio of regiomers on the aromatic ring established by the Claisen rearrangement was still intact.

Intramolecular cyclization of the mixture of phenol/primary alcohol(s) (**11a** and **11b**) was smoothly accomplished using the previously described intramolecular Mitsunobu conditions (excess DEAD, Ph_3P) to afford the dihydrobenzopyrans (**12a** and **12b**, 97%) as a continued 2:1 mixture of regiomers, respectively. Even at this stage in the synthesis, the level of separation of the isomers was slight, and chromatography could not satisfactorily separate them. Therefore, a Batcho-Leimgruber indole synthesis[18] was effected using the 2:1 mixture of 5-methyl-6-nitro-3,4-dihydrobenzo[2,3]pyran (**12a**) and 7-methyl-6-nitro-3,4-dihydrobenzo-[2,3]pyran (**12b**). Reaction of **12a** and **12b** with N,N-dimethylformamide dimethyl acetal, followed by reductive cyclization (H_2/Pd on C) of the resulting β-aminostyrene derivatives afforded dihydropyrano[3,2-e]indole (**13a**) and dihydropyrano[2,3-f]indole (**13b**) as a 4:1

mixture, respectively, as determined by the weights of isolated material (68% total). Apparently, the formation of **13a** occurred more efficiently than the formation of **13b**, resulting in an increased ratio of **13a**:**13b**. Luckily, these isomers were separable at this stage by flash chromatography to yield the individual indoles. This synthesis represents the first reported synthesis of either of these fused-indole heterocycles.

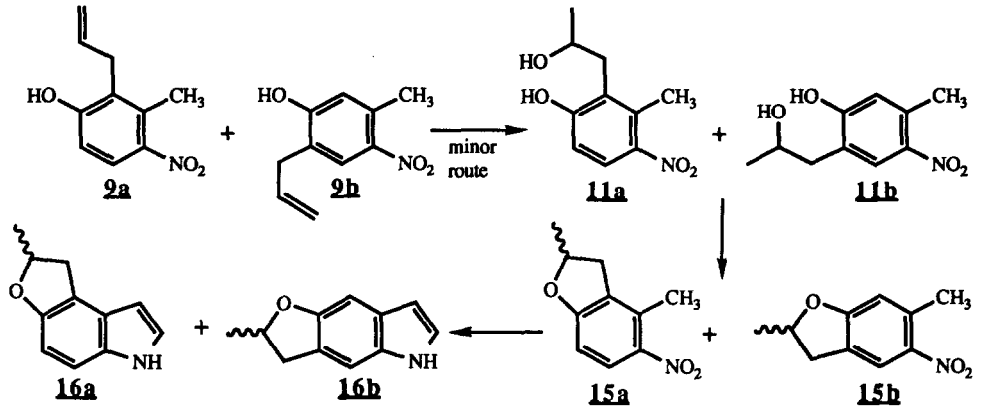
Scheme 2



Treatment of **13a** with oxalyl chloride and phthalimide, followed by dimethylamine in ether (as described above in the synthesis of **3**) afforded the dihydropyrano[3,2-e]indole-3-glyoxamide (**14a**, 78%). Reduction of the glyoxamide with borane in THF followed by destruction of the amine/borane complex with CsF in refluxing ethanol completed this second synthesis of our desired serotonin analog **1a** (54% for last two steps, 8% overall from 3-methyl-4-nitrophenol). Analogously, treatment of **13b** with oxalyl chloride and phthalimide in ether, followed by dimethylamine in ether yielded the dihydropyrano[2,3-f]indole-3-glyoxamide (**14b**, 95%), which was reduced by borane in THF as above. Following the destruction of the amine/borane complex, the other regiomeric serotonin analog **1b** (47% for last two steps, 3% overall from 3-methyl-4-nitrophenol) was obtained.

It is worth noting that the secondary alcohols (**11a** and **11b**) obtained as by-products from the hydroboration reaction could themselves be converted into novel fused indole derivatives (Scheme 3). When the 2:1 mixture of **11a** and **11b**, respectively, was subjected to the intramolecular Mitsunobu reaction conditions described for **10**, the dihydrobenzofurans (**15a** and **15b**, 77%) were obtained in a 2:1 mixture of isomers, respectively. When this mixture was treated with dimethylformamide dimethyl acetal, and the resulting β-aminostyrenes were hydrogenated as above, a 3:1 mixture of 2-methyl-2,3-dihydrofuro[3,2-e]indole (**16a**) and 2-methyl-2,3-dihydrofuro[2,3-f]indole (**16b**) was obtained (36%). Consistent with the synthesis of **13**, it appeared that the formation of the [3,2-e]indole ring was more efficient than the formation of the [2,3-f]indole ring. While a slight separation of these isomers was discernable by TLC (1:1 ether/hexanes), no such individual isolation was pursued.

Scheme 3



The pharmacological evaluation of **1a** and **1b** is ongoing, but initial results indicate that neither **1a** nor **1b** demonstrate potency at 5-HT_1 receptors similar to that of the natural substrate, serotonin. However, **1a** shows potent activity at 5-HT_2 receptors, and the results of the pharmacological evaluation of this compound and its analogs will be reported elsewhere.

In conclusion, we have synthesized two "unnatural" analogs (**1a** and **1b**) of the neurotransmitter serotonin to test directionality requirements of the indole-C5 oxygen lone pairs in hydrogen bonding interactions with 5-HT receptors. In order to synthesize these targets, the first syntheses of 2,3-dihydropyrano[3,2-e]indole (**13a**) and 2,3-dihydropyrano[2,3-f]indole (**13b**) were devised using indole and benzene Claisen rearrangements, hydroborations, and intramolecular Mitsunobu reactions to form the fused pyrano rings. The dihydropyranoindoles in **1a** and **1b** can be viewed as rotationally restricted phenolic analogs of the 5-hydroxyindole portion of the neurotransmitter serotonin.

Experimental: Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer IR-283B Infrared Spectrophotometer, and NMR spectra were recorded on either a Bruker AM-300 (300 MHz), Varian XL300 (300 MHz), or Varian XL250 (250 MHz) spectrometer. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Low resolution mass spectra were obtained on a Finnigan 4310 instrument; high resolution mass

spectra (EI and FAB) were obtained on a Kratos Concept IS instrument. Elemental analyses were performed at Central Research Division, Pfizer Inc., Groton, CT.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich anhydrous solvents. Diethyl ether was dried via distillation over sodium hydride. Chromatography refers to column chromatography performed using 32-63 μm silica gel (approx 50 g 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.

1-(2-Dimethylaminoethyl)-8,9-dihydropyrano[3,2-e]indole (1a). Method A. A mixture of **6** (0.180 g, 0.70 mmol), sodium carbonate (0.18 g), and cesium fluoride (0.18 g) in absolute ethanol (5 mL) was heated at reflux under nitrogen for 16 h. The reaction solution was then evaporated under reduced pressure, and the residue chromatographed using elution with absolute methanol to afford **1a** (0.122 g, 0.50 mmol, 71%) as a white solid: mp 139-141 °C; IR (KBr) 1620, 1590, 1550, 1505, 1465, 1445, 1425 cm^{-1}; ^1H NMR (CD_3OD) δ 7.00 (d, J=8.7 Hz, 1H), 6.93 (s, 1H), 6.53 (d, J=8.7 Hz, 1H), 5.47 (s, H_2O exchanging protons, approx 1H), 4.10 (t, J=5.6 Hz, 2H), 3.17 (t, J=6.6 Hz, 2H), 3.01 (t, J=8.3 Hz, 2H), 2.61-2.56 (m, 2H), 2.32 (s, 6H), 2.09-1.98 (m, 2H); ^{13}C NMR (CD_3OD) δ 149.2, 133.3, 126.9, 124.1, 114.1, 113.6, 111.1, 66.9, 63.3, 45.5, 26.1, 24.0, 23.9; LRMS (m/z, relative intensity) 245 (13), 244 (M^+, 53), 200 (4), 186 (15), 170 (10), 77 (14), 59 (41), 58 (100); HRMS calcd for $C_{15}H_{20}N_2O$ 244.1576, found 244.1562. Anal. calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.65; H, 8.41; N, 11.72.

Method B. To a stirred solution of triphenylphosphine (0.813 g, 3.10 mmol, 1.2 eq) and diethyl azodicarboxylate (DEAD, 0.49 mL, 3.11 mmol, 1.2 eq) in anhydrous tetrahydrofuran (THF, 20 mL) at 0 °C was added dropwise a solution of **7** (0.677 g, 2.58 mmol) in anhydrous THF (10 mL). The resultant reaction solution was stirred at room temperature (rt) under nitrogen for 5 h. A saturated solution of sodium hydrogen carbonate (20 mL) was added, and this aqueous mixture was extracted with ethyl acetate (2 x 50 mL). The extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue using with absolute methanol afforded **1a** (0.509 g, 2.08 mmol, 81%) as an off-white solid identical in its physical and spectral properties with the material synthesized above.

Method C. To a stirred mixture of **14a** (0.570 g, 2.09 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen was added borane in THF (1.0 M, 9.00 mL, 9.00 mmol, 4.3 eq) dropwise. The resultant reaction solution was stirred at rt under nitrogen for 24 h. A saturated solution of sodium hydrogen carbonate (15 mL) was added carefully, and the resulting mixture was vigorously stirred at rt under nitrogen for 30 min. The aqueous mixture was then extracted with ether (2 x 25 mL), and the extracts combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford a white foam (0.7 g). This foam was dissolved in absolute ethanol (10 mL), cesium fluoride (0.70 g) and sodium carbonate (0.70 g) were added to this solution, and the resultant mixture was heated at reflux under nitrogen for 25 h. The resultant mixture was filtered through Celite®, the filtrate evaporated under reduced pressure, and the residue was chromatographed using elution with 6% triethylamine in ethyl acetate to afford **1a** (0.275 g, 1.13 mmol, 54%) as a white crystalline solid identical in its physical and spectral properties with the material synthesized above.

3-(2-Dimethylaminoethyl)-7,8-dihydropyrano[2,3-f]indole (1b). To a stirred solution of **14b** (0.600 g, 2.20 mmol) in anhydrous THF (5 mL) at 0 °C was added borane in THF (1.0 M, 9.00 mL, 9.00 mmol, 4.1 eq) dropwise. The resultant reaction solution was stirred at rt under nitrogen for 6 h. A saturated solution of sodium hydrogen carbonate (15 mL) was added carefully, and the resulting mixture was vigorously stirred at rt under nitrogen for 30 min. The aqueous mixture was then extracted with ether (2 x 25 mL), and the extracts combined, dried ($MgSO_4$), and evaporated under

reduced pressure to afford a white foam (0.68 g). This foam was dissolved in absolute ethanol (10 mL), cesium fluoride (0.70 g) and sodium carbonate (0.70 g) were added to this solution, and the resultant mixture was heated at reflux under nitrogen for 25 h. The resultant mixture was filtered through Celite®, the filtrate evaporated under reduced pressure, and the residue was chromatographed using elution with 6% triethylamine in ethyl acetate to afford **1b** (0.252 g, 1.03 mmol, 47% for two steps) as a white, crystalline solid: mp 146.0-149.0 °C; IR (KBr) 1575, 1500, 1470, 1460 cm^{-1}; ^1H NMR ($CHCl_3$) δ 7.83 (br m, NH), 6.98 (s, 1H), 6.97 (s, 1H), 6.90 (d, J=2.3 Hz, 1H), 4.19 (t, J=5.2 Hz, 2H), 2.93 (t, J=6.5 Hz, 2H), 2.88-2.82 (m, 2H), 2.62-2.57 (m, 2H), 2.31 (s, 6H), 2.06-1.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.9, 131.8, 127.0, 122.2, 118.2, 113.7, 111.0, 104.4, 66.6, 60.3, 45.5, 25.8, 23.8, 23.0; LRMS (m/z, relative intensity) 244 (M^+, 43), 186 (27), 158 (15), 130 (8), 107 (15), 58 (100). Anal. calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.35; H, 8.37; N, 11.25.

5-(2-Propenyloxy)indole (2). To a stirred mixture of 5-hydroxyindole (5.57 g, 41.8 mmol) and cesium carbonate (15.0 g, 46.0 mmol, 1.1 eq) in acetone (55 mL, H_2O < 0.5%) was added allyl iodide (3.90 mL, 41.8 mmol, 1.0 eq) dropwise. The resultant reaction mixture was stirred at rt under nitrogen for 20 h. Acetone (200 mL) was added to the reaction mixture, and remaining solid was filtered and discarded. The filtrate was evaporated under reduced pressure, and partitioned between ethyl acetate (100 mL) and a saturated solution of sodium hydrogen carbonate (50 mL). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (75 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford a brown oil. Chromatography of this oil using elution with a 50-60% gradient of methylene chloride in hexanes afforded a 9:1 mixture of **2** and 1-(2-propenyloxy)indole, respectively (6.25 g, 36.3 mmol, 87%), as a pale yellow oil: IR ($CHCl_3$) 1625, 1580, 1470, 1450 cm^{-1}; ^1H NMR (CD_3OD, **2**) δ 7.24 (d, J=8.8 Hz, 1H), 7.15 (d, J=3.0 Hz, 1H), 7.04 (d, J=2.4 Hz, 1H), 6.77 (dd, J=2.3 and 8.8 Hz, 1H), 6.35 (d, J=3.0 Hz, 1H), 6.12-5.99 (m, 1H), 5.37 (dq J=17.3 and 1.7 Hz, 1H), 5.20 (dq, J=10.4 and 1.5 Hz, 1H), 4.89 (s, 1H), 4.49-4.46 (m, 2H); ^{13}C NMR (CD_3OD, **2**) δ 154.0, 135.7, 133.1, 129.8, 126.3, 117.1, 113.2, 112.7, 104.8, 102.2, 70.9; LRMS (m/z, relative intensity) 174 (39), 173 (M^+, 100), 132 (100), 104 (89), 77 (63), 51 (62). HRMS calcd. for $C_{11}H_{11}NO$ 173.0841, found 173.0839. Anal. calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.00; H, 6.54; N, 8.06.

5-(2-Propenyloxy)indole-3-N,N-dimethylglyoxamide (3). To a well-stirred mixture of the above 9:1 mixture of **2** and 1-(2-propenyloxy)indole (6.24 g, 36.2 mmol) and phthalimide (2.50 g, 40% by weight) in anhydrous ether (170 mL) at 0 °C under nitrogen was added a solution of oxalyl chloride (3.50 mL, 40.0 mmol, 1.1 eq) in anhydrous ether (5 mL) dropwise. The resultant orange suspension was stirred at 0 °C under nitrogen for 30 min. To this mixture was then added rapidly a solution of dimethylamine (20 mL, condensed in dry ice/acetone bath) in ether (15 mL), and the resultant white suspension was stirred at rt under nitrogen for 1h. A saturated solution of sodium hydrogen carbonate (80 mL) was then added, and the resulting aqueous mixture was extracted with 5% absolute methanol in ethyl acetate (3 x 125 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to a white solid (11 g). This solid was placed in refluxing ethyl acetate (75 mL), undissolved solid was removed via hot filtration, and cooling of the filtrate afforded **3** (6.80 g, 25.0 mmol, 69%) as a white, crystalline solid: mp > 250 °C; IR (KBr) 1635, 1620, 1590, 1520, 1510, 1490, 1475, 1460, 1445, 1415, 1405 cm^{-1}; ^1H NMR (CD_3OD) δ 7.93 (s, 1H), 7.71 (d, J=2.3 Hz, 1H), 7.37 (d, J=8.8 Hz, 1H), 6.94 (dd, J=2.5 and 8.9 Hz, 1H), 6.15-6.02 (m, 1H), 5.42 (dq, J=17.3 and 1.7 Hz, 1H), 5.24 (dq, J=10.6 and 1.6 Hz, 1H), 4.89 (s, 1H), 4.59-4.56 (m, 2H), 3.07 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (CD_3OD) δ 170.0, 157.1, 138.2, 135.1, 133.6,

127.4, 117.5, 115.6, 114.7, 114.2, 105.7, 70.4, 37.9, 34.4; LRMS (m/z, relative intensity) 273 (12), 272 (M^+, 49), 200 (100), 159 (52), 131 (43); HRMS calcd. for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1163. Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.47; H, 5.90; N, 10.25. The residue from the filtrate from this crystallization could be chromatographed using elution with ethyl acetate to afford additional **3** (0.82 g, 3.01 mmol, 77% total yield).

5-Hydroxy-4-(2-propenyl)indole-3-N,N-dimethylglyoxamide (4). A mixture of **3** (5.96 g, 22.0 mmol) and bromobenzene (80 mL) was heated at reflux (156 °C) under nitrogen for 8 h (all solid dissolved before reflux was achieved). The resultant reaction solution was directly chromatographed using elution with an 18% acetone gradient in methylene chloride[19] to afford first returned **3** (2.01 g, 7.38 mmol, 34% returned) as a white solid, identical in all respects to material fully described previously in this report. Further elution using a 20% acetone gradient in methylene chloride afforded **4** (3.01 g, 11.1 mmol, 51% yield, 76% conversion) an off-white crystalline solid: mp 200.0-201.0 °C; IR (KBr) 1635, 1610, 1580, 1515, 1495, 1420, 1400, 1360, 1315 cm^{-1}; ^1H NMR (CD_3OD) δ 7.87 (s, 1H), 7.18 (d, J=8.7 Hz, 1H), 6.87 (d, J=8.7 Hz, 1H), 6.06-5.93 (m, 1H), 4.90 (s, 2H), 4.82-4.76 (m, 2H),4.22-4.19 (m, 2H), 3.06 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (CD_3OD) δ 168.5, 151.0, 139.7, 138.8, 132.3, 125.0, 118.1, 113.8, 113.4, 110.8, 36.8, 33.3, 31.7; LRMS (m/z, relative intensity) 273 (17), 272 (M^+, 13), 254 (70), 200 (100), 172 (93), 144 (56), 127 (30), 115 (45), 72 (73); HRMS calcd. for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1163. Anal calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.88; H, 5.64; N, 10.19.

3-(2-Dimethylaminoethyl)-5-hydroxy-4-(3-hydroxypropyl)indole, N-borane complex (5). To a stirred solution of **4** (1.85 g, 6.79 mmol) in anhydrous THF (20 mL) under nitrogen at 0 °C was added a solution of borane in THF (1.0 M, 34.0 mL, 34.0 mmol, 5.0 eq) dropwise. After effervescence ceased, the reaction solution was stirred at rt under nitrogen for 3 h. Water (10 mL) was then cautiously added to the reaction solution followed by the addition of a solution of sodium hydroxide (3.0 M, 11.3 mL, 33.9 mmol, 5.0 eq). Finally, a solution of hydrogen peroxide (30%, 0.75 mL, 7.5 mmol, 1.1 eq) was added dropwise, and the resultant mixture was stirred at rt for 1h. A solution of saturated sodium hydrogen carbonate (25 mL) was added to this mixture, and the resulting aqueous mixture was then extracted with ethyl acetate (2 x 50 mL). These extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed using elution with 2.5-5% absolute methanol gradient in methylene chloride to afford **5** (0.575 mg, 2.08 mmol, 31%) as a white foam: IR (KBr) 2370, 2325, 2320, 2280, 1580, 1480, 1470, 1455, 1445, 1420, 1400, 1360 cm^{-1}; ^1H NMR (CD_3OD) δ 7.01 (d, J=8.6 Hz, 1H), 6.96 (s, 1H), 6.68 (d, J=8.6 Hz, 1H), 4.89 (s, 3H), 3.65 (t, J=6.5 Hz, 2H), 3.31-3.23 (m, 2H), 3.06 (t, J=7.6 Hz, 2H), 2.98-2.91 (m, 2H), 2.60 (s, 6H), 1.92-1.82 (m, 2H); ^{13}C NMR (CD_3OD) δ 148.6, 133.9, 127.0, 124.8, 119.4, 113.0, 112.1, 110.5, 67.5, 62.7, 52.2, 35.0, 23.3, 23.1; LRMS (m/z, relative intensity) 276 (M^+, 3), 262 (9), 160 (25), 130 (12), 115 (12), 58 (100); HRMS calcd. for $C_{15}H_{22}N_2O_2 \cdot BH_3$ (with B^{11}) 276.2009, found 276.2001. Further elution with absolute methanol afford the amine, free-base (**7**, 0.117 g, 0.45 mmol, 7%) as a clear, pale yellow oil identical in its physical and spectral properties with similar material described elsewhere in this report.

1-(2-Dimethylaminoethyl)-8,9-dihydropyrano[3,2-e]indole, N-borane complex (6). To a stirred solution of triphenylphosphine (0.57 g, 2.17 mmol, 2.0 eq) and DEAD (0.34 mL, 2.16 mmol, 2.0 eq) in anhydrous THF (8 mL) at 0 °C under nitrogen was added a solution of **5** (0.300 g, 1.09 mmol) in anhydrous THF (5 mL) dropwise. The resulting reaction was stirred at rt under nitrogen overnight. A saturated solution of sodium hydrogen carbonate (15 mL) was

added to the reaction, and this aqueous mixture was extracted with ethyl acetate (2 x 25 mL). These extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residual oil was chromatographed using elution with 0-5% absolute methanol gradient in methylene chloride to afford **6** (0.180 g, 0.70 mmol, 64%) as a white foam: mp 143.0-144.0 °C with gas evolution; IR (KBr) 3410-3325, 2370, 2320, 2275, 1615, 1585, 1495, 1480, 1465, 1455, 1440, 1415, 1405 cm^{-1}; ^1H NMR (CD_3OD) δ 7.02 (d, J=8.8 Hz, 1H), 6.97 (s, 1H), 6.54 (d, J=8.8 Hz, 1H), 4.89 (s, HDO), 4.12 (t, J=5.1 Hz, 2H), 3.30-3.20 (m, 4H), 2.99-2.93 (m, 2H), 2.64 (s, 6H), 2.10-2.02 (m, 2H); ^{13}C NMR (CD_3OD) δ 148.7, 131.4, 125.5, 122.9, 113.7, 112.9, 112.5, 110.2, 66.7, 65.9, 51.9, 22.8, 22.6, 22.1; LRMS (m/z, relative intensity) 259 (13), 258 (M^+, 73), 257 (36), 244 (14), 212 (19), 199 (25), 170 (19), 143 (15), 115 (17), 58 (100); HRMS calcd for $C_{15}H_{20}N_2O{\cdot}BH_3$ (with B^{11}) 258.1903, found 258.1884. Anal. calcd for $C_{15}H_{20}N_2O{\cdot}BH_3$: C, 69.78; H, 8.98; N, 10.85. Found: C, 69.95; H, 8.98; H, 10.69.

3-(2-Dimethylaminoethyl)-5-hydroxy-4-(3-hydroxypropyl)indole (7). To a stirred solution of **4** (0.920 g, 3.37 mmol) in anhydrous THF (10 mL) under nitrogen at 0 °C was added a solution of borane in THF (1.0 M, 16.9 mL, 16.9 mmol, 5.0 eq) dropwise. After effervescence ceased, the reaction solution was stirred at rt under nitrogen for 3 h. Water (10 mL) was then cautiously added to the reaction solution followed by the addition of a solution of sodium hydroxide (3.0 M, 5.60 mL, 16.8 mmol, 5.0 eq). Finally, a solution of hydrogen peroxide (30%, 0.37 mL, 3.7 mmol, 1.1 eq) was added dropwise, and the resultant mixture was stirred at rt for 1h. A solution of saturated sodium hydrogen carbonate (15 mL) was added to this mixture, and the resulting aqueous mixture was then extracted with ethyl acetate (2 x 50 mL). These extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residual tan foam (1.00 g) was dissolved in absolute ethanol (15 mL), and cesium fluoride (1.00 g) and sodium carbonate (1.00 g) were added. The resultant mixture was heated at reflux under nitrogen for 16 h. The reaction was then filtered through Celite®, and the filtrate was evaporated under reduced pressure. The residual oil was chromatographed using elution with absolute methanol to afford **7** (0.325 g, 1.23 mmol, 37%) as a pale yellow, hygroscopic oil: IR (CH_2Cl_2) 3470, 1605, 1490, 1415 cm^{-1}; ^1H NMR (CD_3OD) δ 7.00 (d, J=8.5 Hz, 1H), 6.95 (s, 1H), 6.66 (d, J=8.6 Hz, 1H), 4.91 (s, HDO, slightly greater than 3H), 3.62 (t, J=6.5 Hz, 2H), 3.07-3.01 (m, 4H), 2.65-2.60 (m, 2H), 2.34 (s, 6H), 1.91-1.81 (m, 2H); ^{13}C NMR (CD_3OD) δ 148.5, 133.9, 127.1, 124.4, 119.5, 113.4, 112.8, 110.4, 62.7, 45.5, 35.1, 26.1, 23.4; LRMS (m/z, relative intensity) 263 (17), 262 (M^+, 47), 160 (36), 130 (18), 115 (13), 58 (100); HRMS calcd for $C_{15}H_{22}N_2O_2$ 262.1681, found 262.1659. Anal. calcd for $C_{15}H_{22}N_2O_2{\cdot}0.5\ H_2O$: C, 66.39; H, 8.54; N, 10.32. Found: C, 66.0; H, 8.17; N, 9.99.

2-Nitro-5-(2-propenyloxy)toluene (8). To a stirred mixture of 3-methyl-4-nitrophenol (30.6 g, 0.200 mol) and cesium carbonate (70.6 g, 0.217 mol, 1.08 eq) in acetone (H_2O < 0.5%, 350 mL) was added dropwise allyl iodide (37.0 g, 0.220 mmol, 1.11 eq), and the resultant reaction mixture was stirred at rt under nitrogen for 24 h. Water (400 mL) was then added to the reaction mixture, and acetone was removed by evaporation under reduced pressure. The residual mixture was extracted with ether (2 x 500 mL), and the extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford **8** (38.17 g, 0.198 mol, 99%) as a clear, pale yellow liquid, which crystallized upon cooling: mp 32.0-35.0 °C; IR (KBr) 1650, 1610, 1580, 1510, 1495, 1490, 1455, 1425, 1410, 1385, 1340, 1315 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (dd, J=2.6 and 7.0 Hz, 1H), 6.83-6.79 (m, 2H), 6.11-5.96 (m, 1H), 5.43 (dq, J=17.3 and 1.7 Hz, 1H), 5.34 (dq, J=10.5 and 1.4 Hz, 1H), 4.62-4.59 (m, 2H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.0, 142.2, 137.0, 132.1, 127.5, 118.4, 118.2, 112.5, 69.2, 21.6, 15.3; LRMS (m/z, relative intensity) 194 (33), 193 (M^+, 97), 176 (100), 163 (11), 136 (48), 89 (50), 77 (68), 63 (63). Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.18; H, 5.57; N, 7.39.

3-Methyl-4-nitro-2-(2-propenyl)phenol (9a) and 5-Methyl-4-nitro-2-(2-propenyl)phenol (9b). A solution of **8** (34.50 g, 0.179 mol) in 1,2-dichlorobenzene (60 mL) was heated at reflux (180 °C) under nitrogen for 6 h. The reaction solution was cooled and poured through a silica gel filter (approx 500 g) followed by a solution of 20% ether in hexanes (6 L). The latter 5 liters of eluent were evaporated under reduced pressure to afford a 2:1 mixture[17] of **9a** : **9b**, respectively (14.07 g), as a pale brown oil which partially crystallized upon cooling: IR (KBr) 1640, 1610, 1580, 1520, 1480, 1455, 1415, 1380, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, **9a**) δ 7.76 (d, J=8.9 Hz, 1H), 6.77 (d, J=8.9 Hz, 1H), 6.20 (br s, 1H, -OH), 6.01-5.86 (m, 1H), 5.09 (dq, J=10.2 and 1.6 Hz, 1H), 4.97 (dq, J=17.1 and 1.7 Hz, 1H), 3.53-3.49 (m, 2H), 2.47 (s, 3H); ^1H NMR ($CDCl_3$, **9b**) δ7.96 (s, 1H), 6.74 (s, 1H), 6.20 (br s, 1H, -OH), 6.05-5.90 (m, 1H), 5.23-5.14 (m, 2H), 3.44-3.40 (br d, 2H), 2.58 (s, 3H); LRMS (m/z, relative intensity) 194 (38), 193 (M^+, 95), 176 (100), 163 (23), 148 (59), 132 (56), 131 (70), 115 (61), 103 (64), 91 (84), 80 (51), 79 (57), 77 (78), 65 (66), 63 (56). Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.20; H, 5.78; N, 7.21. The first liter of eluent was evaporated under reduced pressure to afford a solution of recovered starting material (**8**) in 1,2-dichlorobenzene (approx 60 mL). This solution was heated at reflux under nitrogen for 6 h, cooled, and poured through a silica gel filter (approx 100 g) followed by a solution of 10% ether in hexanes (1 L) and a solution of 20% ether in hexanes (1 L). The latter filtrate was evaporated under reduced pressure to afford more of the 2:1 mixture of **9a** : **9b** (4.30 g, 18.37 g total, 95.3 mmol total, 53% yield, 58% conversion), which was identical in its physical and spectral properties with the material described above. While some starting material (**8**) remained in the first liter of eluent, its recovery was not pursued.

2-(3-Hydroxypropyl)-3-methyl-4-nitrophenol (10a), 2-(3-hydroxypropyl)-5-methyl-4-nitrophenol (10b), 2-(2-hydroxypropyl)-3-methyl-4-nitrophenol (11a), and 2-(2-hydroxypropyl)-5-methyl-4-nitrophenol (11b). To a stirred solution of the 2:1 mixture of **9a** : **9b** (18.14 g, 93.89 mmol) in anhydrous THF (300 mL) at -10 °C under nitrogen was added dropwise a solution of borane in THF (1.0 M, 95.0 mL, 95.0 mmol, 1.01 eq). The resultant reaction solution was allowed to warm to rt overnight. A saturated solution of sodium hydrogen carbonate (200 mL) was added cautiously, followed by a solution of hydrogen peroxide (30%, approx 10M, 10.0 mL, 100 mmol, 1.1 eq). The resulting mixture was stirred vigorously for 1 h, and then extracted with ether (2 x 200 mL). These extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil (20 g) was chromatographed using elution with ether/hexanes (1:1) to afford first a 2:1 mixture of **11a** : **11b** (2.25 g, 10.65 mmol, 11%) as a solid/oil mixture: IR (KBr) 3500-3450, 1605, 1580, 1515, 1480, 1455, 1440, 1415 cm^{-1}; ^1H NMR ($CDCl_3$, **11a**) δ 7.73 (d, J=8.9 Hz, 1H), 6.83 (d, J=8.9 Hz, 1H), 4.30-4.20 (m, 1H), 2.97-2.85 (m, 2H), 2.43 (s, 3H), 1.36 (d, J=6.2 Hz, 3H); ^1H NMR ($CDCl_3$, **11b**) δ 7.87 (s, 1H), 6.79 (s, 1H), 4.32-4.22 (m, 1H), 2.87-2.75 (m, 2H), 2.58 (s, 3H), 1.29 (d, J=6.2 Hz, 3H); LRMS (m/z, relative intensity) 212 (16), 211 (M^+, 63), 176 (33), 167 (79), 150 (100), 120 (63), 91 (67), 77 (53), 65 (49). Anal. calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.01; H, 6.46; N, 6.41. Further elution using 25% hexanes in ether afforded a 2:1 mixture of **10a** : **10b** (14.48 g, 68.55 mmol, 73%) as a tan solid: mp 111-122 °C; IR (KBr) 3275-3240, 1630, 1585, 1485, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, **10a**) δ 7.73 (d, J=8.9 HZ, 1H), 6.80 (d, J=8.9 Hz, 1H), 3.67 (t, J=6.0 Hz, 2H), 2.90 (t, J=6.7 Hz, 2H), 2.49 (s, 3H), 1.97-1.84 (m, 2H); ^1H NMR ($CDCl_3$, **10b**) δ 7.94 (s, 1H), 6.75 (s, 1H), 3.70 (t, J=6.0 Hz, 2H), 2.79 (t, J=6.8 Hz, 2H), 2.57 (s, 3H), 1.97-1.84 (m, 2H); LRMS (m/z, relative intensity) 212 (20), 211 (M^+, 87), 176 (100), 166 (43), 148 (72), 120 (59), 91 (89), 77 (76), 65 (69). Anal. calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.09; H, 6.27; N, 6.60.

5-Methyl-6-nitro-3,4-dihydrobenzo[2,3]pyran (12a) and 7-Methyl-6-nitro-3,4-dihydrobenzo-[2,3]pyran (12b). To a stirred solution of triphenylphosphine (23.00 g, 87.7 mmol, 1.3 eq) and DEAD (15.27 g, 8.7.7 mmol, 1.3 eq) in anhydrous THF (300 mL) at 0 °C under nitrogen was added dropwise a solution of the 2:1 mixture of **10a** : **10b** (14.24 g, 67.41 mmol) in anhydrous THF (140 mL). The resultant reaction solution was stirred at rt under nitrogen for 4.5 h, then evaporated under reduced pressure. The residual oil was passed through a silica gel filter (approx 900 g) followed first by a solution of 10% ether in hexanes (3 L), and then by a solution of 20% ether in hexanes (4 L). The latter 4 liters of eluent were evaporated under reduced pressure to yield a 2:1 mixture of **12a** : **12b** (12.64 g, 65.42 mmol, 97%) as a white solid: mp 71-84 °C; IR (KBr) 1625, 1600, 1585, 1570, 1505, 1480, 1465, 1435, 1380, 1355, 1320, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, **12a**) δ 7.73 (d, J=9.1 Hz, 1H), 6.73 (d, J=9.1 Hz, 1H), 4.20 (t, J=5.2 Hz, 2H), 2.73 (t, J=6.6 Hz, 2H), 2.43 (s, 3H), 2.13-2.01 (m, 2H); ^1H NMR ($CDCl_3$, **12b**) δ 7.89 (s, 1H), 6.68 (s, 1H), 4.26 (t, J=5.3 Hz, 2H), 2.81 (t, J=6.4 Hz, 2H), 2.57 (s, 3H), 2.11-1.99 (m, 2H); LRMS (m/z, relative intensity) 194 (8), 193 (M^+, 75), 176 (100), 163 (6), 91 (63). Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.26; H, 5.98; N, 7.31.

8,9-Dihydropyrano[3,2-e]indole (13a) and 7,8-Dihydropyrano[2,3-f]indole (13b). A solution of the 2:1 mixture of **12a** : **12b** (11.30 g, 58.49 mmol) in dimethylformamide dimethyl acetal (50 mL) and dimethylformamide (100 mL) was heated at reflux under nitrogen for 48 h. The dark red reaction solution was evaporated under reduced pressure, and the residual oil was dissolved in absolute ethanol (60 mL). Palladium on carbon (10%, 2.10 g) was added to this solution, and this mixture was shaken under a hydrogen atmosphere (3 atm) for 5 h. The resultant mixture was filtered through Celite®, and the filtrate was evaporated under reduced pressure. Chromatography of the residue using elution with 40% methylene chloride in hexanes first afforded **13b** (0.56 g) as a white solid: mp 129.0-133.0 °C; IR (KBr) 3390, 1565, 1485, 1470, 1460, 1445, 1340, 1320, 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (br m, NH), 7.11-7.09 (m, 1H), 7.05 (s, 1H), 7.03 (s, 1H), 6.41-6.39 (m, 1H), 4.20 (t, J=5.2 Hz, 2H), 2.95 (t, J=6.5 Hz, 2H), 2.07-2.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 149.3, 131.3, 127.3, 124.8, 118.4, 110.8, 106.1, 101.9, 66.6, 25.9, 23.0; LRMS (m/z, relative intensity) 174 (27), 173 (M^+, 100), 145 (67), 130 (16), 117 (67), 89 (15). Anal. calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.28; H, 6.55; N, 7.98. Further elution afforded a 2:1 mixture of **13a** : **13b** (2.31 g) as a white solid. Still further elution using the same solvent system afforded **13a** (4.01 g) as a white crystalline solid: mp 110.5-112.5 ° C; IR (KBr) 3435, 1615, 1585, 1505, 1490, 1435, 1415, 1345, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (br m, NH), 7.17-7.11 (m, 2H), 6.77 (d, J=8.7 Hz, 1H), 6.47-6.45 (m, 1H), 4.24 (t, J=5.1 Hz, 2H), 2.98 (t, J=6.6 Hz, 2H), 2.16-2.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.5, 130.3, 127.7, 124.4, 113.0, 112.4, 109.8, 100.1, 66.4, 22.5, 22.1; LRMS (m/z, relative intensity) 174 (40), 173 (100, M^+), 145 (84), 130 (21), 117 (63), 89 (36). Anal. calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.45; H, 6.78; N, 8.32. Total yield of both isomers: 6.88 g, 39.72 mmol, 68% for the two steps.

8,9-Dihydropyrano[3,2-e]indole-1-N,N-dimethylglyoxamide (14a). To a stirred solution of **13a** (0.61 g, 3.52 mmol) and phthalimide (0.24 g, 40% by weight) in anhydrous ether (15 mL) at 0 °C under nitrogen was added dropwise oxalyl chloride (0.36 mL, 4.12 mmol, 1.2 eq). The resultant yellow/orange reaction mixture was stirred at rt under nitrogen for 1 h, at which time a solution of dimethylamine (condensed using a dry ice/acetone bath, 10 mL) in ether (10 mL) was added rapidly to the mixture. The resultant white mixture was stirred at rt under nitrogen for 1h. A saturated solution of sodium hydrogen carbonate (20 mL) was then added, and this aqueous mixture was extracted with 5% methanol in ethyl acetate (5 x 25 mL). These extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Trituration of the residual solid in absolute methanol (10 mL) with cooling afforded **14a** (0.752 g,

2.76 mmol, 78%) as a white solid: mp > 250 °C; IR (KBr) 1635, 1620, 1605, 1505, 1475, 1465, 1430, 1420, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.2 (br m, NH), 7.61 (d, J=3.5 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.77 (d, J=8.8 Hz, 1H), 4.19 (t, J=5.1 Hz, 2H), 3.41 (t, J=6.6 Hz, 2H), 3.07 (s, 3H), 3.02 (s, 3H), 2.08-1.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.2, 151.3, 137.6, 132.0, 124.7, 115.7, 115.7, 115.6, 110.7, 66.1, 37.6, 34.2, 25.4, 22.4; LRMS (m/z, relative intensity) 272 (M^+, 15), 200 (100), 142 (28). Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.49; H, 6.11; N, 10.36.

7,8-Dihydropyrano[2,3-f]indole-3-N,N-dimethylglyoxamide (14b). To a stirred solution of **13a** (0.45 g, 2.60 mmol) and phthalimide (0.20 g, 40% by weight) in anhydrous ether (10 mL) at 0 °C under nitrogen was added dropwise oxalyl chloride (0.25 mL, 2.86 mmol, 1.1 eq). The resultant yellow/orange reaction mixture was stirred at rt under nitrogen for 1 h, at which time a solution of dimethylamine (condensed using a dry ice/acetone bath, 10 mL) in ether (10 mL) was added rapidly to the mixture. The resultant pale green mixture was stirred at rt under nitrogen for 1h. A saturated solution of sodium hydrogen carbonate (20 mL) was then added, and this aqueous mixture was extracted with 5% methanol in ethyl acetate (6 x 25 mL). These extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residual oil using elution with ethyl acetate afforded **14b** (0.670 g, 2.46 mmol, 95%) as a white solid: mp 217.0-218.0 °C; IR (KBr) 1630, 1575, 1525, 1495, 1455, 1445, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.6 (br m, NH), 7.62 (s, 1H), 7.53 (d, J=3.2 Hz,1H), 6.83 (s, 1H), 4.16 (t, J=5.0 Hz, 2H), 3.05 (s, 3H), 2.98 (s, 3H), 2.73 (t, J=6.5 Hz, 2H), 1.99-1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 185.5, 168.5, 151.8, 136.1, 131.8, 124.5, 120.2, 113.3, 112.4, 107.5, 66.5, 37.5, 34.2, 25.5, 22.5; LRMS (m/z, relative intensity) 273 (15), 272 (M^+, 49), 200 (100), 172 (40), 144 (12), 116 (19). Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.03; H, 6.04; N, 10.29.

2,4-Dimethyl-5-nitro-2,3-dihydrobenzo[2,3]furan (15a) and 2,6-Dimethyl-5-nitro-2,3-dihydrobenzo[2,3]furan (15b). To a stirred solution of triphenylphosphine (3.60 g, 13.7 mmol, 1.3 eq) and DEAD (2.40 g, 13.8 mmol, 1.3 eq) in anhydrous THF (50 mL) at 0 °C under nitrogen was added dropwise a solution of the 4:1 mixture of **11a** : **11b** (2.22 g, 10.51 mmol) in anhydrous THF (10 mL). TLC (1:1 ether/hexanes) indicated that the reaction was complete in 5 min. The reaction solution was then evaporated under reduced pressure, and the residual oil was passed through a silica gel filter (approx 50 g) followed first by a solution of 10% ether in hexanes (1 L) and then by a solution of 15% ether in hexanes (500 mL). The latter eluent (500 mL) was evaporated under reduced pressure to afford a 4:1 mixture of **15a** : **15b** (1.57 g, 8.13 mmol, 77%) as solid/oil mixture; IR (KBr) 1630, 1615, 1590, 1520, 1490, 1460, 1440, 1410 cm^{-1}; ^1H NMR ($CDCl_3$, **15a**) δ 7.94 (d, J=9.1 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 5.12-5.00 (m, 1H), 3.34 (dd, J=15.6 and 9.1 Hz, 1H), 2.80 (dd, J=15.6 and 7.2 Hz, 1H), 2.48 (s, 3H), 1.50 (d, J=6.1 Hz, 3H); ^1H NMR ($CDCl_3$, **15b**) δ 7.92 (s, 1H), 6.60 (s, 1H), 5.12-5.00 (m, 1H), 3.34 (dd, J=15.6 and 9.1 Hz, 1H), 2.82 (dd, J=15.6 and 7.2 Hz, 1H), 2.57 (s, 3H), 1.48 (d, J=6.1 Hz, 3H); LRMS (m/z, relative intensity) 194 (8), 193 (M^+, 64), 176 (68), 132 (33), 120 (98), 91 (100). Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.24; H, 5.52; N, 7.18.

2-Methyl-1,2-dihydrofuro[3,2-e]indole (16a) and 2-Methyl-2,3-dihydrofuro[2,3-f]indole (16b). A solution of the 4:1 mixture of **15a** : **15b** (1.30 g, 6.73 mmol) in dimethylformamide dimethyl acetal (5 mL) and dimethylformamide (10 mL) was heated at reflux under nitrogen for 48 h. The dark red reaction solution was evaporated under reduced pressure, and the residual oil was dissolved in absolute ethanol (20 mL). Pd/C (0.34 g) was added to this solution, and the resulting mixture was shaken under a hydrogen atmosphere (3 atm) for 4 h. The reaction mixture was then filtered through Celite®, and the filtrate was evaporated under reduced pressure. The residual oil was

chromatographed using a 10-15% ether gradient in hexanes to afford a 4:1 mixture of **16a** : **16b** (0.42 g, 2.42 mmol, 36% for the two steps) as a clear, colorless oil; IR ($CHCl_3$) 3480, 1630, 1600, 1485, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, **16a**) δ 8.10 (br m, NH), 7.19-7.17 (m, 1H), 7.13 (d, J=8.6 Hz, 1H), 6.74 (d, J=8.5 Hz, 1H), 6.35-6.33 (m, 1H), 5.06-4.96 (m, 1H), 3.48 (dd, J=15.6 and 8.2 Hz, 1H), 2.98 (dd, J=15.5 and 6.9 Hz, 1H), 1.51 (d, J=6.3 Hz, 1H); ^1H NMR ($CDCl_3$, **16b**) δ 7.98 (br m, NH), 7.11 (s, 1H), 7.10-7.08 (m, 1H), 6.94 (s, 1H), 6.42-6.40 (m, 1H), 4.96-4.86 (m, 1H), 3.35 (dd, J=15.6 and 8.2 Hz, 1H), 2.89 (dd, J=15.5 and 6.9 Hz, 1H), 1.48 (d, J=6.3 Hz, 1H); LRMS (m/z, relative intensity) 174 (44), 173 (M^+, 100), 172 (74), 158 (44), 146 (50), 130 (62), 117 (27), 77 (31), 51 (31). Anal. calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.06; H, 6.59; N, 8.09.

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References:

1. Twarog, B.M. and Page, I. Am. J. Psychiat., **1953**, *175*, 157.
2. For a review of serotonin pharmacology, see: Peroutka, S.J. Ann. Rev. Neurosci., **1988**, *11*, 45.
3. Glennon, R.A. J. Med. Chem., **1987**, *30*, 1.
4. 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.; and Koe, B.K. J. Med. Chem., **1990**, 33, 2087; b) Macor, J.E. and Newman, M.E. Heterocycles, **1990**, *31*, 805; c) Macor, J.E. and Ryan, K. Heterocycles, **1990**, *31*, 1497; d) Macor, J.E. and Newman, M.E., Tetrahedron Letters, **1991**, *32*, 3345.
5. Since 5-methoxy-3-(2-aminoethyl)indole [5-methoxytryptamine, the C5-methyl ether of serotonin] is as potent as serotonin in binding to serotonergic receptors (see: Glennon, R.A.; Ismaiel, A.M.; Chaurasia, C. and Titeler, M. Drug Dev. Res., **1991**, *22*, 25), it can be inferred that: a) the C5-phenol in serotonin functions as a hydrogen bond acceptor, and b) the replacement of a phenol with an ether does not lead to a weaker hydrogen bond acceptor in this case.
6. Binding studies have shown that the aminoethyl sidechain of serotonin can effectively be replaced by a 1,2,5,6-tetrahydropyrid-2-yl ring (see reference 4a) within the series of 5-HT_1 receptors.
7. The original synthesis of **1a** has been previously disclosed in a communication: Macor, J.E. and Newman, M.E., Tetrahedron Letters, **1991**, *32*, 3345.
8. The choice of the N,N-dimethylaminoethyl sidechains in **1a** and **1b** was to provide the 5-HT receptors with an analog as close as possible the the natural substrate. The tertiary amine was originally chosen for ease of synthesis and purification.
9. Ito, C. and Furukawa, H. Chem. Pharm. Bull. Tokyo, **1990**, *38*, 1551.
10. Von Strandtmann, M.; Cohen, M.P.; and Shavel, J. J. Heterocyclic Chem., **1970**, *7*, 1311.
11. Waldner, E.E.; Hesse, M.; Taylor, W.I.; and Schmid, H. Helv. Chim. Acta, **1967**, *50*, 1926.
12. a) Julia, M. and Lallemand, J.-Y. Bull. Soc. Chim. Fr., **1973**, 2046; b) Cannon, J.G. and Roufos, I., J. Heterocyclic Chem., **1990**, *27*, 2093; c) Moody, C. J. Chem. Soc., Chem. Comm., **1983**, 1129.
13. There was some variability in this reaction in that in some cases the precipitated material was slightly contaminated by starting material (**3**). Therefore, to insure purity in these cases, the reaction mixture was directly chromatographed to separate desired product (**4**) from returned starting material (**3**).
14. For a review see: Bennett, G.B. Synthesis, **1977**, 589.
15. The reduction of indole-3-glyoxamides has been an important approach in the synthesis of tryptamine derivatives. For a discussion of this work, see: Remers, W.A. "Indole Aldehydes and Ketones," Vol. 25, Part III in the series "The Chemistry of Heterocyclic Compounds," Weissberger, A. and Taylor, E.C. (eds), John Wiley and Sons, New York, **1979**, p. 405.
16. O. Mitsunobu, Synthesis, **1981**, 1.
17. Except in the case of **13a** and **13b**, the ratios (of isomers) throughout this report were determined by examination of the integration of appropriate, analogous resonances in the ^1H NMR spectrum of the mixtures.
18. For a review of this methodology see: Clark, R.D. and Repke, D.B. Heterocycles, **1984**, *22*, 195.
19. Chromatography using a 0-5% methanol gradient in methylene chloride afforded equally successful separation of **3** from **4**.