to give the desired d4A (**29**) as a white crystalline solid (2.6 g, 56% from adenosine): mp 191–192 °C (lit.[28] mp 194–195 °C); ^{1}H NMR (360 MHz, DMSO-d_6) 8.18 (s, 1 H, H-2), 8.17 (s, 1 H, H-8), 7.34 (s, 2 H, NH_2), 6.95 (s, 1 H, H-1′), 6.46 (d, 1 H, J = 6.0 Hz, H-3′), 6.14 (d, 1 H, J = 6.0 Hz, H-2′), 5.07 (t, 1 H, J = 5.5 Hz, OH), 4.89 (m, 1 H, H-4′), and 3.57 (m, 2 H, H-5′); ^{13}C NMR (75.5 MHz, DMSO-d_6) 156.07 (C-2), 152.67 (C-6), 149.18 (C-4), 139.22 (C-8), 134.39 (C-2′), 125.54 (C-3′), 118.81 (C-5), 88.07 (C-1′), 87.89 (C-4′), and 62.81 (C-5′).

2′,3′-Dideoxyadenosine (ddA) (5). Palladium on carbon (5%) (2.3 g) was added to a slurry of d4A (**29**) (4.48 g, 19.3 mmol) in 90% aqueous ethanol (240 mL). The reaction mixture was exposed to hydrogen (pressure is not necessary) and stirred for 4 h. The mixture was filtered through Celite, and the Celite was washed with ethanol (100 mL). The combined filtrate was concentrated in vacuo to ca. 20 mL. The resulting slurry was dissolved in boiling ethanol (total volume 80 mL) and filtered hot through a dicalite pad. The filtrate was allowed to cool slowly to 20 °C and then stored at 0–5 °C for 18 h. The solid was collected, washed with ethanol (2 × 10 mL), and dried to give 3.23 g (72%) of ddA (**5**) as a white solid. This sample contained 96.8% of ddA by HPLC and 1.31% adenine. The amount of adenine could be reduced to 0.67% by a recrystallization from ethanol: mp 185–186 °C (lit.[29] mp 185–187 °C); ^{1}H NMR (360 MHz, DMSO-d_6) 8.35 (s, 1 H, H-2), 8.13 (s, 1 H, H-8), 7.27 (s, 2 H, NH_2), 6.21 (t, 1 H, J = 5.2, J = 5.5 Hz, H-1′), 5.06 (br s, 1 H, OH), 4.17 (m, 1 H, H-4′), 3.61 (m, 1 H, H-5′a), 3.50 (m, 1 H, H-5′b), 2.39 (m, 2 H, H-3′), and 2.04 (m, 2 H, H-2′); ^{13}C NMR (75.5 MHz, DMSO-d_6) 155.93 (C-2), 152.33 (C-6), 148.72 (C-4), 138.97 (C-8), 119.03 (C-5), 84.39 (C-1′), 81.67 (C-4′), 62.91 (C-5′), 31.77 (C-3′), and 25.70 (C-2′).

1-(2-Bromo-2-deoxy-3,5-di-*O*-acetylribosyl)thymine (30). Acetyl bromide (13.8 mL, 113 mmol) was added dropwise over 0.5 h to a suspension of 5-methyluridine (**22**) (5 g, 19.38 mmol) in acetonitrile (250 mL) heated at reflux. On completion of addition, the solution was allowed to cool and then concentrated. The residue was dissolved in methylene chloride (50 mL) and washed with water (50 mL). The organic phase was concentrated to leave **30** as a beige solid (7.8 g, 97%): mp 55–57 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 11.51 (s, 1 H, NH), 7.51 (s, 1 H, H-6), 6.12 (d, 1 H, J = 7.9 Hz, H-1′), 5.25 (dd, 1 H, J = 2.9 Hz, J = 6.0 Hz, H-3′), 4.97 (dd, 1 H, J = 6.0 Hz, J = 7.8 Hz, H-2′), 4.3 (m, 1 H, H-4′), 4.27 (m, 2 H, H-5′), 2.12 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), and 1.79 (s, 3 H, CH_3);[37] ^{13}C NMR (75.5 MHz, DMSO-d_6) 170.23 (C=O), 169.36 (C=O), 163.52 (C-4), 150.67 (C-2), 135.46 (C-6), 110.65 (C-5), 88.38 (C-1′), 79.74 (C-4′), 71.35 (C-3′), 62.98 (C-5′), 47.25 (C-2′), 20.63 (2 CH_3), and 12.22 (CH_3).

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (31). A Zn/Cu couple (3 g, Fairfield chemicals) was heated at reflux in acetic acid (20 mL) for 0.5 h. The suspension was filtered and washed with methanol. The couple was suspended in methanol (70 mL), and 1-(2-bromo-2-deoxy-3,5-di-*O*-acetylribosyl)thymine (**30**) (1 g, 2.4 mmol) was added, and the mixture was stirred for 0.5 h. The mixture was filtered and concentrated, to leave an oil, which was purified by flash column chromatography, methanol/methylene chloride (1:9). The desired product **31** was isolated as a white solid (0.64 g, 53%): mp 179–181 °C (lit.[39] mp 179–181 °C); ^{1}H NMR (300 MHz, DMSO-d_6) 11.37 (s, 1 H, NH), 7.25 (s, 1 H, H-6), 6.78 (s, 1 H, H-1′), 6.38 (d, 1 H, J = 6 Hz, H-3′), 5.98 (d, 1 H, J = 6 Hz, H-2′), 4.95 (s, 1 H, H-4′), 4.18 (m, 2 H, H-5′), 2.00 (s, 3 H, CH_3), and 1.75 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) 170.44 (C-4), 164.04 (C=O), 151.02 (C-2), 136.14 (C-6), 133.91 (C-3′), 126.75 (C-2′), 109.75 (C-5), 89.99 (C-1′), 83.90 (C-4′), 64.76 (C-5′), 20.83 (CH_3), and 12.35 (CH_3).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T) (2). Sodium methoxide (0.12 g, 2.35 mmol) was added to a suspension of 1-(5-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (**31**) (0.5 g, 1.88 mmol) in methanol (20 mL) and the solution stirred at ambient temperature for 2 h. The solution was neutralized with strongly acidic ion-exchange resin (Dowex 50 × 8-200), which had been washed with methanol. The resin was filtered and then washed with methanol (2 × 20 mL). The filtrate was concentrated and purified by flash column chromatography on silica gel, methylene chloride/methanol/ammonium hydroxide (90:10:1) to give a white solid (0.36 g, 87%): mp 165–166 °C (lit.[7,35] mp 164–166 °C); ^{1}H NMR (360 MHz, DMSO-d_6) 11.29 (s, 1 H, NH), 7.63 (s, 1 H, H-6), 6.80 (dt, 1 H, J = 1.3 Hz, J = 0.4 Hz, H-1′), 6.36 (dt, 1 H, J = 6.1 Hz, J = 1.7 Hz, H-3′), 5.90 (dt, 1 H, J = 6.1 Hz, J = 1.4 Hz, H-2′), 5.01 (m, 1 H, OH), 4.76 (s, 1 H, H-4′), 3.60 (m, 2 H, H-5′), and 1.71 (s, 3 H, CH_3).

Acknowledgment. We thank Maureen D'lugozima for technical assistance in part of this work.

Registry No. **2**, 3056-17-5; **5**, 4097-22-7; **9**, 58-96-8; **10**, 6195-94-4; **12**, 6038-55-7; **13**, 5974-93-6; **15**, 16628-81-2; **16**, 42867-74-3; **20** R = AciBu, 42867-75-4; **22**, 1463-10-1; **22** (2′,3′,5′-tri-*O*-benzoyl deriv), 3180-76-5; **23** R = AciBu, 122383-24-8; **24** R = AciBu, 122383-25-9; **25**, 58-61-7; **26** R = AciBu, 122383-26-0; **27** R = AciBu, 122383-27-1; **28** R = AciBu, 122383-28-2; **29**, 7057-48-9; **30**, 110483-43-7; **31**, 77421-68-2; AciBuBr, 40635-67-4; 5′-*O*-trityluridine, 6554-10-5; thymine, 65-71-4; 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribose, 14215-97-5.

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Synthesis of Pyrano[4,3-*b*]indoles as Conformationally Restricted Analogues of the Serotonin Antagonist ICS 205-930 and as Precursors to 2-Vinylindoles

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Received April 12, 1989

A useful synthesis of some pyrano[4,3-*b*]indoles is described that allows access to conformationally restricted analogues of the serotonin ($5HT_3$) antagonist, ICS 205-930. These pyrano[4,3-*b*]indoles can be converted in one step to 2-vinylindole derivatives.

Introduction

Recently, in conjunction with attempts to discover the active conformation of the extremely novel and potent serotonin ($5HT_3$) antagonist ICS 205-930, there was a desire to synthesize the spiropyrano[4,3-*b*]indole **1** as a conformationally restricted analogue of the drug. A survey of the literature revealed that while the generic pyranoindole heterocycle has received some attention, pyrano-

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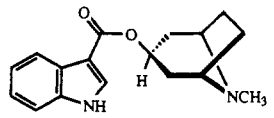

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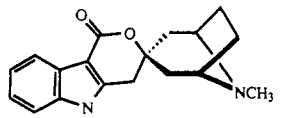

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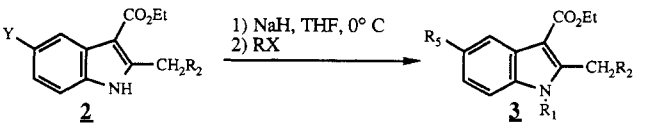
[4,3-*b*]indoles have not been studied to any appreciable extent. 2-(3-Carbethoxy-1-methylindol-2-yl)acetic acid (formed via the appropriate Fischer indolization route) has been dehydrated to yield 4,5-dihydro-5-methylpyrano-[4,3-*b*]indole-1,3-dione,[1] which has been used as a precursor to an indole *o*-quinodimethane useful in Diels–Alder reactions with activated dienophiles.[2] There have been a few other isolated reports of pyrano[4,3-*b*]indoles[3] in the literature, but a synthetically useful approach to these compounds has not yet appeared.

In the course of our investigations it was found that pyrano[4,3-*b*]indoles were excellent precursors to 2-vinylindoles,[4] a relatively inaccessible but synthetically useful class of indole derivatives.[5] 2-Vinylindoles have been used as intermediates in the synthesis of *Aspidosperma* alkaloids[6] and are useful building blocks for the synthesis of natural products. A small number of limited syntheses of this indole derivative have been recently reported,[7] but the need for a simpler approach to those compounds still remains. This paper will therefore describe a novel approach to pyrano[4,3-*b*]indoles and detail their use as precursors to 2-vinylindoles.

Results and Discussion

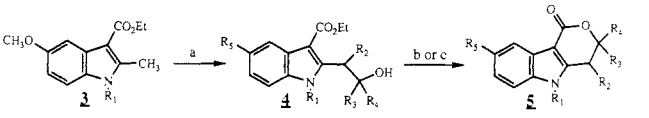
Annulation of a readily available indole nucleus was the strategy of our synthesis of pyrano[4,3-*b*]indoles. 2-Alkylindole-3-carboxylates **2** were easily obtained via either the Nenitzescu or Fischer[8] indole synthesis. Protection of the indole nitrogen in these compounds was easily effected via NH deprotonation with sodium hydride followed by alkylation or acylation with the appropriate electrophile to yield **3** (Scheme I). Treatment of **3** with a slight excess of lithium diisopropylamide (LDA) at −78 °C rapidly deprotonated the C2-methyl (or methylene) group of these molecules. The resulting anions of **3** were stable at this temperature as a result of electron density delocalization by both the indole ring and the vinylogous 3-carboxylate. These anions readily reacted with aldehydes or ketones to form the alkoxides of **4** (Schemes II and III), which generally did not spontaneously lactonize at −78 °C. With quenching at −78 °C, a good to excellent yield of alcohols **4** could be obtained (Scheme II). Lactonization of these alcohols via heating under acid catalysis (use of refluxing acetic acid was preferred) gave varying yields of the desired pyranoindoles **5** (Scheme II). When R_3 and R_4 were alkyl, the lactonization proceeded well, but when R_3 or R_4 was phenyl, the yield of **5c** was low, and other byproducts were seen.

Scheme I



	R_1	R_2	R_5	% Yield (3)
a	CH_3	H	H	99
b	CH_3	H	OCH_3	80
c	CH_3	CH_3	H	92
d	CH_2OCH_2Ph	H	H	78
e	CH_2OCH_2Ph	CH_3	H	83
f	CO_2tBu	H	H	85
g	CO_2Et	H	H	27
h	$SO_2C_6H_4CH_3$	H	H	62

Scheme II



	R_4	R_3	% Yield (4)	% Yield (5)
a	$-(CH_2)_5-$		87	73 [Note 1]
b	CH_3	CH_3	83	81
c	H	Ph	79	32 [Note 2]
i	$-NCH_3$-piperidyl-		67	62

[a] (1) LDA, THF, −78 °C; (2) R_3COR_4. [b] Acetic acid reflux. [c] TsOH/dioxane reflux. Note 1: 35% using TsOH/dioxane reflux (19% of 2-vinylindole ethyl ester also isolated). Note 2: 34% acetylation of alcohol.

Alternatively, warming the alkoxides (often all the way to room temperature) slowly led to their lactonization to yield the desired pyrano[4,3-*b*]indoles **5** (Scheme III). This slow lactonization can easily be understood by viewing the indoles **3** as vinylogous carbamates. In the cases where the indole nitrogen was protected as its *p*-toluenesulfonamide, **5m** and **5n**, it should be noted that lactonization (among other reactions) did occur at −78 °C; this was a result of the decreased donation of electron density from the indole nitrogen to the 3-carboxylate as a result of the electron-withdrawing nature of R_1. As one would expect, the rate of lactonization was dependent on the nature of the substituents R_3 and R_4. Geminal disubstitution (i.e., use of ketones) accelerated this rate of lactonization (Thorpe–Ingold effect), and phenyl substituents (i.e., from benzaldehyde, acetophenone, and benzophenone) retarded the rate of lactonization and gave lower yields of the desired heterocycle (Scheme III). Additionally, when R_3 or R_4 was phenyl, not only was the lactonization slowed, but the rate of formation of the byproduct 2-vinylindole (see below) was increased. This combination of results led to low isolated yields of pyrano[4,3-*b*]indoles **5** where R_3 or R_4 was phenyl. It should be noted that the combined yield of **5a** from the formation of **4a** (isolated) and cyclization to **5a** (Scheme II) was not significantly better than in the one-step, base-controlled reaction (Scheme III).

These lactonizations were achieved through warming from −78 °C to ambient temperature, and their progress was monitored closely by TLC. This was necessary because these compounds represented intermediates on a thermodynamically driven pathway to 2-vinylindoles **6**. The pyrano[4,3-*b*]indoles **5** still retained acidic protons α to C2 of the indole ring, and therefore, under the basic reaction conditions (slight excess of LDA and ethoxide

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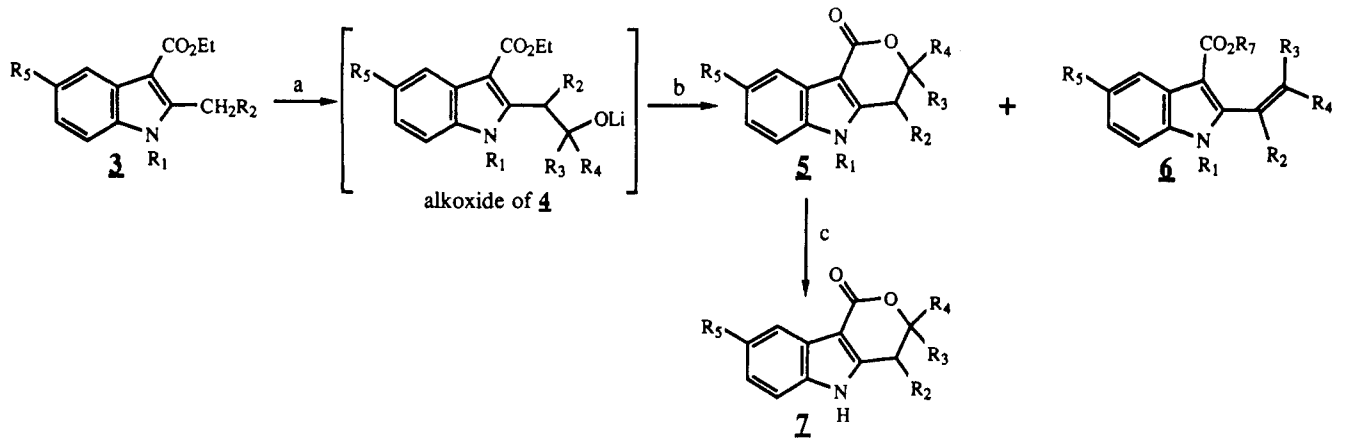
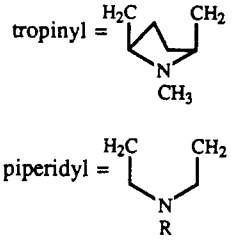
Scheme III



	R_1	R_2	R_3	R_4	R_5	% Yield (5)	% Yield (6)	% Yield (7)
a	CH_3	H	-$(CH_2)_5$-		OCH_3	58	(12)	--
c	CH_3	H	Ph	H	OCH_3	39	35	--
d	CH_3	H	Ph	CH_3	OCH_3	32	--	--
e	CH_3	H	$CH_2CH_2CH_3$	H	OCH_3	63	--	--
f	CH_3	H	Ph	Ph	OCH_3	17	26	--
g	CH_3	H	-tropinyl-		OCH_3	79	0	--
h	CH_3	H	-N-tBOC-piperidyl-		OCH_3	55	5 (21)	--
j	CH_3	H	-tropinyl-		H	58	0	--
k	CH_3	H	-N-tBOC-piperidyl-		H	52	19	--
l	CH_3	CH_3	-$(CH_2)_5$-		H	43	--	--
m	$SO_2C_6H_4CH_3$	H	$CH_2CH_2CH_3$	H	H	23	--	--
n	$SO_2C_6H_4CH_3$	H	CH_3	CH_3	H	43	--	--
o	CH_2OCH_2Ph	H	$CH_2CH_2CH_3$	H	H	53	--	47
p	CH_2OCH_2Ph	H	CH_3	CH_3	H	64	--	74
q	CH_2OCH_2Ph	CH_3	CH_3	CH_3	H	84	--	57

( ) = Yield determined by NMR spectroscopy



[a] (1) LDA, THF, −78 °C; (2) R_3COR_4, −78 °C. [b] Warming −78 °C to room temperature. [c] When R_1 = (benzyloxy)methylene: NH_4CO_2, Pd/C, ethanol reflux.

from the lactonization), deprotonation of this methylene occurred. This was manifested upon warming of the reaction solution by the rapid appearance of 2-vinylindole-3-carboxylic acids **6** resulting from "internal elimination" of the acid functionality from the deprotonated lactones (Scheme III). **6** represented the thermodynamically most stable product in this reaction sequence. Therefore, TLC was used to determine the optimized yield of the lactone **5**, while minimizing the amount of the olefin **6** that was formed as a byproduct. The transformation of **5** to **6** could be effected simply with the ethoxide liberated in the lactonization, since a reaction using exactly 1 equiv of LDA still slowly yielded the olefin **6** upon warming to room temperature. It should be noted that this "internal elimination" was retarded in cases where the resulting olefin was congested (i.e., **5g**, **5j**, and **5q**).

Other attempts to lactonize **4** led primarily to the olefin **6** (under basic conditions), decomposition or olefin **6** (under acidic conditions), or no reaction (under thermal conditions). The use of ambient warming of the alkoxide of **4** with careful monitoring of the reaction by TLC was the most general and reproducible route to the pyrano[4,3-*b*]indoles **5**. Deprotection of the pyrano[4,3-*b*]indoles **5o**, **5p**, and **5q** using Pd/C and ammonium formate in refluxing ethanol smoothly led to the corresponding NH pyrano[4,3-*b*]indoles **7** (Scheme III).

Compounds **5g** and **5j** represent our desired conformationally restricted analogues of ICS 205-930. An X-ray diffraction study of **5g** (supplemental material; see the paragraph at the end of the paper) indicated that the anion of **3b** attacked the ketone of tropinone from its less hindered (β) face, yielding the expected α-ol in the lactone which was completely analogous to the tropinyl (α-ol) ester in ICS 205-930. Unfortunately, these compounds did not demonstrate any in vivo[9] or in vitro[10] activity as $5HT_3$ antagonists, thus indicating that they do not represent the active conformation of ICS 205-930.

While the synthesis of the pyranoindoles **5** was plagued by their propensity to "internally eliminate" the carboxylic acid yielding 2-vinylindole derivatives **6**, this side reaction could be optimized as a directed synthesis of these important indole building blocks. Direct treatment of the reaction mixture containing **5** and traces of **6** with excess methoxide in methanol followed by heating led rapidly to the 2-vinylindole-3-carboxylic acids **6** in good yields (Scheme IV). When the starting indole-3-carboxylates **3** were protected with an alkyl substituent (R_1 = methyl or (benzyloxy)methyl), the resulting carboxylic acid (R_7 = H) **6** could be readily decarboxylated by heating in refluxing bromobenzene for a few hours to deliver nearly quantitative yields of the 2-vinylindoles **8a,b,d,e,g**. When the starting indole-3-carboxylate **3** was protected with a carbamate derivative, a different reaction pathway was seen (Scheme V). Rapid transacylation occurred from the indole nitrogen to the alkoxide forming a carbonate **9**, which then easily eliminated under the standard reaction

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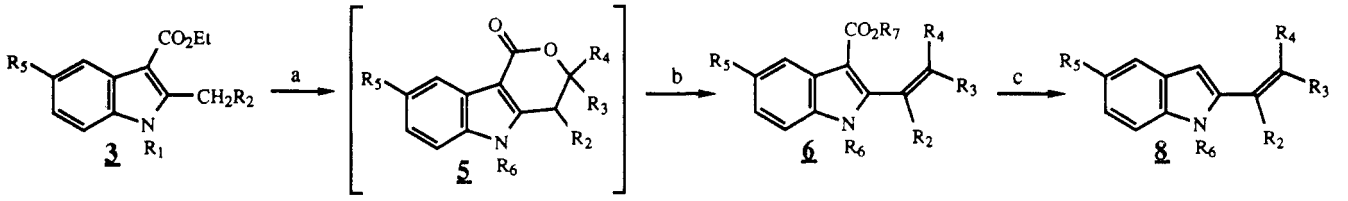
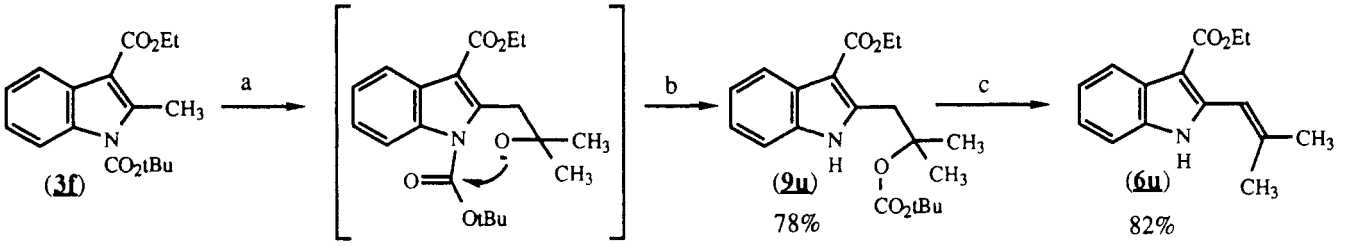
Scheme IV



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	% Yield (6)	% Yield (8)
a	CH_3	H	$-(CH_2)_5-$		OCH_3	CH_3	H	50	90
b	CH_3	H	CH_3	CH_3	OCH_3	CH_3	H	86	94
d	CH_3	H	Ph	H	OCH_3	CH_3	H	85	95
e	CH_3	H	$(CH_2)_2CH_3$	H	OCH_3	CH_3	H	53	93
g	CH_3	H	-tropinyl-		OCH_3	CH_3	H	100	99
q	CH_2OCH_2Ph	CH_3	CH_3	CH_3	H	CH_2OCH_2Ph	H	77	--
r	CO_2Et	H	$(CH_2)_5CH_3$	H	H	H	CH_3	33	--
s	CO_2Et	H	$(CH_2)_4CH_3$	CH_3	H	H	CH_2CH_3	87	--
t	CO_2tBu	H	Ph	CH_3	H	H	CH_2CH_3	75	--
u	CO_2tBu	H	CH_3	CH_3	H	H	CH_2CH_3	64	--

[a] (1) LDA, THF, −78 °C; (2) R_3COR_4, −78 °C to room temperature. [b] NaOMe/MeOH, heat. [c] Refluxing bromobenzene (156 °C).

Scheme V



[a] (1) LDA; (2) acetone. [b] H_2O. [c] NaH/THF, heat.

conditions (base in refluxing tetrahydrofuran). This mechanism was supported by the formation of the alkyl 2-vinylindole-3-carboxylates **6s–v** (R_7 = Me or Et; Scheme IV) and by the isolation (78%) and characterization of the carbonate **9u** via quenching the reaction solution at −78 °C after the addition of acetone (Scheme V).

Although there were no attempts to hydrolyze and decarboxylate these 2-vinylindoles, there is ample literature evidence that this is a straightforward transformation.[11]

As one would expect, the relative size of R_3 and R_4 dictated the cis:trans ratio of the olefins formed in Scheme IV. When R_4 was H and R_3 was alkyl or phenyl, the trans olefin was the only product seen in the reaction as shown by the typical trans coupling constant of the olefin in the isolated product. When the relative sizes of the two groups were similar, a mixture of olefins was produced, with the trans olefin assumed to be predominate on the basis of chemical precedent and analogy. Finally, it is worth noting that this method has the ability to form tetrasubstituted olefins, as shown by the formation of **6q**. The NMR spectrum of **6q** attested to the steric congestion surrounding the tetrasubstituted olefin in that molecule as hindered rotation of the (benzyloxy)methylene group on N1 led to the protons on the animal methylene appearing as a pair of AB doublets.

In conclusion, we have demonstrated a useful synthesis of some pyrano[4,3-*b*]indoles and the use of that heterocycle as a precursor to 2-vinylindoles. Work continues in our laboratories exploring further uses of these compounds.

(11) Brown, R. K. The Synthesis of the Indole Nucleus. Houlihan, W. J., Ed. In the series *The Chemistry of Heterocyclic Compounds*; Weissberger, A. W., Taylor, E. C., Eds.; Wiley: New York, 1972; Vol. 25, Part 1, p 414.

Experimental Section

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 obtained on either a Bruker AM-300 (300 MHz) or a Varian XL300 (300 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 were obtained on a AEI MS-30 instrument. Elemental analyses were performed at Central Research Division, Pfizer, Inc., Groton, CT, and at Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich Gold Label tetrahydrofuran (THF) and diisopropylamine. General procedures listed here represent typical reaction procedures for the class of compounds described. Column chromatography was performed by using 32–63-μm silica gel and was executed under nitrogen pressure (flash chromatography) conditions. Room temperature refers to 20–25 °C.

General Synthesis of N-Substituted 2-Alkylindole-3-carboxylates (3). A mixture of the ethyl 2-alkylindole-3-carboxylate **2** (20.0 mmol) and sodium hydride (60% in oil, 0.88 g, 22.0 mmol, 1.1 equiv) in anhydrous THF (50 mL) was stirred at 0 °C under nitrogen for 2 h or until effervescence ceased for 15 min. To this solution was added the appropriate electrophile (22.0 mmol, 1.1 equiv), and the resulting reaction mixture was allowed to warm to room temperature. The mixture was then either stirred at room temperature under nitrogen or refluxed under nitrogen for times depending on substrate. A saturated aqueous solution of sodium bicarbonate (25 mL) was then added

to the resulting reaction mixture, and this aqueous mixture was extracted with ether (3 × 25 mL). The ether extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The extraction residue was purified by either recrystallization or column chromatography using silica gel (approximately 100 g) and elution with an appropriate solvent system depending on substrate to afford the desired 1-substituted 2-alkylindole-3-carboxylate **3**.

Ethyl 1,2-Dimethylindole-3-carboxylate (3a). Ethyl 2-methylindole-3-carboxylate[8a] and methyl iodide were used, and the reaction time was 2 h at room temperature. The extraction residue was passed through a silica gel filter followed by 1:1 ether/hexanes to yield **3a** (99%) as a white, crystalline solid: mp 92.0–94.0 °C (lit.[12] mp 95 °C); ^{1}H NMR ($CDCl_3$) δ 8.13–8.09 (m, 1 H), 7.26–7.19 (m, 3 H), 4.38 (q, J = 7.3 Hz, 2 H), 3.64 (s, 3 H), 2.74 (s, 3 H), 1.44 (t, J = 7.1 Hz, 3 H).

Ethyl 1,2-Dimethyl-5-methoxyindole-3-carboxylate (3b). A mixture of ethyl 5-hydroxy-2-methylindole-3-carboxylate[13] (30.0 g, 137 mmol), sodium hydride (60% in oil, 6.90 g, 172 mmol, 1.3 equiv), and anhydrous THF (500 mL) was stirred at 0 °C under nitrogen for 1 h. Then methyl iodide (9.0 mL, 145 mmol, 1.1 equiv) was added, and the resulting mixture was stirred at room temperature under nitrogen for 3 h. The mixture was then cooled to 0 °C, and more sodium hydride (60% in oil, 6.90 g, 172 mmol, 1.3 equiv) was added, and this mixture was stirred at 0 °C under nitrogen for 1 h. Methyl iodide (9.0 mL, 145 mmol, 1.1 equiv) was again added, and the resulting mixture was stirred at room temperature under nitrogen for an additional 24 h. Water (200 mL) was then added to this mixture, and the resulting mixture was extracted with ether (3 × 100 mL). These extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was dissolved in methylene chloride (50 mL), and this solution was passed through a silica gel filter (approximately 1 kg) followed by an elution of 20% ethyl acetate in hexanes (6 L). This filtrate was then evaporated under reduced pressure to yield **3b** (27.08 g, 110 mmol, 80%) as a white, crystalline solid: mp 117.5–118.0 °C (lit.[14] mp 122–124 °C); IR (KBr) 1645, 1610, 1590, 1465, 1445, 1425, 1405, 1350, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 2.5 Hz, 1 H), 7.15 (d, J = 8.8 Hz, 1 H), 6.85 (dd, J = 2.5 and 8.8 Hz, 1 H), 4.38 (q, J = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.64 (s, 3 H), 2.72 (s, 3 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.2, 155.6, 145.3, 131.6, 127.4, 111.6, 109.7, 103.6, 59.3, 55.7, 29.7, 14.6, 12.0; LRMS (m/z, rel intensity) 248 (18), 247 (M^+, 100), 218 (49), 232 (14), 218 (49), 202 (74), 175 (43), 131 (34), 130 (31), 101 (20). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 6.91; N, 5.50.

Ethyl 2-Ethyl-1-methylindole-3-carboxylate (3c). Ethyl 2-ethylindole-3-carboxylate[8b] and methyl iodide were used, and the reaction time was 5 h at room temperature. Recrystallization of extraction residue in hexanes yielded **3c** (92%) as a white, crystalline solid: mp 78.5–79.5 °C; IR (KBr) 1685, 1530, 1480, 1475, 1450, 1445, 1410, 1280, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14–8.10 (m, 1 H), 7.31–7.20 (m, 3 H), 4.38 (q, J = 7.4 Hz, 2 H), 3.72 (s, 3 H), 3.23 (q, J = 7.5 Hz, 2 H), 1.43 (t, J = 7.3 Hz, 3 H), 1.25 (t, J = 7.6 Hz, 3 H); LRMS (m/z rel intensity) 232 (32), 231 (M^+, 100), 202 (37), 188 (66), 186 (88), 184 (37), 159 (49), 158 (75), 143 (53), 115 (37). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.66; H, 7.46; N, 6.01.

Ethyl 1-[(Benzyloxy)methyl]-2-methylindole-3-carboxylate (3d). Ethyl 2-methylindole-3-carboxylate and benzyl chloromethyl ether were used, and the reaction was heated at reflux (66 °C) for 2 h. Chromatography of the extraction residue using silica gel and elution with 15% ethyl acetate in hexanes afforded **3d** (78% actual, 100% conversion based on returned starting material) as a clear pale yellow oil, which crystallized on cooling: mp 49.0–50.5 °C; IR (KBr) 1690, 1550, 1460, 1410, 1385, 1335, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.17–8.14 (m, 1 H), 7.38–7.22 (m, 8 H), 5.57 (s, 2 H), 4.44 (s, 2 H), 4.42 (q, J = 7.1 Hz, 2 H), 2.81 (s, 3 H), 1.47 (t, 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 145.3, 136.8, 136.6, 128.6, 128.1, 127.7, 126.7, 122.6, 122.1, 121.6, 109.4, 105.9, 71.7, 69.9, 59.6, 14.6, 11.7; LRMS (m/z rel intensity) 324 (47), 323 (M^+, 100), 293 (45), 217 (18), 144 (16), 91 (57), 87 (27), 85 (84), 83 (97). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 73.95; H, 6.52; N, 4.34.

Ethyl 1-[(Benzyloxy)methyl]-2-ethylindole-3-carboxylate (3e). Ethyl 2-ethylindole-3-carboxylate and benzyl chloromethyl ether were used, and the reaction was heated at reflux (66 °C) for 2 h. Column chromatography of the extraction residue using silica gel and elution with 10% ethyl acetate in hexanes yielded **3e** (83%) as a pale yellow oil: IR ($CHCl_3$) 1690, 1540, 1460, 1420, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19–8.16 (m, 1 H), 7.40–7.24 (m, 8 H), 5.59 (s, 2 H), 4.47 (s, 2 H), 4.42 (q, J = 7.1 Hz, 2 H), 3.27 (q, J = 7.5 Hz, 2 H), 1.47 (t, J = 7.5 Hz, 3 H), 1.29 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 151.1, 136.8, 136.6, 128.6, 128.1, 127.8, 126.8, 122.6, 122.2, 121.7, 109.6, 105.1, 71.6, 70.1, 59.6, 19.0, 14.6, 14.2; LRMS (m/z, rel intensity) 338 (22), 337 (M^+, 66), 307 (20), 292 (14), 262 (15), 231 (53), 158 (49), 91 (100). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.38; H, 6.86; N, 4.13.

Ethyl 1-(*tert*-Butoxycarbonyl)-2-methylindole-3-carboxylate (3f). Ethyl 2-methylindole-3-carboxylate and di-*tert*-butyl dicarbonate were used, and the reaction time was 48 h at room temperature. Column chromatography of the extraction residue using silica gel and elution with 3% ethyl acetate in hexanes yielded **3f** (85%) as a white solid: mp 67.0–69.0 °C; IR (KBr) 1740, 1695, 1560, 1460, 1375, 1355, 1320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07–8.01 (m, 2 H), 7.26–7.20 (m, 2 H), 4.40 (q, J = 7.3 Hz, 2 H), 2.96 (s, 3 H), 1.68 (s, 9 H), 1.44 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.5, 150.0, 145.8, 135.5, 127.2, 124.1, 123.6, 121.3, 114.9, 110.4, 85.0, 60.1, 28.2, 15.0, 14.5; LRMS (m/z, rel intensity) 304 (27), 303 (M^+, 54), 248 (41), 247 (89), 203 (74), 174 (45), 158 (63), 57 (100). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.40; H, 7.09; N, 4.62.

Ethyl 1-(Ethoxycarbonyl)-2-methylindole-3-carboxylate (3g).[15] A solution of 2-methylindole (57.7 mmol) and ethylmagnesium bromide (3 M in ether, 21.0 mL, 63 mmol, 1.1 equiv) in anhydrous THF (125 mL) was stirred at room temperature under nitrogen for 1 h. Then, ethyl chloroformate (6.0 mL, 62.7 mmol, 1.1 equiv) was added dropwise, and the resulting reaction mixture was stirred at reflux (66 °C) under nitrogen for 12 h. Then, sodium hydride (60% in oil, 2.30 g, 57.5 mmol, 1 equiv) was added, and this mixture was heated at reflux for 3 h and then stirred at room temperature for 12 h. A dilute solution of hydrochloric acid (3%, 50 mL) was added to the reaction mixture, and this aqueous mixture was extracted with ethyl acetate (3 × 50 mL). These extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was dissolved in ether, and upon cooling of this solution a solid precipitated. This solid was filtered to yield **3g** (4.35 g, 15.80 mmol, 27%) as a pale pink, crystalline solid: mp 93.5–95.5 °C; IR (KBr) 1735, 1695, 1605, 1560, 1480, 1470, 1455, 1435, 1315, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09–8.04 (m, 2 H), 7.29–7.24 (m, 2 H), 4.52 (q, J = 7.4 Hz, 2 H), 4.40 (q, J = 7.4 Hz, 2 H), 2.97 (s, 3 H), 1.49 (t, J = 7.4 Hz, 3 H), 1.44 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.3, 151.6, 145.9, 135.3, 127.3, 124.3, 123.8, 121.4, 115.1, 110.9, 63.8, 60.2, 14.9, 14.5, 14.3; LRMS (m/z rel intensity) 276 (17), 275 (M^+, 100), 230 (19), 202 (18), 186 (26), 174 (34), 158 (63), 130 (33). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.30; H, 6.12; N, 5.18.

Ethyl 1-(*p*-Tolylsulfonyl)-2-methylindole-3-carboxylate (3h). Ethyl 2-methylindole-3-carboxylate and *p*-toluenesulfonyl chloride were used, and the reaction time was 12 h at room temperature. Chromatography of the extraction residue using silica gel and elution with ether/hexanes (1:4) yielded **3h** (62% actual, 85% conversion based on returned starting material) as a white solid: mp 108.0–110.0 °C; IR (KBr) 1655, 1600, 1590, 1585, 1540, 1525, 1495, 1390, 1385, 1315, 1190, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25–8.22 (m, 1 H), 8.06–8.03 (m, 1 H), 7.69 (d, J = 8.6 Hz, 2 H), 7.34–7.28 (m, 2 H), 7.21 (d, J = 8.4 Hz, 2 H), 4.37 (q, J = 7.2 Hz, 2 H), 2.96 (s, 3 H), 2.33 (s, 3 H), 1.41 (t, J = 7.1 Hz,

(12) (a) Kornet, M. J.; Thio, A. P.; Tolbert, L. M. *J. Org. Chem.* **1980**, *45*, 30. (b) Degen, J. *Justus Liebigs Ann.* **1886**, *236*, 157.
(13) Aldrich Chemical Co.
(14) Parr, R. W.; Reiss, J. A. *Aust. J. Chem.* **1984**, *37*, 1263.

(15) This procedure was designed to yield ethyl 2-methylindole-3-carboxylate, but fortuitously provided ample quantities of the *N*-carbethoxy-protected analogue **3g**, which we ultimately desired. This procedure in no way represents an optimized procedure for the formation of **3g**. Optimization of this procedure, although not studied, should include use of an excess of 2 equiv of ethyl chloroformate in the reaction.

3 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 145.5, 145.0, 135.9, 130.1, 127.3, 126.6, 124.7, 124.3, 121.7, 114.2, 111.6, 60.4, 21.6, 14.4, 13.8; LRMS (*m/z* rel intensity) 358 (8), 357 (M^+, 35), 202 (34), 174 (31), 157 (34), 155 (54), 146 (57), 130 (29), 91 (100). Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.83; H, 5.27; N, 3.82.

General Procedure for the Synthesis of Ethyl 2-(2-Hydroxyalkyl)-5-methoxyindole-3-carboxylates (4). To a stirred solution of lithium diisopropylamide (7.5 mmol made from 1.05 mL of diisopropylamine and 3.0 mL of 2.5 M *n*-butyllithium in hexanes, 1.5 equiv) in anhydrous THF (15 mL) at −78 °C under nitrogen was added rapidly a solution of ethyl 5-methoxy-2-methylindole-3-carboxylate (**3b**, 5.00 mmol) in anhydrous THF (10 mL) while maintaining the reaction temperature below −40 °C. The resultant yellow solution was stirred at −78 °C for 15 min, at which time a solution of the appropriate aldehyde or ketone (7.5 mmol, 1.5 equiv) in anhydrous THF (10 mL) was added dropwise, maintaining the reaction temperature below −60 °C. The resultant reaction solution was stirred at −78 °C under nitrogen for 30 min, at which time a solution of saturated sodium hydrogen carbonate (20 mL) was added to quench the reaction. This reaction mixture was then warmed to room temperature and was extracted with methylene chloride (3 × 25 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The extractive residue was purified either by trituration in ether or column chromatography using silica gel (approximately 100 g) and elution with an appropriate solvent system to afford **4**.

Ethyl 2-[(1-Hydroxycyclohexyl)methyl]-5-methoxyindole-3-carboxylate (4a). The electrophile used was cyclohexanone. The extraction residue was chromatographed eluting with ether/hexanes (1:2) to afford **4a** (87%) as a white solid: mp 123.0–126.0 °C; IR (KBr) 3450, 1670, 1650, 1615, 1580, 1515, 1485, 1445, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 2.2 Hz, 1 H), 7.16 (d, *J* = 8.9 Hz, 1 H), 6.86 (dd, *J* = 2.7 and 8.9 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.30 (br s, 2 H), 1.66–1.41 (m, 9 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 1.28–1.12 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.9, 155.8, 145.9, 132.2, 127.1, 111.9, 110.2, 105.5, 104.0, 72.9, 59.9, 55.7, 38.5, 38.4, 31.0, 25.8, 21.9, 14.5; LRMS (*m/z*, rel intensity) 345 (M^+, 9), 248 (29), 247 (100), 218 (30), 201 (26), 175 (23). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.43; H, 8.00; N, 4.02.

Ethyl 2-(2-Hydroxy-2-methylpropyl)-5-methoxyindole-3-carboxylate (4b). The electrophile used was acetone. The extraction residue was chromatographed eluting with ethyl acetate/hexanes (1:2) to afford **4b** (83%) as a white solid: mp 129.0–130.0 °C; IR ($CHCl_3$) 3405, 1660, 1620, 1585, 1510, 1480, 1380, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J* = 2.7 Hz, 1 H), 7.19 (d, *J* = 8.9 Hz, 1 H), 6.88 (dd, *J* = 2.7 and 8.9 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.38 (br 2, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.8, 155.9, 146.0, 132.2, 127.1, 112.1, 110.3, 105.5, 104.1, 72.4, 59.9, 55.7, 38.1, 30.8, 30.2, 14.5; LRMS (*m/z*, rel intensity) 306 (21), 305 (M^+, 52), 288 (17), 260 (16), 248 (40), 247 (100), 218 (63), 201 (60), 175 (66), 131 (35), 59 (58). Anal. Calcd for $C_{17}H_{23}NO_4$; C, 66.86; H, 7.59; N, 4.59. Found: C, 66.99; H, 7.68; N, 4.50.

Ethyl 2-(2-Hydroxy-2-phenylethyl)-5-methoxyindole-3-carboxylate (4c). The electrophile used was benzaldehyde. The extraction residue was chromatographed eluting with ethyl acetate/hexanes (1:2) to afford **4c** (79%) as a white solid: mp 128.0–130.0 °C; IR ($CHCl_3$) 3380, 1665, 1620, 1580, 1515, 1480, 1445, 1170, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, *J* = 2.2 Hz, 1 H), 7.35–7.23 (m, 5 H), 7.12 (d, *J* = 9.0 Hz, 1 H), 6.87 (dd, *J* = 2.8 and 8.9 Hz, 1 H), 5.16–5.08 (m, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 4.03 (d, *J* = 3.6 Hz, OH), 3.87 (s, 3 H), 3.63 (dd, *J* = 4.3 and 12.6 Hz, 1 H), 3.43 (dd, *J* = 6.6 and 12.6 Hz, 1 H), 3.30 (s, 3 H), 1.47 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 155.8, 145.3, 144.2, 131.9, 128.5, 127.6, 127.0, 125.6, 112.1, 110.3, 104.9, 103.8, 74.2, 60.0, 55.7, 36.0, 29.7, 14.6; LRMS (*m/z* rel intensity) 353 (M^+, 16), 248 (42), 247 (100), 232 (24), 218 (65), 201 (51), 175 (57), 79 (36). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.18; H, 6.55; N, 3.90.

Ethyl 2-((1-Hydroxypiperid-4-yl)methyl)-5-methoxyindole-3-carboxylate (4i). The electrophile was *N*-methyl-4-piperidone. The extraction residue was recrystallized in ether to yield **4i** (67%) as a white solid: mp 139.0–141.0 °C; IR (KBr) 3420, 1665, 1620, 1580, 1515, 1485, 1405, 1380, 1305, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, *J* = 2.2 Hz, 1 H), 7.18 (d, *J* = 8.9 Hz, 1 H), 6.87 (dd, *J* = 2.2 and 8.9 Hz, 1 H), 4.39 (br s, OH), 4.37 (q, *J* = 7.0 Hz, 2 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.32 (br s, 2 H), 2.62–2.58 (br d, 2 H), 2.34–2.24 (m, 2 H), 2.26 (s, 3 H), 1.85–1.75 (m, 2 H), 1.61–1.57 (br d, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H); LRMS (*m/z*, rel intensity) 360 (M^+, 3), 248 (13), 247 (76), 218 (18), 201 (13), 175 (19), 114 (100), 99 (23), 97 (44), 70 (34). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.33; H, 7.84; N, 7.63.

General Procedure for the Direct Synthesis of 1,4-Dihydropyrano[4,3-*b*]indoles (5) [Method A]. To a stirred solution of lithium diisopropylamide (7.5 mmol made from 1.05 mL of diisopropylamine and 3.0 mL of 2.5 M *n*-butyllithium in hexanes, 1.5 equiv) in anhydrous THF (15 mL) at −78 °C under nitrogen was added rapidly a solution of the appropriate ethyl 2-alkylindole-3-carboxylate **3** (5.00 mmol) in anhydrous THF (10 mL) while maintaining the reaction temperature below −40 °C. The resultant yellow solution was stirred at −78 °C for 15 min, at which time a solution of the appropriate aldehyde or ketone[16] (7.5 mmol, 1.5 equiv) in anhydrous THF (10 mL) was added dropwise maintaining the reaction temperature below −60 °C. This resultant reaction solution was then allowed to warm (usually to room temperature), and the course of the reaction was closely monitored by using thin-layer chromatography.[17] Quenching occurred at a temperature when the formation of the lactone appeared to be optimized as indicated by TLC. The reaction solution was quenched with a saturated solution of sodium bicarbonate (20 mL), and this aqueous mixture was extracted with methylene chloride (3 × 20 mL). These extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid or oil was then purified either via trituration with the appropriate solvent or column chromatography using silica gel (approximately 100 g) and elution with the appropriate solvent system to yield the desired 1,4-dihydropyrano[4,3-*b*]indole **5**.

Spiro[cyclohexane-1,3′-(8′-methoxy-5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5a). **3b** and cyclohexanone were used. The reaction solution was stirred at 10–20 °C for approximately 10 min before quenching. An NMR spectrum of the crude extraction residue shows a mixture of **5a** and **6a** in a ratio of 5:1, respectively. Chromatography of the crude extraction residue eluting with 4% ether in methylene chloride afforded **6a** (58%) as a white solid: mp 175.0–177.0 °C; IR (KBr) 1695, 1625, 1490, 1460, 1395, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, *J* = 2.4 Hz, 1 H), 7.14 (d, *J* = 8.9 Hz, 1 H), 6.85 (dd, *J* = 2.4 and 8.9 Hz, 1 H), 3.87 (s, 3 H), 3.61 (s, 3 H), 2.87 (s, 2 H), 2.07–2.00 (m, 2 H), 1.88–1.76 (m, 2 H), 1.60–1.31 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 163.1, 156.2, 145.3, 132.5, 126.2, 112.9, 110.3, 102.4, 100.9, 81.3, 60.4, 55.9, 36.6, 32.2, 30.0, 25.4, 21.8, 14.2; LRMS (*m/z* rel intensity) 300 (24), 299 (M^+, 63), 243 (16), 202 (36), 201 (100), 186 (22), 173 (49), 158 (19), 130 (26). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.06; H, 6.96; N, 4.58.

8-Methoxy-5-methyl-3-phenyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5c). **3b** and benzaldehyde were used. The reaction solution was stirred at 30 °C for 2 h before quenching. After quenching, a solid precipitated. This solid was filtered and triturated in methylene chloride to afford **6c** (35%), which was identical in all respects with the solid directly synthesized elsewhere in this paper. The extraction residue was chromatographed eluting with 2.5% ether in methylene chloride to afford **5c** (39%) as a white solid: mp 224.0–225.0 °C; IR (KBr) 1705, 1625, 1490, 1460, 1270, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, *J* = 2.8 Hz, 1 H), 7.50–7.47 (br d, 2 H), 7.43–7.35 (m, 3 H), 7.20 (d, *J* = 8.6 Hz, 1 H), 6.91 (dd, *J* = 2.1 and 8.9 Hz, 1 H), 5.59 (dd, *J* = 5.3 and 10.9 Hz, 1 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.26–3.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 163.4, 156.4, 146.0, 138.8, 132.6, 128.7, 128.7, 126.3, 126.3, 113.4, 110.5, 102.4, 101.6, 79.2, 55.9, 30.2, 29.6; LRMS (*m/z*, rel intensity) 308 (32), 307 (M^+, 69), 202 (33), 201 (100), 186 (28), 173 (57), 158 (26), 130 (33), 82 (27). Anal. Calcd for

(16) When applicable, liquid aldehdyes or ketones were added neat.

(17) The general order of TLC polarity of the possible products from this reaction was (least polar) alcohol **4** < olefin carboxylic acid **6** ≪ lactone **5** (most polar) in ethyl acetate/hexanes (1:3). In 5% ether/methylene chloride the polarity is reversed: lactone **5** < alcohol **4** ≪ olefin acid **6**.

$C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.96; H, 5.44; N, 4.48.

3,5-Dimethyl-8-methoxy-3-phenyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5d). 3b and acetophenone were used. The reaction solution was warmed to 40 °C for 15 min before quenching. Chromatography of the extraction residue eluting with 3.5% ether in methylene chloride afforded **5d** (32%) as a white, crystalline solid: mp 144.0 °C; IR (KBr) 1700, 1625, 1495, 1460, 1390, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, J = 2.5 Hz, 1 H), 7.47–7.43 (br d, 2 H), 7.31–7.25 (br t, 2 H), 7.22–7.15 (m, 1 H), 7.10 (d, J = 8.8 Hz, 1 H), 6.83 (dd, J = 2.5 and 8.9 Hz, 1 H), 3.84 (s, 3 H), 3.62 (s, 3 H), 3.45 (d, J = 16.8 Hz, 1 H), 3.25 (d, J = 16.8 Hz, 1 H), 1.79 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.2, 156.3, 145.2, 144.4, 132.5, 128.6, 127.6, 126.1, 124.4, 113.1, 110.4, 102.4, 101.7, 83.2, 55.8, 33.2, 30.6, 30.1; LRMS (m/z rel intensity) 322 (29), 321 (M^+, 67), 202 (37), 201 (100), 186 (23), 173 (58), 158 (27), 130 (40), 105 (31), 77 (41). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.59; H, 5.98; N, 4.28.

8-Methoxy-5-methyl-3-propyl-[2*H*]-1,4-dihydropyrano-[4,3-*b*]indole (5e). 3b and butyraldehyde were used. The reaction solution was stirred at room temperature for 10 min before quenching. Chromatography of the extraction residue eluting with ethyl acetate/hexanes (1:2) afforded **5e** (63%) as a white solid: mp 194.0–197.0 °C; IR (KBr) 1700, 1625, 1490, 1450, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (d, J = 2.5 Hz, 1 H), 7.14 (d, J = 8.9 Hz, 1 H), 6.86 (dd, J = 2.5 and 8.9 Hz, 1 H), 4.58–4.49 (m, 1 H), 3.86 (s, 3 H), 3.61 (s, 3 H), 2.85 (dd, J = 4.5 and 16.6 Hz, 1 H), 2.78 (dd, 11.1 and 16.7 Hz, 1 H), 1.96–1.84 (m, 1 H), 1.75–1.46 (m, 3 H), 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.0, 156.2, 146.4, 132.5, 126.2, 113.1, 110.4, 102.4, 101.5, 77.5, 55.9, 37.2, 30.1, 27.1, 18.4, 13.9; LRMS (m/z rel intensity) 274 (31), 273 (M^+, 100), 230 (21), 202 (42), 201 (100), 186 (24), 173 (47), 158 (19), 130 (30). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.18; H, 6.86; N, 5.15.

3,3-Diphenyl-8-methoxy-5-methyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5f). 3b and benzophenone were used. The reaction solution was warmed to 50 °C over 5 min before quenching. Chromatography of the extraction residue eluting with 2.5% ether in methylene chloride first afforded **5f** (17% actual, 22% based on returned starting indole) (R_f = 0.3 in 2.5% ether in methylene chloride) as a white, crystalline solid: mp 248.0–249.0 °C; IR (KBr) 1715, 1705, 1625, 1500, 1460, 1275 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.58 (d, J = 7.4 Hz, 4 H), 7.44 (d, J = 8.9 Hz, 1 H), 7.37–7.32 (br t, 4 H), 7.25–7.20 (m, 3 H), 6.84 (dd, J = 2.4 and 8.9 Hz, 1 H), 4.19 (s, 2 H), 3.86 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 161.8, 155.7, 147.5, 144.2, 132.3, 128.5, 127.5, 125.5, 125.4, 112.1, 111.7, 101.3, 100.9, 85.9, 55.3, 31.4, 30.3; LRMS (m/z, rel intensity) 384 (7), 383 (M^+, 19), 202 (26), 201 (100), 186 (11), 173 (24), 158 (12), 130 (17), 105 (18), 77 (15). Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.07; H, 5.40; N, 3.64. Further elution afforded **6f** (26% actual, 33% based on returned starting indole) (R_f = 0.2 in 2.5% ether in methylene chloride) as yellow needles: mp 214.0–216.0 °C (with effervescence); IR (KBr) 1640, 1590, 1510, 1475 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.53 (d, J = 2.4 Hz, 1 H), 7.42 (s, 5 H), 7.25–7.17 (m, 5 H), 7.01–6.97 (m, 2 H), 6.80 (dd, J = 2.4 and 8.9 Hz, 1 H), 3.79 (s, 3 H), 3.07 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.1, 155.3, 146.7, 143.3, 141.7, 139.4, 131.6, 129.7, 128.5, 128.4, 128.3, 128.1, 127.2, 118.9, 112.3, 111.3, 105.2, 102.6, 55.3, 30.9; LRMS (m/z rel intensity) 384 (29), 383 (M^+, 100), 338 (86), 337 (58), 323 (22), 307 (17), 294 (17), 170 (18); HRMS calcd for $C_{25}H_{21}NO_3$ 383.1521, found 383.1502.

Spiro[8-methyl-8-azabicyclo[3.2.1]octane-3,3′-(8′-methoxy-5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5g). 3b and tropinone were used. The reaction solution was stirred at room temperature for 2 h before quenching. Trituration of the extraction residue with ether afforded **5g** (79%) as a white powder: mp 258.0–261.0 °C (with effervescence); IR (KBr) 1695, 1620, 1495, 1455, 1410, 1390, 1275, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, J = 2.2 Hz, 1 H), 7.13 (d, J = 9.0 Hz, 1 H), 6.84 (dd, J = 2.2 and 8.9 Hz, 1 H), 3.85 (s, 3 H), 3.56 (s, 3 H), 3.14–3.06 (br m, 2 H), 2.79 (s, 2 H), 2.26 (s, 3 H), 2.22–2.16 (m, 4 H), 2.02–1.96 (m, 2 H), 1.91–1.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 163.1, 156.2, 145.1, 132.4, 126.1, 113.0, 110.3, 102.2, 101.1, 79.9, 60.2, 55.8, 43.4, 40.6, 35.5, 30.0, 25.2; LRMS (m/z, rel intensity) 341 (3), 340 (M^+, 12), 259 (10), 243 (6), 201 (8), 110 (12), 98 (100), 97 (35), 96 (34), 82 (74). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.17; H, 7.06; N, 8.09.

Spiro[1-(*tert*-butoxycarbonyl)piperidine-4,3′-(8′-methoxy-5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5h). 3b and *N*-(*tert*-butoxycarbonyl)-4-piperidone were used. The reaction solution was stirred at 0 °C for 7 h before quenching. An NMR spectrum of the crude extraction residue indicated a 4:1.5:1 ratio of lactone **5h**:olefin carboxylic acid **6h**:alcohol **4h**. Chromatography of the extraction residue eluting with ether yielded first (R_f = 0.6 in ether) an oil which was crystallized in ether to yield **6h** (5%) as a white solid: mp 160–165 °C (with efferevescence); IR (KBr) 1690, 1645, 1480, 1460, 1430, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 2.5 Hz, 1 H), 7.22 (d, J = 8.9 Hz, 1 H), 6.93 (dd, J = 2.5 and 8.9 Hz, 1 H), 6.41 (br s, 1 H), 3.92 (s, 3 H), 3.63 (s, 3 H), 3.64–3.54 (br m, 2 H), 3.45–3.33 (br m, 2 H), 2.51–2.45 (br t, 2 H), 2.15 (t, J = 5.5 Hz, 2 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 156.2, 154.7, 145.9, 144.2, 132.0, 127.8, 114.0, 113.0, 110.4, 104.0, 103.6, 79.8, 56.0, 35.7, 30.8, 30.7, 30.7, 28.4; LRMS (m/z, rel intensity) 400 (M^+, 7), 344 (32), 300 (21), 281 (13), 239 (25), 238 (34), 226 (89), 212 (40), 81 (22), 57 (100). Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.78; H, 6.91; N, 7.01. Further elution yielded another oil (R_f = 0.5 in ether) which was crystallized in ether to yield **4h** (10%) as a white solid: mp 136.5–138.0 °C; IR (KBr) 3365, 1690, 1655, 1510, 1485, 1415, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (d, J = 2.5 Hz, 1 H), 7.20 (d, J = 8.9 Hz, 1 H), 6.90 (dd, J = 2.5 and 8.9 Hz, 1 H), 4.53 (br s, OH), 4.39 (q, J = 7.1 Hz, 2 H), 4.03–3.86 (br m, 2 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.43–3.27 (m, 2 H), 3.19–3.00 (m, 2 H), 1.73–1.51 (m, 4 H), 1.46 (t, J = 7.1 Hz, 3 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.4, 156.0, 154.9, 144.9, 132.2, 127.0, 112.3, 110.3, 105.8, 104.1, 79.3, 71.1, 60.2, 55.7, 39.6, 38.3, 38.0, 30.9, 28.5, 14.5; LRMS (m/z rel intensity) 446 (M^+, 2), 248 (28), 247 (100), 218 (22), 201 (22), 175 (17), 57 (27). Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 64.56; H, 7.67; N, 6.27. Found: C, 64.34; H, 7.49; N, 6.48. Still further elution yielded **5h** (55%) as a white solid: mp 236.0–237.5 °C; IR (KBr) 1685, 1620, 1540, 1500, 1460, 1440, 1415, 1405, 1390, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 2.8 Hz, 1 H), 7.20 (d, J = 8.9 Hz, 1 H), 6.90 (dd, J = 2.3 and 8.9 Hz, 1 H), 3.93–3.82 (br m, 2 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.41–3.31 (br m, 2 H), 2.96 (s, 2 H), 2.13–2.02 (m, 2 H), 1.67–1.53 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 162.3, 156.4, 154.7, 124.4, 132.5, 126.1, 113.2, 110.4, 102.3, 100.8, 79.7, 78.8, 55.9, 39.5, 36.0, 32.9, 30.1, 28.4; LRMS (m/z, rel intensity) 401 (16), 400 (M^+, 48), 327 (10), 256 (16), 241 (11), 227 (41), 226 (65), 212 (13), 201 (57), 173 (12), 57 (100); HRMS calcd for $C_{22}H_{28}N_2O_5$ 400.1998, found 400.1996. Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.68; H, 6.88; N, 6.87.

Spiro[8-methyl-8-azabicyclo[3.2.1]octane-3,3′-(5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5j). 3a and tropinone were used. The reaction solution was stirred at room temperature for 2 h before quenching. Trituration of the extraction residue with ether afforded **5j** (58%) as a white solid: mp 209.0–210.0 °C; IR (KBr) 1695, 1670, 1485, 1455, 1415 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07–8.03 (m, 1 H), 7.28–7.22 (m, 3 H), 3.62 (s, 3 H), 3.15–3.06 (br m, 2 H), 2.85 (s, 2 H), 2.26 (s, 3 H), 2.26–2.18 (m, 4 H), 2.05–1.88 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 162.9, 145.2, 137.6, 125.3, 122.9, 122.4, 120.7, 109.5, 101.5, 79.9, 60.3, 43.4, 40.6, 35.4, 29.9, 25.2; LRMS (m/z, rel intensity) 311 (7), 310 (M^+, 40), 229 (15), 171 (16), 143 (17), 115 (14), 110 (23), 98 (100), 97 (48), 96 (62), 82 (91); HRMS calcd for $C_{19}H_{22}N_2O_2$ 310.1681, found 310.1684. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.14; H, 7.10; N, 8.93.

Spiro[1-(*tert*-butoxycarbonyl)piperidine-4,3′-(5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5k). 3a and *N*-(*tert*-butoxycarbonyl)-4-piperidone were used. The reaction solution was stirred at 0 °C for 7 h before quenching. Chromatography of the extraction residue eluting with ether afforded an oil (R_f = 0.7 in ether) which was crystallized in ether to yield **6k** (19%) as a white solid: mp 174.5–175.0 °C (with effervescence); IR (KBr) 1690, 1655, 1505, 1470, 1425, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29–8.26 (m, 1 H), 7.34–7.26 (m, 3 H), 6.42 (s, 1 H), 3.66 (s, 3 H), 3.66–3.53 (br m, 2 H), 3.46–3.33 (br m, 2 H), 2.55–2.45 (br t, 2 H), 2.14 (t, J = 5.6 Hz, 2 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 154.7, 146.1, 144.2, 136.9, 127.1, 122.7, 122.3, 122.0, 113.8, 109.6, 104.4, 79.7, 35.7, 30.7, 28.4; LRMS (m/z, rel intensity) 370 (M^+, 2), 314 (25), 270 (11), 209 (21), 208 (22), 197 (25), 196 (100),

182 (19), 57 (75). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.03; H, 7.13; N, 7.51. Further elution yielded a foam (R_f = 0.20 in ether) which was crystallized in ether to afford **5k** (52%) as a white, crystalline solid: mp 203.5–207.5 °C (with efferevescence); IR (KBr) 1700, 1685, 1555, 1480, 1420, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09–8.06 (m, 1 H), 7.34–7.24 (m, 3 H), 3.96–3.76 (br m, 2 H), 3.68 (s, 3 H), 3.42–3.24 (br m, 2 H), 2.96 (s, 2 H), 2.12–2.08 (br d, 2 H), 1.68–1.56 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 162.1, 154.7, 144.6, 137.7, 125.3, 123.1, 122.6, 120.7, 109.6, 101.0, 79.7, 78.8, 39.5, 36.0, 32.8, 30.0, 28.4; LRMS (m/z, rel intensity) 371 (15), 370 (M^+, 61), 297 (25), 270 (10), 226 (33), 211 (17), 197 (67), 196 (83), 171 (58), 143 (40), 81 (77), 57 (100). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.89; H, 6.99; N, 7.33.

Spiro[cyclohexane-1,3′-(4′,5′-dimethyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5l). **3c** and cyclohexanone were used. The reaction solution was heated at reflux (66 °C) for 24 h. The extraction residue was recrystallized in ether to afford **5l** (43%) as a white, crystalline solid: mp, 186.0–189.0 °C; IR (KBr) 1685, 1615, 1580, 1545, 1480, 1460, 1440, 1395 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11–8.07 (m, 1 H), 7.35–7.21 (m, 3 H), 3.72 (s, 3 H), 2.98 (q, J = 7.0 Hz, 1 H), 2.09–1.97 (m, 2 H), 1.97–1.84 (m, 1 H), 1.70–1.50 (m, 4 H), 1.48–1.31 (m, 3 H), 1.23 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.8, 151.4, 137.7, 125.3, 122.8, 122.3, 120.9, 109.6, 100.1, 83.2, 35.3, 34.4, 33.6, 29.7, 25.4, 22.3, 21.5, 14.5; LRMS (m/z, rel intensity) 284 (9), 283 (M^+, 44), 227 (9), 186 (27), 185 (100), 157 (32), 156 (21), 115 (12). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.31; H, 7.32; N, 4.95.

3-Propyl-4-(*p*-tolylsulfonyl)-[2*H*]-1,4-dihydropyrano-[4,3-*b*]indole (5m). **3h** and butyraldehyde were used. The reaction solution was quenched at −78 °C. Chromatography of the extraction residue eluting with ether/hexanes (1:3) afforded **5m** (23%) as a white powder: mp 160.0–162.0 °C; IR (KBr) 1715, 1595, 1570, 1485, 1465, 1420, 1380, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11–8.06 (m, 2 H), 7.72 (d, J = 8.2 Hz, 2 H), 7.38–7.30 (m, 2 H), 7.26 (d, J = 8.6 Hz, 2 H), 4.64–4.54 (m, 1 H), 3.60 (dd, J = 4.0 and 18.1 Hz, 1 H), 3.09 (dd, J = 11.5 and 18.1 Hz, 1 H), 2.36 (s, 3 H), 1.99–1.85 (m, 1 H), 1.85–1.48 (m, 3 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.7, 146.2, 145.4, 136.1, 135.1, 130.4, 126.6, 126.1, 125.6, 125.0, 121.3, 114.0, 109.3, 78.1, 36.9, 29.3, 21.7, 18.4, 13.8; LRMS (m/z, rel intensity) 385 (14), 384 (36), 383 (M^+, 61), 311 (11), 247 (61), 228 (17), 212 (23), 211 (15), 183 (34), 158 (18), 156 (100), 155 (57), 128 (74), 91 (88), 65 (23). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.97; H, 5.70; N, 3.41.

3,3-Dimethyl-4-(*p*-tolylsulfonyl)-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5n). **3h** and acetone were used. The reaction solution was quenched when the reaction temperature reached −40 °C. The extraction residue was chromatographed eluting with methylene chloride/hexanes (2:1) to afford **5n** (43%) as a white solid: mp 137.0–140.0 °C; IR (KBr) 1710, 1660, 1595, 1575, 1485, 1450, 1420, 1410, 1380, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12–8.03 (m, 2 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.37–7.29 (m, 2 H), 7.24 (d, J = 8.2 Hz, 2 H), 3.42 (s, 2 H), 2.34 (s, 3 H), 1.51 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 162.2, 146.2, 144.5, 136.1, 135.1, 130.3, 126.6, 126.0, 125.5, 125.0, 121.3, 114.0, 108.6, 81.0, 35.3, 27.9, 21.6; LRMS (m/z, rel intensity) 370 (9), 369 (M^+, 28), 247 (42), 197 (18), 157 (28), 156 (100), 128 (65), 91 (67). Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 65.06; H, 5.22; N, 3.84.

4-[(Benzyloxy)methyl]-3-propyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5o). **3d** and butyraldehyde were used. The reaction solution was quenched when the temperature reached 5 °C. Chromatography of the extraction residue eluting with 1% ether in methylene chloride afforded **5o** (53%) as a white powder: mp 120.0–122.0 °C; IR ($CHCl_3$) 1705, 1560, 1455, 1400, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14–8.08 (m, 1 H), 7.41–7.19 (m, 8 H), 5.49 (s, 2 H), 4.60–4.52 (m, 1 H), 4.48 (d, J = 12.1 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 2.91–2.75 (m, 2 H), 1.96–1.84 (m, 1 H), 1.74–1.44 (m, 3 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.7, 146.4, 137.4, 136.3, 128.7, 128.3, 127.8, 125.5, 123.6, 122.9, 121.0, 110.0, 103.7, 77.7, 72.1, 70.3, 37.1, 27.1, 18.4, 13.9; LRMS (m/z, rel intensity) 350 (32), 349 (M^+, 52), 276 (14), 247 (44), 218 (18), 171 (46), 156 (24), 128 (37), 115 (33), 91 (100), 64 (32). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.21; H, 6.56; N, 3.80.

4-[(Benzyloxy)methyl]-3,3-dimethyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5p). **3d** and acetone were used. The reaction solution was stirred at 0 °C for 10 min. Chromatography of the extraction residue eluting with 2.5% ether in methylene chloride afforded **5p** (64%) as a clear, colorless oil: IR ($CHCl_3$) 1700, 1565, 1455, 1395, 1375, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15–8.09 (m, 1 H), 7.41–7.20 (m, 8 H), 5.49 (s, 2 H), 4.43 (s, 2 H), 2.97 (s, 2 H), 1.52 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 162.9, 145.6, 137.5, 136.3, 128.6, 128.3, 127.8, 125.4, 123.5, 122.9, 121.0, 110.0, 103.0, 80.5, 72.1, 70.2, 33.3, 28.1; LRMS (m/z rel intensity) 336 (59), 335 (M^+, 85), 318 (16), 247 (46), 246 (25), 228 (29), 218 (23), 214 (49), 171 (86), 170 (58), 156 (27), 128 (48), 91 (100), 65 (30); HRMS calcd for $C_{21}H_{21}NO_3$ 335.1522, found 335.1519.

4-[(Benzyloxy)methyl]-3,3,4-trimethyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5q). **3e** and acetone were used. The reaction solution was quenched when it reached 0 °C. Chromatography of the extraction residue afforded **5q** (84%) as a clear, colorless oil: IR ($CHCl_3$) 1700, 1560, 1465, 1460, 1400, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18–8.12 (m, 1 H), 7.45–7.24 (m, 8 H), 5.63 (d, J = 11.2 Hz, 1 H), 5.50 (d, J = 11.2 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 4.48 (d, J = 11.7 Hz, 1 H), 2.99 (q, J = 7.0 Hz, 1 H), 1.54 (s, 3 H), 1.45 (s, 3 H), 1.32 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.8, 151.2, 137.5, 136.4, 128.7, 128.4, 127.8, 125.3, 123.5, 122.9, 121.2, 109.9, 102.0, 82.7, 72.0, 70.4, 36.1, 27.4, 25.7, 16.0; HRMS calcd for $C_{22}H_{23}NO_3$ 349.1679, found 349.1687.

General Procedure for the Synthesis of 1,4-Dihydropyrano[4,3-*b*]indoles (5) via Acid-Catalyzed Lactonization of 2-(2-Hydroxyalkyl)indole-3-carboxylates (4) [Method B]. A solution of **4** (5.00 mmol) in either glacial acetic acid (25 mL) or in dioxane (20 mL) with *p*-toluenesulfonic acid (1.43 g, 7.5 mmol, 1.5 equiv) was heated at reflux under nitrogen for a time dependent on the substrate. The resulting reaction solution was evaporated under reduced pressure, the residue was partitioned between a saturated solution of sodium hydrogen carbonate (20 mL) and methylene chloride (25 mL), and this mixture was shaken well. The methylene chloride layer was removed, and the aqueous layer was extracted with additional methylene chloride (2 × 25 mL). The methylene chloride extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified via either trituration of the residual solid in ether or column chromatography using silica gel (approximately 100 g) and elution with the appropriate solvent system to afford **5**.

Spiro[cyclohexane-1,3′-(8′-methoxy-5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5a). A solution of **4a** in glacial acetic acid was heated at reflux (116 °C) for 10 h. Chromatography of the extraction residue eluting with ethyl acetate/hexanes (1:2) first afforded **6a** (9%) and then **5a** (73%) as a white solid identical in all respects with the analogous material synthesized via method A and fully characterized. Note: Use of *p*-toluenesulfonic acid in refluxing dioxane (101 °C) followed by the exact purification procedure afforded **5a** (35%).

3,3-Dimethyl-8-methoxy-5-methyl-[2*H*]-1,4-dihydropyrano[4,3-*b*]indole (5b). A solution of **4b** in glacial acetic acid was heated at reflux (116 °C) for 18 h. Chromatography of the extraction residue afforded **5b** (81%) as a white solid: mp 172.0–174.0 °C; IR ($CHCl_3$) 1695, 1625, 1490, 1460, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (d, J = 2.7 Hz, 1 H), 7.18 (d, J = 9.0 Hz, 1 H), 6.88 (dd, J = 2.7 and 8.9 Hz, 1 H), 3.87 (s, 3 H), 3.64 (s, 3 H), 2.95 (s, 2 H), 1.53 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 163.2, 156.3, 145.4, 132.5, 126.2, 113.1, 110.3, 102.3, 100.9, 80.1, 55.9, 33.4, 30.1, 28.2; LRMS (m/z, rel intensity) 260 (44), 259 (M^+, 94), 244 (18), 202 (37), 201 (100), 186 (48), 173 (67), 158 (36), 130 (47). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.36; H, 6.59; N, 5.36.

8-Methoxy-5-methyl-3-phenyl-[2*H*]-1,4-dihydropyrano-[4,3-*b*]indole (5c). A solution of **4c** in glacial acetic acid was heated at reflux (116 °C) for 22 h. Chromatography of the extraction residue eluting with ethyl acetate/hexanes (1:2) afforded **5c** (32%) as a white powder identical with the analogous material formed in method A.

Spiro[1-methylpiperidine-4,3′-(8′-methoxy-5′-methyl-[2*H*]-1′,4′-dihydropyrano[4,3-*b*]indole)] (5i). A solution of **4i** and *p*-toluenesulfonic acid in dioxane was heated at reflux (101 °C) for 31 h. Chromatography of the extraction residue using neutral alumina and eluting with 1% methanol in methylene chloride afforded **5i** (62%) as an off-white, crystalline solid: mp

218.0–220.0 °C: IR (KBr) 1680, 1620, 1580, 1540, 1495, 1460, 1420, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (d, J = 2.7 Hz, 1 H), 7.18 (d, J = 9.0 Hz, 1 H), 6.88 (dd, J = 2.7 and 8.9 Hz, 1 H), 3.86 (s, 3 H), 3.65 (s, 3 H), 2.93 (s, 2 H), 2.64–2.60 (br d, 4 H), 2.34 (s, 3 H), 2.17–2.13 (br d, 2 H), 1.86–1.76 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 162.6, 156.3, 144.7, 132.5, 126.2, 113.2, 110.4, 102.4, 100.8, 78.1, 55.9, 50.8, 45.8, 36.2, 32.8, 30.2; LRMS (m/z, rel intensity) 314 (M^+, 13), 243 (10), 203 (9), 112 (73), 96 (100), 70 (28); HRMS calcd for $C_{18}H_{22}N_2O_3$ 314.1630, found 314.1628.

General Synthesis of 2-Vinylindole-3-carboxylates (6). To a stirred solution of lithium diisopropylamide (12.0 mmol from 1.70 mL of diisopropylamine and 4.8 mL of 2.5 M *n*-butyllithium in hexanes, 1.5 equiv) in anhydrous THF (20 mL) at −78 °C under nitrogen was added a solution of the ethyl 2-alkylindole-3-carboxylate (**3**, 8.00 mmol) in anhydrous tetrahydrofuran (10 mL) dropwise rapidly. The resulting yellow/orange solution was stirred at −78 °C for 15 min, at which time a solution of the appropriate ketone or aldehyde[16] (12.0 mmol, 1.5 equiv) in anhydrous THF (10 mL) was added dropwise such that the reaction temperature was maintained below −50 °C. The resulting reaction solution was then allowed to warm to room temperature, and a solution of sodium hydride (60% in oil, 1.20 g, 30.0 mmol) in methanol or ethanol (10 mL) was added. The reaction solution was heated at reflux under nitrogen for 3–8 h depending on substrate. Water (20 mL) was then added to the reaction mixture, and the pH was adjusted to pH 3 with concentrated hydrochloric acid. This aqueous mixture was then extracted wit ethyl acetate (3 × 25 mL), and the extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The extraction residue was then either triturated with ether or column chromatographed by using silica gel (approximately 50 g) and elution with the appropriate solvent system to afford the 2-vinylindole-3-carboxylate **6**.

2-(Cyclohexylidenemethyl)-5-methoxy-1-methylindole-3-carboxylic Acid (6a). **3b** and cyclohexanone were used, and the THF/methanol reflux was for 5 h. Trituration of the extraction residue with ether yielded **6a** (50%) as a white, crystalline solid: mp 181.0–182.0 °C (with effervescence); IR (KBr) 3440, 1660, 1640, 1510, 1475, 1460, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J = 2.2 Hz, 1 H), 7.20 (d, J = 8.9 Hz, 1 H), 6.90 (dd, J = 2.2 and 9.0 Hz, 1 H), 6.26 (br s, 1 H), 3.91 (s, 3 H), 3.62 (s, 3 H), 2.41 (br t, 2 H), 2.03 (br t, 2 H), 1.77–1.68 (m, 2 H), 1.63–1.47 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 156.0, 150.5, 145.5, 131.9, 128.0, 112.6, 111.6, 110.3, 103.7, 103.6, 56.0, 36.8, 31.1, 30.8, 28.3, 27.1, 26.3; LRMS (m/z, rel intensity) 300 (44), 299 (M^+, 100), 282 (34), 254 (75), 218 (53). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.23; H, 7.15; N, 4.58.

5-Methoxy-1-methyl-2-(2-methyl-1-propenyl)indole-3-carboxylic Acid (6b). **3b** and acetone were used, and the THF/methanol reflux was for 3 h. Trituration of the extraction residue with ether yielded **6b** (86%) as an off-white solid: mp 166.0–169.0 °C (with effervescence); IR (KBr) 3440, 1635, 1605, 1580, 1500, 1480, 1445, 1430, 1390, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J = 2.2 Hz, 1 H), 7.21 (d, J = 8.9 Hz, 1 H), 6.90 (dd, J = 2.1 and 9.1 Hz, 1 H), 6.36 (t, J = 1.4 Hz, 1 H), 3.91 (s, 3 H), 3.61 (s, 3 H), 2.03 (d, J = 1.3 Hz, 3 H), 1.64 (d, J = 1.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.8, 156.1, 145.7, 143.2, 132.0, 128.0, 115.2, 112.7, 110.4, 103.6, 103.6, 56.0, 30.8, 25.7, 20.6; LRMS (m/z, rel intensity) 260 (25), 259 (M^+, 100), 244 (70), 242 (31), 214 (36), 199 (19). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.15; H, 6.63; N, 5.46.

5-Methoxy-1-methyl-2-(*trans*-benzylidene)indole-3-carboxylic Acid (6d). **3b** and benzaldehyde were used, and the THF/methanol reflux was for 5 h. Upon acidification of the aqueous reaction mixture, a solid precipitated which was filtered and triturated in methylene chloride/methanol (1:1) to yield **6d** (85%) as a pale yellow solid: mp 207.0–209.0 °C (with effervescence); IR (KBr) 3430, 1640, 1595, 1505, 1470, 1450, 1210, 1180 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.82 (d, J = 17.2 Hz, 1 H), 7.63 (br d, J = 7.3 Hz, 2 H), 7.57 (d, J = 2.2 Hz, 1 H), 7.46–7.30 (m, 4 H), 7.18 (d, J = 17.2 Hz, 1 H), 6.90 (dd, J = 2.7 and 8.9 Hz, 1 H), 3.87 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.3, 155.2, 142.8, 136.8, 135.3, 132.9, 128.9, 128.5, 127.2, 126.8, 118.3, 112.8, 111.3, 104.8, 102.9, 55.3, 32.2; LRMS (m/z, rel intensity) 308 (20), 307 (M^+, 100), 263 (62), 262 (58), 261 (27), 247 (29), 231 (19), 218 (21), 204 (15). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.96; H, 5.60; N, 4.67.

5-Methoxy-1-methyl-2-(*trans*-1-pentenyl)indole-3-carboxylic Acid (6e). **3b** and butyraldehyde were used, and the THF/methanol reflux was for 8 h. Chromatography of the extraction residue [elution with ethyl acetate/hexanes (1:1)], followed by trituration of the resulting solid with ether yielded **6e** (53%) as a white solid: mp 156.0–157.5 °C (with effervescence); IR (KBr) 1660, 1645, 1615, 1505, 1475, 1435, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J = 2.4 Hz, 1 H), 7.20 (d, J = 8.9 Hz, 1 H), 7.04 (dt, J = 16.5 and 1.5 Hz, 1 H), 6.92 (dd, J = 2.5 and 8.9 Hz, 1 H), 6.13 (dt, J = 16.5 and 6.9 Hz, 1 H), 3.93 (s, 3 H), 3.76 (s, 3 H), 2.41–2.33 (m, 2 H), 1.67–1.54 (m, 2 H), 1.03 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 156.1, 145.4, 140.4, 132.7, 127.8, 120.0, 113.1, 110.4, 103.6, 103.2, 55.9, 35.8, 31.9, 22.3, 13.7; LRMS (m/z, rel intensity) 274 (15), 273 (M^+, 100), 230 (36), 228 (42), 218 (15), 200 (13), 184 (11), 156 (11), 127 (11); HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1361. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.14; H, 6.93; N, 5.29.

1-[(Benzyloxy)methyl]-2-(1,2-dimethyl-1-propenyl)-indole-3-carboxylic Acid (6q). To a stirred solution of lithium diisopropylamide (1.4 mmol from 0.6 mL of 2.5 M *n*-butyllithium in hexanes and 0.20 mL of diisopropylamine, 1.5 equiv) in anhydrous THF (6 mL) at −78 °C under nitrogen was added a solution of **5q** (0.326 g, 0.93 mmol, 1.0 equiv) in anhydrous THF (6 mL) dropwise. The resulting reaction solution was stirred at −78 °C under nitrogen for 1 h. Water (1 mL) was then added to the reaction solution at −78 °C, and this mixture was allowed to warm to room temperature. Water (10 mL) and ethyl acetate (10 mL) were added to the reaction mixture, and the pH of the aqueous layer adjusted to pH 2 with concentrated hydrochloric acid. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the extraction residue using silica gel (25 g) and elution with 15% ether in methylene chloride, followed by recrystallization of the isolated product in ethyl acetate/hexanes afforded **6q** (0.25 g, 0.72 mmol, 77%) as a white, crystalline solid: mp 160.0–161.5 °C; IR (KBr) 3435, 1650, 1525, 1460, 1385, 1055 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.9 (br s, CO_2H), 8.10–8.07 (m, 1 H), 7.64–7.61 (m, 1 H), 7.37–7.19 (m, 7 H), 5.54 (d, J = 10.4 Hz, 1 H), 5.41 (d, J = 10.4 Hz, 1 H), 4.48 (s, 2 H), 1.93 (s, 3 H), 1.81 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 165.6, 148.9, 137.4, 136.0, 133.3, 128.3, 127.7, 127.6, 126.8, 122.4, 121.7, 121.1, 119.9, 110.9, 104.4, 72.5, 69.8, 22.2, 19.8, 19.2; LRMS (m/z, rel intensity) 350 (21), 349 (M^+, 73), 304 (26), 241 (66), 228 (20), 184 (27), 168 (24), 91 (100). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.46; H, 6.63; N, 4.09.

Methyl 2-(*trans*-1-Heptenyl)indole-3-carboxylate (6r). **3g** and hexanal were used, and the THF/methanol reflux was for 4 h. Chromatography of the extraction residue using 1:5 ether/hexanes yielded (R_f = 0.70 in methylene chloride) **6r** (33%) as a clear, pale yellow oil: IR (neat) 3315, 1665, 1520, 1490, 1450, 1345, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.04 (br s, NH), 8.15–8.09 (m, 1 H), 7.43–7.18 (m, 4 H), 6.31 (dt, J = 16.4 and 6.9 Hz, 1 H), 3.95 (s, 3 H), 2.27–2.20 (m, 2 H), 1.48–1.39 (m, 2 H), 1.31–1.23 (m, 4 H), 0.88 (t, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 142.3, 135.5, 135.4, 127.4, 123.3, 121.9, 121.7, 120.0, 110.7, 104.1, 51.0, 33.2, 31.4, 28.7, 22.5, 14.0. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.18; H, 8.10; N, 4.88.

Ethyl 2-(2-Methyl-1-hexenyl)indole-3-carboxylate (6s). **3g** and 2-hexanone were used, and the THF/ethanol reflux was for 3 h. Chromatography of the extraction residue using methylene chloride/hexanes (1:1) yielded **6s** (87%) as a 2:1 mixture of trans:cis isomers as a clear, colorless oil: IR (neat) 3300, 1665, 1445, 1270, 1200 cm^{-1}; LRMS (m/z, rel intensity) 286 (18), 285 (M^+, 100), 240 (37), 228 (46), 212 (63), 202 (44), 197 (70), 182 (35), 174 (42), 169 (70), 168 (98), 167 (47), 154 (37). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.70; H, 8.27; N, 5.03. Small amounts of the individual isomers were separated via the chromatography described above and characterized. The less polar isomer (R_f = 0.60 in 1:1 methylene chloride/hexanes, assumed trans by its preponderance) was isolated as a clear colorless oil: ^1H NMR ($CDCl_3$) δ 8.73 (br s, NH), 8.16–8.13 (m, 1 H), 7.35–7.32 (m, 1 H), 7.23–7.18 (m, 2 H), 6.94 (br d, J = 1.7 Hz, 1 H), 4.39 (q, J = 7.4 Hz, 2 H), 2.21 (br t, 2 H), 1.98 (d, J = 1.6 Hz, 3 H), 1.56–1.26 (m, 4 H), 1.43 (t, J = 7.3 Hz, 3 H), 0.91 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 144.2, 142.7, 135.2,

126.9, 122.8, 121.8, 121.7, 115.8, 110.8, 104.8, 59.6, 40.7, 30.0, 22.4, 19.0, 14.6, 14.0; HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1747. The more polar isomer (R_f = 0.57 in 1:1 methylene chloride/hexanes, assumed cis) was isolated as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.36 (br s, NH), 8.14–8.11 (m, 1 H), 7.34–7.31 (m, 1 H), 7.24–7.19 (m, 2 H), 6.85 (br s, 1 H), 4.38 (q, J = 7.3 Hz, 2 H), 2.31 (br t, 2 H), 1.95 (d, J = 1.4 Hz, 3 H), 1.56–1.24 (m, 4 H), 1.43 (t, J = 7.3 Hz, 3 H), 0.90 (t, J = 7.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.8, 144.8, 142.4, 134.9, 126.8, 122.8, 121.7, 121.5, 116.4, 110.7, 105.0, 59.6, 33.6, 30.3, 24.5, 22.8, 14.6, 13.9; HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1743.

Ethyl 2-(2-Phenyl-1-propenyl)indole-3-carboxylate (6t). **3f** and acetophenone were used, and the THF/ethanol reflux was for 1 h. Chromatography of the extraction residue using 10% ether in hexanes afforded the less polar isomer (R_f = 0.20 in 10% ether in hexanes, assumed cis), which was recrystallized in hexanes to yield ***cis*-6t** (30%) as a white, crystalline solid: mp 114.5–116.0 °C; IR (KBr) 3280, 1675, 1665, 1635, 1490, 1460, 1440, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (dd, J = 1.2 and 8.8 Hz, 1 H), 7.58 (br s, NH), 7.50 (d, J = 1.2 Hz, 1 H), 7.47–7.40 (m, 3 H), 7.32–7.29 (m, 2 H), 7.15–7.05 (m, 2 H), 6.87 (dd, J = 1.4 and 7.0 Hz, 1 H), 4.43 (q, J = 7.1 Hz, 2 H), 2.30 (d, J = 1.8 Hz, 3 H), 1.47 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 142.9, 141.7, 141.1, 134.8, 129.4, 128.3, 127.7, 126.3, 123.1, 121.9, 121.6, 116.6, 110.5, 105.4, 59.7, 27.8, 14.6; LRMS (m/z, rel intensity) 306 (21), 305 (M$^+$, 100), 260 (59), 232 (97), 231 (87), 217 (52), 115 (33). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.57; H, 6.58; N, 4.36. Further elution yielded the more polar isomer which was triturated in ether/hexanes (1:1) to yield ***trans*-6t** (44%) as a white solid: mp 153.5–154.5 °C; IR (KBr) 3295, 1670, 1530, 1430, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.58 (br s, NH), 8.19–8.16 (m, 1 H), 7.58–7.55 (m, 3 H), 7.40–7.22 (m, 6 H), 4.41 (q, J = 7.4 Hz, 2 H), 2.43 (d, J = 1.4 Hz, 3 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 142.8, 141.9, 140.3, 135.4, 128.5, 128.0, 126.9, 126.2, 123.3, 122.0, 122.0, 118.1, 110.8, 106.5, 59.8, 18.4, 14.6; LRMS (m/z, rel intensity) 306 (33), 305 (M$^+$, 100), 260 (76), 232 (90), 231 (88), 217 (48), 115 (39). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.57; H, 6.58; N, 4.36.

Ethyl 2-(2-Methyl-1-propenyl)indole-3-carboxylate (6u). Sodium hydride (60% in oil, 0.138 g, 3.44 mmol, 1.0 equiv) was added to a solution of **9u** (1.25 g, 3.46 mmol, 1.0 equiv) in anhydrous THF (15 mL) at room temperature under nitrogen. This mixture was then heated at reflux (66 °C) under nitrogen for 1 h. Water (30 mL) was then added to the reaction solution, and this aqueous mixture was extracted with ethyl acetate (2 × 25 mL). The ethyl acetate extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual tan solid was triturated in hexanes to afford **6u** (0.692 g, 2.84 mmol, 82%) as an off-white powder: mp 95.0–97.0 °C; IR (KBr) 3340, 1675, 1515, 1490, 1445, 1340, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.56 (br s, NH), 8.16–8.11 (m, 1 H), 7.37–7.32 (m, 1 H), 7.25–7.18 (m, 2 H), 6.94–6.93 (m, 1 H), 4.42 (q, J = 7.1 Hz, 2 H), 2.00 (d, J = 0.9 Hz, 3 H), 1.97 (d, J = 1.3 Hz, 3 H), 1.45 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 142.6, 140.4, 135.1, 126.8, 122.8, 121.8, 116.4, 110.7, 104.9, 59.6, 27.2, 20.5, 14.6; LRMS (m/z, rel intensity) 244 (43), 243 (M$^+$, 100), 228 (25), 198 (84), 170 (70), 154 (50), 128 (23). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.92; H, 7.08; N, 5.69.

General Method for Deprotection of 5-[(Benzyloxy)methyl]-1,4-dihydropyrano[4,3-*b*]indoles (5o,p,q) to the Corresponding 1,4-Dihydropyrano[4,3-*b*]indoles (7o,p,q). A mixture of **5** (3.00 mmol), 10% Pd/C (1.0 g), and ammonium formate (1.00 g, 15.8 mmol, 5.3 equiv) in absolute ethanol (25 mL) was heated at reflux under nitrogen for 6 h. The resulting reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was partitioned between a saturated solution of sodium hydrogen carbonate (10 mL) and ethyl acetate (10 mL). The ethyl acetate layer was removed, and the aqueous layer extracted with ethyl acetate (10 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was either triturated in hexanes or chromatographed by using silica gel (approximately 50 g) and elution with an appropriate solvent system to yield **7**.

3-Propyl-1,4-dihydropyrano[4,3-*b*]indole (7o). Chromatorgraphy eluting with ethyl acetate/hexanes (2:3) yielded **7o** (47%) as a white solid: mp 222.0–223.0 °C; IR (KBr) 1662, 1620, 1590, 1555, 1500, 1480, 1460 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.0 (br s, NH), 7.84–7.79 (m, 1 H), 7.49–7.43 (m, 1 H), 7.23–7.14 (m, 2 H), 4.67–4.58 (m, 1 H), 3.13–2.95 (m, 2 H), 1.87–1.65 (m, 2 H), 1.62–1.39 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 163.2, 147.0, 136.3, 125.1, 122.5, 121.5, 119.3, 112.1, 100.9, 77.7, 36.5, 27.6, 18.0, 13.8; LRMS (m/z, rel intensity) 230 (11), 229 (M$^+$, 58), 186 (24), 158 (24), 157 (100), 129 (70), 102 (29). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.30; H, 6.69; N, 6.00.

3,3-Dimethyl-1,4-dihydropyrano[4,3-*b*]indole (7p). The extraction residue was triturated in hexanes to afford **7p** (74%) as a white solid: mp 195.0–197.0 °C; IR ($CHCl_3$) 3450, 1700, 1680, 1590, 1470, 1455, 1395, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.25 (br s, NH), 8.09–8.03 (m, 1 H), 7.50–7.45 (m, 1 H), 7.26–7.20 (m, 2 H), 3.12 (s, 2 H), 1.52 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.5, 145.5, 136.5, 125.3, 123.2, 122.3, 120.2, 112.1, 101.4, 81.3, 34.5, 28.0; LRMS (m/z, rel intensity) 216 (22), 215 (M$^+$, 73), 200 (19), 158 (39), 157 (100), 129 (87), 102 (39), 77 (14). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.46; H, 6.11; N, 6.39.

3,3,4-Trimethyl-1,4-dihydropyrano[4,3-*b*]indole (7q). Chromatography eluting with 4% ether in methylene chloride afforded **7q** (57%) as a white solid: mp 206.0–208.0 °C; IR (KBr) 3185, 1680, 1665, 1590, 1475, 1455, 1395, 1380, 1325, 1205 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.0 (br s, NH), 7.84–7.79 (m, 1 H), 7.50–7.44 (m, 1 H), 7.23–7.15 (m, 2 H), 3.31 (d, J = 7.1 Hz, 1 H), 1.46 (s, 3 H), 1.33 (d, J = 7.0 Hz, 3 H), 1.32 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 162.2, 150.7, 136.4, 125.1, 122.3, 121.6, 119.4, 112.2, 99.7, 83.5, 36.8, 27.1, 22.8, 14.0; LRMS (m/z, rel intensity) 230 (19), 229 (M$^+$, 73), 172 (37), 171 (100), 170 (46), 143 (84), 115 (47). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.19; H, 6.71; N, 6.03.

General Procedure for the Decarboxylation of Indole-3-carboxylic Acids 6 To Form 8. A mixture of the indole-3-carboxylic acid **6** (2.00 mmol) and bromobenzene (10 mL) was heated at reflux (156 °C) under nitrogen for 2–7 h depending on substrate. The resulting reaction solution was then passed through a silica gel filter (approximately 50 g) followed first by hexanes (500 mL, to remove bromobenzene) and then by methylene chloride/hexanes (1:1, 500 mL). The methylene chloride/hexanes filtrate was evaporated under reduced pressure to yield analytically pure 2-vinylindole **8**.

2-(Cyclohexylidenemethyl)-5-methoxy-1-methylindole (8a). The reaction time was 3 h. Evaporation of the methylene chloride/hexanes filtrate under reduced pressure afforded **8a** (90%) as a white, crystalline solid: mp 104.0–106.0 °C; IR (KBr) 1645, 1615, 1600, 1575, 1480, 1450, 1445, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J = 9.0 Hz, 1 H), 7.03 (d, J = 2.3 Hz, 1 H), 6.82 (dd, J = 2.2 and 9.0 Hz, 1 H), 6.30 (br s, 1 H), 6.09 (br s, 1 H), 3.84 (s, 3 H), 3.62 (s, 3 H), 2.48 (br t, J = 6.6 Hz, 2 H), 2.33 (br t, J = 6.6 Hz, 2 H), 1.69–1.55 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 154.1, 147.7, 137.8, 132.3, 128.2, 111.5, 111.0, 109.6, 101.9, 100.5, 56.0, 37.7, 30.3, 30.0, 28.7, 27.7, 26.6; LRMS (m/z, rel intensity) 256 (24), 255 (M$^+$, 100), 240 (23), 226 (16), 212 (21), 174 (64). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.69; H, 8.13; N, 5.44.

5-Methoxy-1-methyl-2-(2-methyl-1-propenyl)indole (8b). The reaction time was 7 h. Evaporation of the methylene chloride/hexanes filtrate under reduced pressure afforded **8b** (74% actual, 94% conversion based on returned starting material) as a white, crystalline solid: mp 172.0–174.0 °C; IR (KBr) 1615, 1600, 1575, 1485, 1455, 1430, 1395, 1370, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 1 H), 7.04 (d, J = 2.3 Hz, 1 H), 6.83 (dd, J = 2.2 and 8.5 Hz, 1 H), 6.33 (s, 1 H), 6.18 (br s, 1 H), 3.84 (s, 3 H), 3.63 (s, 3 H), 1.98 (s, 3 H), 1.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.0, 139.4, 138.2, 132.1, 128.2, 114.6, 111.2, 109.6, 101.9, 100.7, 55.9, 29.9, 27.0, 20.2; LRMS (m/z, rel intensity) 216 (20), 215 (M$^+$, 100), 200 (57), 174 (41), 172 (25), 107 (11). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.89; H, 7.94; N, 6.38.

5-Methoxy-2-(benzylidenemethyl)-1-methylindole (8d). The reaction time was 2 h. Evaporation of the methylene chloride/hexanes filtrate under reduced pressure afforded **8d** (95%) as a yellow, crystalline solid: mp 170.0–171.5 °C; IR (KBr) 1615, 1595, 1575, 1495, 1480, 1450, 1400, 1355, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54–7.51 (br d, 2 H), 7.40–7.35 (br t, 2 H), 7.30–7.25 (br t, 1 H), 7.18 (d, J = 8.9 Hz, 1 H), 7.14 (d, J = 2.2 Hz, 2 H),

7.04 (d, J = 2.2 Hz, 1 H), 6.87 (dd, J = 2.2 and 8.9 Hz, 1 H), 3.86 (s, 3 H), 3.76 (s, 3 H); LRMS (m/z, rel intensity) 264 (48), 263 (M^+, 100), 262 (68), 248 (30), 220 (36), 204 (18). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.98; H, 6.47; N, 5.06.

5-Methoxy-1-methyl-2-(*trans*-1-pentenyl)indole (8e). The reaction time was 4 h. Evaporation of the methylene chloride/hexanes filtrate under reduced pressure afforded **8e** (93%) as a white, crystalline solid: mp 84.0–85.0 °C; IR (KBr) 1615, 1575, 1520, 1480, 1455, 1430, 1400, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (d, J = 8.9 Hz, 1 H), 7.00 (d, J = 2.3 Hz, 1 H), 6.81 (dd, J = 2.3 and 9.0 Hz, 1 H), 6.48 (s, 1 H), 6.41 (d, J = 15.8 Hz, 1 H), 6.32–6.21 (m, 1 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 2.27–2.19 (m, 2 H), 1.56–1.48 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.2, 139.3, 134.2, 128.3, 119.0, 111.3, 109.7, 101.8, 97.3, 55.9, 35.5, 29.9, 22.5, 18.7; LRMS (m/z, rel intensity) 230 (27), 229 (M^+, 100), 214 (62), 200 (66), 185 (17), 174 (23), 169 (28), 169 (29), 156 (27), 114 (21). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.50; H, 8.31; N, 6.04.

5-Methoxy-1-methyl-2-((8-methyl-8-azabicyclo[3.2.1]octan-3-ylidene)methyl)indole (8g). A solution of **5g** (1.50 g, 4.41 mmol), sodium hydride (60% in oil, 0.27 g, 6.75 mmol, 1.5 equiv), and isopropyl alcohol (25 mL) was heated at reflux (82 °C) under nitrogen for 3 h. The reaction solution was cooled, glacial acetic acid was added (1 mL), and the reaction mixture was evaporated under reduced pressure. The residual solid was triturated with ether to afford a white solid (2.00 g). An NMR spectrum[18] of this solid was consistent with 5-methoxy-1-methyl-2-((8-methyl-8-azabicyclo[3.2.1]octyliden-3-yl)methyl)indole-3-carboxylic acid (**6g**, 100% crude) and sodium acetate. Crude **6g** (0.53 g) was placed in bromobenzene (10 mL), and this mixture was heated at reflux (156 °C) under nitrogen for 8 h. The resulting reaction solution was passed through a silica gel filter (approximately 25 g) followed first by ethyl acetate (250 mL) and then by a solution of ethyl acetate/methanol/triethylamine (18:1:1, 250 mL). This latter filtrate was then evaporated under reduced pressure to yield **8g** (0.35 g, 99% for two steps) as a clear, pale yellow oil: IR (neat) 1620, 1575, 1520, 1480, 1450, 1430, 1400, 1345, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (d, J = 8.8 Hz, 1 H), 7.02 (d, J = 2.4 Hz, 1 H), 6.83 (dd, J = 2.5 and 8.8 Hz, 1 H), 6.27 (s, 1 H), 6.23 (br s, 1 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 3.31–3.26 (m, 1 H), 3.22–3.17 (m, 1 H), 2.85–2.80 (br d, 1 H), 2.74–2.69 (br d, 1 H), 2.52–2.47 (br d, 1 H), 2.38 (s, 3 H), 2.16–2.11 (br d, 1 H), 2.04–1.86 (m, 2 H), 1.64–1.60 (m, 1 H), 1.41–1.37 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.1, 140.3, 137.2, 132.3, 128.1, 116.4, 111.4, 109.7, 101.9, 101.1, 61.8, 61.3, 55.9, 42.1, 39.6, 36.1, 29.9, 26.8, 26.6; LRMS (m/z, rel intensity) 297 (25), 296 (M^+, 64), 215 (69), 200 (18), 174 (16), 162 (58), 148 (15), 82 (100). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.60; H, 8.23; N, 9.30.

***tert*-Butyl (3-(Ethoxycarbonyl)indol-2-yl)-2-methylprop-2-yl Carbonate (9u).** To a stirred solution of lithium diisopropylamide (7.5 mmol made from 1.05 mL of diisopropylamine and 3.0 mL of 2.5 M *n*-butyllithium in hexanes, 1.5 equiv) in anhydrous THF (15 mL) at −78 °C under nitrogen was added rapidly a solution of **3f** (5.00 mmol) in anhydrous THF (10 mL) while the reaction temperature was maintained below −40 °C. The resultant yellow solution was stirred at −78 °C for 15 min, at which time acetone (0.60 mL, 8.17 mmol, 1.6 equiv) was added slowly dropwise. The resultant reaction solution was stirred at −78 °C for 30 min, then a saturated solution of sodium hydrogen carbonate (20 mL) was added, and this mixture was allowed to warm to room temperature. The resultant aqueous mixture was extracted with ethyl acetate (3 × 25 mL), and these extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was triturated in hexanes to afford **9u** (78%) as a white solid: mp 121.0–124.0 °C; IR ($CHCl_3$) 3440, 1740, 1685, 1545, 1455, 1440, 1370, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.95 (br s, NH), 8.14–8.11 (m, 1 H), 7.35–7.32 (m, 1 H), 7.25–7.20 (m, 2 H), 4.39 (q, J = 7.2 Hz, 2 H), 3.71 (s, 2 H), 1.55 (s, 6 H), 1.50 (s, 9 H), 1.45 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 152.1, 143.1, 134.9, 126.5, 122.7, 121.8, 121.6, 110.8, 106.1, 83.6, 82.0, 59.6, 38.1, 27.9, 25.5, 14.6; LRMS (m/z, rel intensity) 361 (M^+, 15), 244 (57), 243 (100, [M^+] − CO_2 − HO-*t*-Bu), 228 (24), 198 (64), 170 (31), 57 (55). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.50; H, 7.47; N, 3.85.

Acknowledgment. We thank the Scientific Proposal Advisory Committee at Pfizer for its support of this work, Dr. Jon Bordner for the X-ray analysis of **5g**, and Anne Schmidt and Chet Siok for the in vitro and in vivo profiling of **5g** and **5j**.

Supplementary Material Available: X-ray data on compound **5g** (7 pages). Ordering information is given on any current masthead page.

(18) ^1H NMR (DMSO-d_6) 7.65 (d, J = 2.8 Hz, 1 H), 7.30 (d, J = 8.9 Hz, 1 H), 6.76 (dd, J = 2.1 Hz and 9.0 Hz, 1 H), 6.42 (s, 1 H), 3.75 (s, 3 H), 3.53 (s, 3 H), 3.19–3.16 (m, 1 H), 2.99–2.96 (m, 1 H), 2.64–2.59 (m, 1 H), 2.31–2.10 (m, 3 H), 2.22 (s, 3 H), 1.90–1.70 (m, 4 H).

Synthesis of Picenadol via Metalloenamine Alkylation Methodology

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Received February 2, 1989

A convenient synthesis of the novel phenylpiperidine analgesic agent picenadol, (±)-**1**, via tetrahydropyridine **2** is described. Tetrahydropyridine **7**, prepared from **6** via metalation (*n*-butyllithium) and alkylation with 1-bromopropane, could not be directly converted to **2**, thus necessitating development of alternative strategies. Dehydration of piperidinol **10** gave a mixture of tetrahydropyridines **11** and **12**. Metalation of **11** followed by alkylation with 1-bromopropane afforded trans-oriented **14**, while **12** provided **2**. Reaction of **7** with excess hot 37% aqueous formaldehyde provided **17** instead of the desired **2**. Exposure of **7** to either Eschenmoser's salt in organic solvent or dimethylamine–formaldehyde (pH 3–3.5) in aqueous solution afforded **15** in high yield. Hydrogenation of **15** to **2** (H_2 Pd/C), demethylation (HBr), and separation of the resulting diastereomeric mixture by recrystallization completed the synthesis of picenadol (**1**).

Extensive investigation of the analgesic activity of 4-alkyl-4-phenylpiperidines and related perhydroisoquinolines has led to the discovery and development of picenadol (*cis*-(±)-3-(1,3-dimethyl-4-propyl-4-piperidinyl)phenol hydrochloride, LY150720, **1**), a unique opioid mixed agonist–antagonist currently undergoing

0022-3263/89/1954-4795$01.50/0