Synthetic Entries to 6-Fluoro-7-substituted Indole Derivatives§

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Three practical synthetic entries of functionalized 6-fluoro-7-substituted indole derivatives were developed in connection with the preparation of 7-fluoro-8-substituted-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid derivatives **11**. The first route, which permits group modification about position 8 of the pyranoindole skeleton, employs 2-bromo-3-fluoroaniline (**18**) as a key intermediate, the preparation of which was achieved by either a novel *ortho* metalation of **15** or *via* the intermediacy of **22**. The second route utilizes **32** to append a terminally functionalized three carbon side chain onto the indole template and in addition leads to **43** from **40**. The third route to the 7-fluoro-8-substituted-pyranoindole skeleton complements route two in that the synthetic pathway exploits **32** in a nucleophilic fashion to construct a terminally functionalized two carbon appendage onto the indole nucleus.

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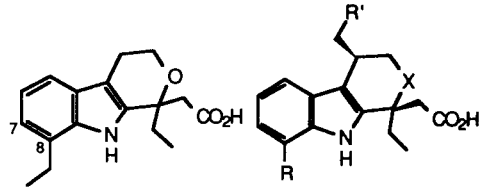
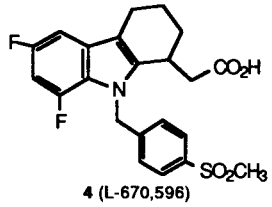
The 1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid and corresponding tetrahydrocarbazole templates have been associated with an increasing number of pharmacologically diverse and therapeutically useful activities such as those found in the antiinflammatory agent etodolac (**1**) [1,2], the analgesics pemedolac (**2**) [3,4] and tetrahydrocarbazole derivative **3** [4], and the potent and selective thromboxane/prostaglandin endoperoxide receptor antagonist L-670,596 **4** [5].



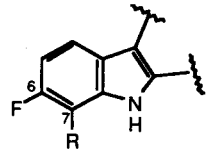
1 (Etodolac)

2 (Pemedolac): X = O, R = H, R' = Ph
3 X = CH_2, R = Et, R' = $CH{=}CH_2$



4 (L-670,596)

In the course of further studies related to these systems, it became of interest to prepare 7-fluorinated derivatives which bore appendages specifically at position 8 of the pyranoindole skeleton. A survey of the literature revealed that only a handful of indoles with this substitution pattern have been prepared and that these compounds were restricted only to those structures related to **5** (R = Me, Et) [1,6]. That so few 6-fluoro-7-substituted indoles have appeared is most likely related to the lack of commercially available fluorinated precursors which would permit facile access to this set of indoles.



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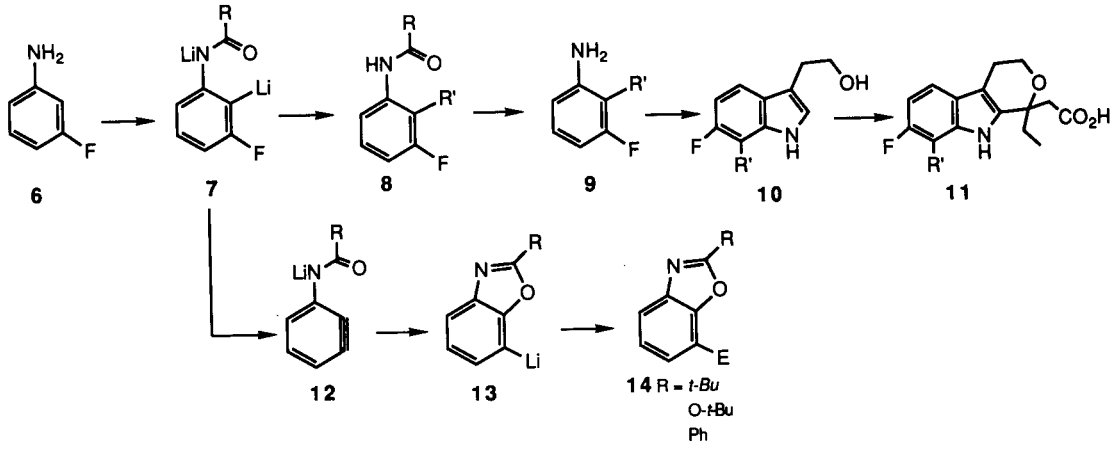
We wish to report multigram synthetic entries to 6-fluoro-7-substituted indole derivatives, in particular, those related to the pyranoindole framework. The methodologies described herein rely upon the syntheses of suitable 3-fluoroaniline derivatives, which then permit elaboration about position 7 of the indole nucleus or manipulation of a functionalized carbon appendage.

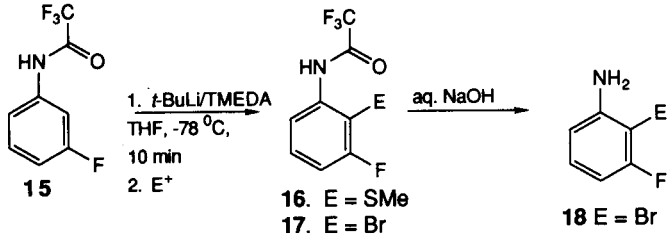
Results and Discussion.

A synthetically appealing route to these fluoroindole derivatives would involve a directed metalation of a derivative of 3-fluoroaniline (Scheme I). This would insure regiocontrol in the placement of a carbon moiety or appropriate heteroatom, such as bromine, which could serve in other useful transformations. However, in the only reported case of such a directed metalation of 3-fluoroaniline (**6**) [7], the pivaloyl-, *N*-*t*-butoxycarbonyl-, and benzoyldirecting groups produced substituted benzoxazole **14**, a consequence of electrophilic trapping of 7-lithiated benzoxazoles **13** generated *via* benzyne formation from *ortho*-lithiated species **7**. In these cases electrophilic quenching of **7** was not reported. In a related application of nonfluorinated ortho lithiated aniline derivatives to the regio-controlled construction of indoles, Wender [8] found the *N*-trifluoroacetyl group to be highly effective; however, in these instances, the dilithiated species were generated *via* a metal-halogen exchange protocol rather than *ortho* lithiation.

SCHEME I



SCHEME II

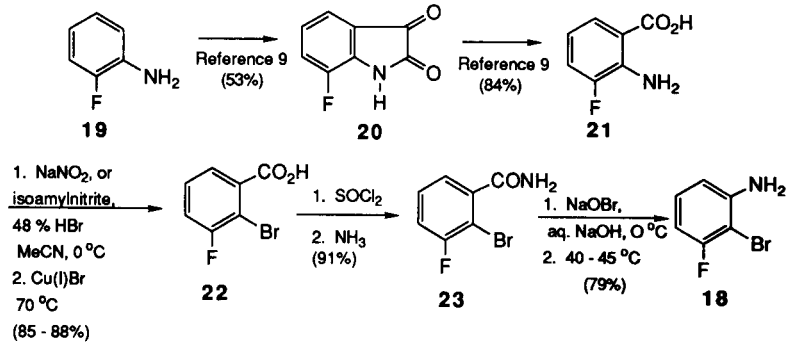


It was gratifying therefore to find that treatment of *N*-trifluoroacetyl-3-fluoroaniline (**15**) with 2.2 equivalents of *t*-butyllithium and 2.1 equivalents of tetramethylethylenediamine in tetrahydrofuran at <-65° produced a dilithiated species which, upon quenching with methyl disulfide, produced **16** as the only product derived from lithiation (Scheme II). By comparison, formation of the known benzoxazole **14** (R = *t*-Bu, E = SMe) [7] could not be suppressed when the reaction was performed in an identical fashion using *N*-pivaloyl-3-fluoroaniline [7]; the benzoxazole product **14** (15% of the product mixture by hplc analysis) was detected after 10 minutes although metalation was only 40% complete. Presumably, the *N*-trifluoroacetyl group stabilizes the dilithiated species **7** (R = $COCF_3$), relative to the *N*-pivaloyl group, such that benzyne formation at low temperature is not apparent.

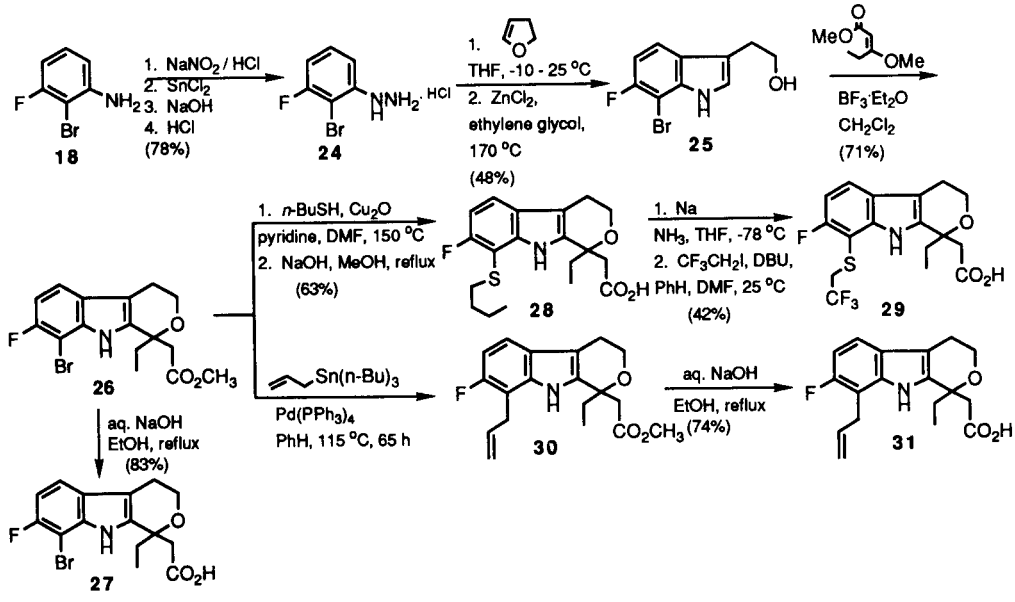
Dilithiation of **15** using the above protocol, bromine quench, basic hydrolysis and salt formation provided 2-bromo-3-fluoroaniline (**18**) in 53% yield from 3-fluoroaniline. This sequence has been successfully scaled-up to hundred gram quantities as described in the Experimental.

Since the metalation sequence proved impractical for further scale-up, an alternative route to **18** was developed from commercially available 2-fluoroaniline (**19**) (Scheme III). Aniline **19** was converted to the known 3-fluoroanthranilic acid (**21**) [9] *via* isatin **20** [9]. Transformation of **21** into **18** was accomplished in 63% yield overall using a simple sequence: 1. modification of the Sandmeyer halide synthesis [10] (a. sodium nitrite or isoamylnitrite, 48% hydrobromic acid, acetonitrile, 0°; b. copper (I) bromide, 70°); 2. amide formation (a. thionyl chloride, methylene chloride; b, ammonia, -5 to -20°); and 3. Hofmann Rearrangement (a. sodium hypobromite, 0°; 40 - 45°; b. concentrated hydrochloric acid). We have used this route successfully to provide kilogram quantities of **18**.

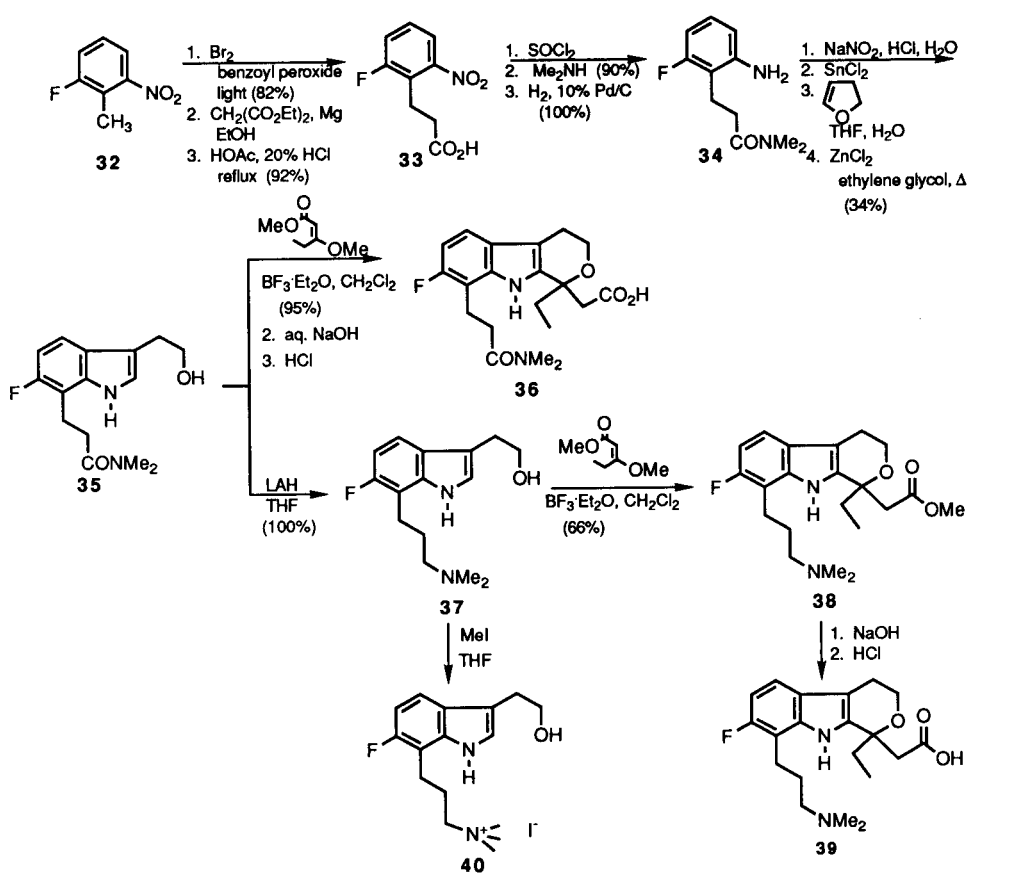
SCHEME III



SCHEME IV



SCHEME V



Aniline **18** was diazotized (sodium nitrite, hydrochloric acid) and then reduced with stannous chloride to provide hydrazine **24** in 78% yield (Scheme IV). Fischer indole synthesis with dihydrofuran [3,4] provided 6-fluoro-7-bromotryptophol (**25**) in 48% isolated yield. Cyclization with methyl 3-methoxypentenoate [3,4] furnished crystalline pyranoindole **26**, mp 107-109°, in 71% yield. Basic hydrolysis of **26** gave the corresponding acid **27**.

Pyranoindole **26** proved to be a useful intermediate for appending sulfur and carbon side chains at position 8 of the pyranoindole skeleton. Thus, copper oxide mediated introduction of thiobutyl side chain [11] followed by ester hydrolysis gave pyranoindole **28** (63% yield). Debutylation (sodium, liquid ammonia, -78°, 93% yield) [12] and realkylation (2,2,2-trifluoroethyl iodide (2.5 equivalents), 1,8-diabicyclo[5.4.0]undec-7-ene (2.5 equivalents), benzene, *N,N*-dimethylformamide, 25°, 4 hours, 49% yield) gave thioether **29**, mp 88-89°. Allylation of **26** was achieved *via* palladium-mediated coupling (tetrakistriphenylphosphinepalladium(0) (0.02 equivalents)) with allyltributyltin (1.3 equivalents) [13]. Basic hydrolysis furnished pyranoindole **31**, mp 122-123°, in 74% yield from **26**.

Additional routes to 6-fluoro-7-carbon substituted indole derivatives, including **30**, from 2-fluoro-6-methyltoluene (**32**), were identified. As described below, these pathways complement that presented in Scheme IV in that the pre-existing methyl group of **32** was elaborated in either an electrophilic or nucleophilic manner. The latter approach successfully relayed **32** to **30** *via* two sequential one carbon homologations. The former scheme utilized a two carbon homologation and unexpectedly presented an entry to the 7-fluoro-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline system.

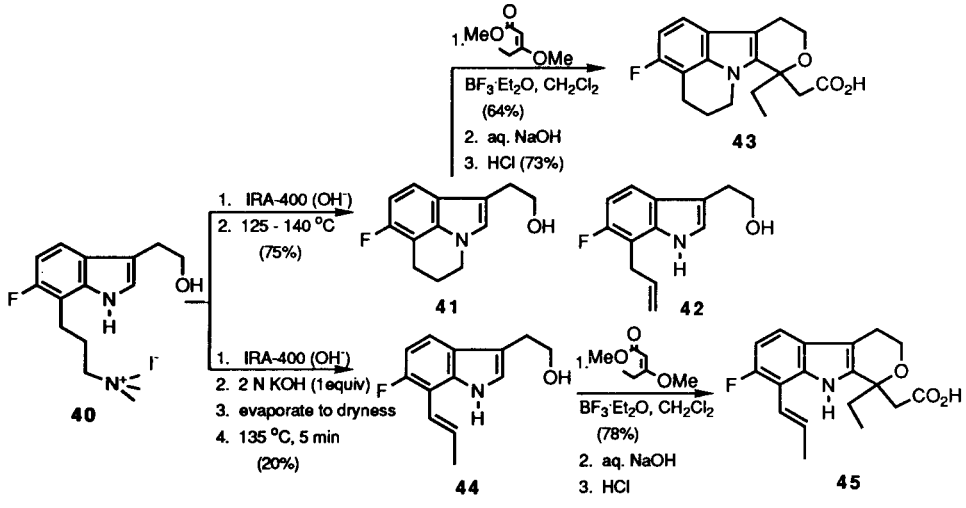
Benzylic bromination of **32** [14] (82% yield), clean displacement with the magnesium anion of diethyl malonate [15], hydrolysis and subsequent decarboxylation (92% yield) gave crystalline **33**, mp 97-98°. It should be noted that with the sodium salt of dimethyl malonate, a plethora of products was obtained.

Conversion of **33** to tryptophol **35** (oil) was accomplished according to the following sequence: 1. amide formation (thionyl chloride; dimethylamine (90% yield); 2. catalytic hydrogenation to **34** (100% yield); 3. and Fischer cyclization (sodium nitrite, hydrochloric acid; stannous chloride; dihydrofuran; zinc chloride; ethylene glycol, 160°, 3 hours (34% yield)). Pyranoindole formation with methyl 3-methoxy-2-pentenoate (95% yield) and basic hydrolysis (53% yield) gave crystalline acid **36**, mp 218-219°. Amide **35** was reduced with lithium aluminum hydride to **37**, mp 115-117°, and converted to the amino acid derivative **39**, mp 159-161°.

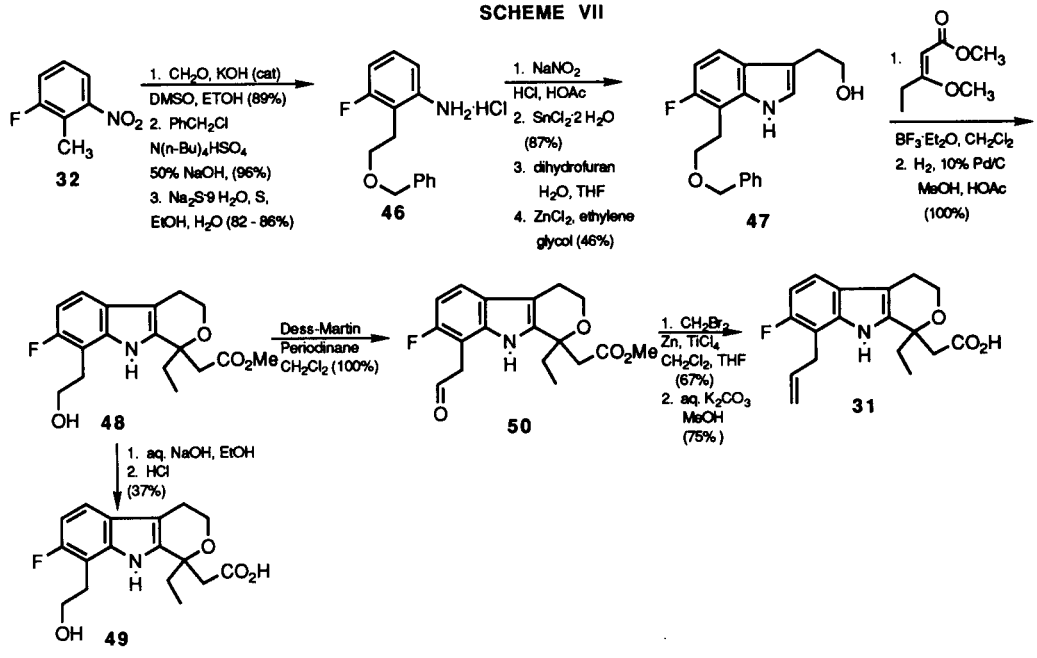
Amine **37** was converted to the methyl quaternary salt. As shown in Scheme VI, anionic exchange [16] (Amberlite IRA 400 (OH)) of **40** and attempted Hofmann elimination (120-135°) gave only 7-fluoro-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline 1-ethanol (**41**), mp 69-70°, in 75% yield from **37**; olefin **42** was never detected. In contrast, anion exchange of **40** and then heating in the presence of 1 equivalent of potassium hydroxide provided olefin **41** and **44** in approximately a 1:1 ratio [17]. Indole **44** was converted to pyranoindole **45**, mp 161-164° dec, isomeric with **31**.

Elaboration of **32** in a nucleophilic manner was addressed as shown in Scheme VII. 2-Fluoro-6-nitroaniline (**32**) was converted in multigram scale to aniline **46**, mp 148-150°, in a carefully defined protocol: 1. treatment of an ethanolic solution of **32** with 1 equivalent of paraformaldehyde in the presence of a catalytic amount of potassium hydroxide (89% yield) [18]; 2. hydroxyl group protection as a benzyl ether under phase transfer conditions (96% yield) [19]; and 3. sodium polysulfide reduction (82-86% yield) [18]. These conditions were necessary to insure reproducibly high yields and clean reactions.

SCHEME VI



SCHEME VII



Diazotization, reduction (87% yield), and Fischer cyclization with dihydrofuran gave tryptophol derivative **47**, mp 75-77°, in 46% yield. Formation of pyranoindole indole **48**, mp 101-103°, was effected in two steps: 1. cyclization with methyl 3-methoxypentenoate, and 2. hydrogenolysis of the benzyl ether. Basic hydrolysis of **48** provided crystalline acid **49**, mp 176-178°. Oxidation of **48** to the stable aldehyde **50**, mp 94-96°, was achieved in quantitative yield with Dess-Martin periodinane [20].

Wittig olefination of **50** to **30** proved problematic using methyltriphenylphosphonium bromide with a host of strong bases [21, 22], potassium carbonate/dioxane/water [23], or potassium carbonate/tetrahydrofuran/methylene chloride [24] Similarly, poor results were obtained with the Peterson olefination [25]. This obstacle was overcome *via* the Lombardo reagent [26]. Thus, treatment of a methylene chloride solution of **50** with the reagent prepared from zinc dust (4.7 equivalent), methylene dibromide (1.5 equivalent) and titanium tetrachloride (1.0 equivalent) in tetrahydrofuran at -40° to 0° gave olefin **30** in 67% yield.

In summary, within the context of elaborated pyranoindole systems, three synthetically useful approaches to 6-fluoro-7-substituted indole derivatives have been developed. The first approach utilizes 2-bromo-3-fluoroaniline (**18**) as a key intermediate whose multi-gram preparation entails a novel lithiation of 3-fluoroaniline or the oxidative rupture of 7-fluoroisatin; this sequence permits group modification about the 7-position of the indole nucleus. The second and third pathways detail entries to 6-fluoro-7-functionally enriched carbon substituted indoles in which the starting material, 2-fluoro-6-nitrotoluene, is differentially exploited. These approaches should be of value to the preparation of other fluoroindole systems.

EXPERIMENTAL

Melting points in capillary tubes were obtained on a Thomas-Hoover apparatus and are uncorrected. Pmr spectra were obtained at either 200 or 400 MHz on a Varian XL-200 or Bruker AM-400 spectrometer. Infrared spectra were recorded with a Perkin-Elmer 781 spectrophotometer. Mass spectra were measured on a Hewlett-Packard 595A mass spectrometer. Elemental analyses were performed by the Wyeth-Ayerst analytical group using a Control Equipment 240-XA elemental analyzer.

Thin-layer chromatography (tlc) analyses were performed on glass-backed (2.5 x 7.5 cm) silica gel 60 F-254 plates (0.25 mm). Visualization of spots was effected with uv light and one of the following stains: 10% phosphomolybdic acid in ethanol, ceric ammonium sulfate (100 mg/ml of 35% sulfuric acid), a staining mixture composed of ammonium molybdate (12 g) and ceric sulfate (0.5 g) in 10% sulfuric acid (250 ml), or iodine-impregnated silica gel.

Flash chromatography refers to the technique described by Still [27].

All reactions were performed under a nitrogen atmosphere.

N-Trifluoroacetyl-3-fluoroaniline (**15**).

The procedure of Wender was used [8]. Trifluoroacetic anhydride (125 ml, 0.819 mole) was added dropwise to a stirring mixture of sodium carbonate (120 g, 1.13 moles) and 3-fluoroaniline (75.2 g, 0.677 mole) in 500 ml of ether at -10°. After 1 hour, hexane (200 ml) was added and the reaction mixture was filtered. The filtrate was washed with ice-water, 10% aqueous sodium bicarbonate, and then brine. The ethereal phase was treated with charcoal, dried (magnesium sulfate), and then concentrated. The resulting tan solid was suspended in hot petroleum ether (500 ml), cooled and filtered to afford 116 g

(83% yield) of title compound which was used in the next step without further purification.

An analytical sample (mp 69-70°) was obtained by crystallization from petroleum ether; pmr (deuteriochloroform): δ 8.0 (bs, 1 H), 7.5 (dt, 1 H), 7.35 (m, 1 H), 7.24 (dd, 1 H), and 6.96 (td, 1 H).

Anal. Calcd. for $C_8H_5F_4NO$: C, 46.39; H, 2.43; N, 6.76. Found: C, 46.00; H, 2.74; N, 6.87.

N-(2-Thiomethyl-3-fluorophenyl)trifluoroacetamide (**16**).

To a solution of 1.9 ml (12.6 mmoles) of tetramethylethylenediamine in anhydrous tetrahydrofuran at -80° was added slowly *t*-butyllithium (7.4 ml, 12.5 mmoles; 1.7 *M* in pentane). After 5 minutes, a solution of **15** (1.03 g, 5.0 mmoles) in tetrahydrofuran (precooled to -80°) was added *via* cannula at a rate such that the temperature did not exceed -65°. After 15 minutes, 0.60 ml (6.7 mmoles) of dimethyl sulfide was added to the reaction mixture at -80°. The reaction mixture was then adjusted to *p*H 5 with 0.5 *N* hydrochloric acid and extracted into ether. The reaction mixture was dried over magnesium sulfate and concentrated to provide 740 mg of crude product. A sample of **16** was obtained as a low melting colorless solid by flash chromatography (ether-hexane 1:20); pmr (deuteriochloroform): 400 MHz δ 9.58 (bs 1 H), 8.25 (d, 1 H), 7.41 (bq, 1 H), and 6.99 (bt, 1 H); ir (potassium bromide): 3320 and 1720 cm^{-1}.

2-Bromo-3-fluoroaniline (**18**) Hydrochloride Salt.

A solution of *t*-butyllithium (1.6 l, 2.72 moles; 1.7 *M* in pentane) was added to tetramethylethylenediamine (407 ml, 2.72 moles) in anhydrous tetrahydrofuran (1.6 l) at -78 to -71° *via* cannula over a 90 minute period. A solution of **15** (281 g, 1.36 moles) in tetrahydrofuran (800 ml) was then added dropwise over 60 minutes. The yellow solution was stirred at -70° for 60 minutes. Bromine (84 ml, 1.63 moles) was then added dropwise over 60 minutes such that the temperature did not exceed -70°. After stirring at -70° for 30 minutes, the cold bath was removed and the reaction mixture was quenched with 1.71 of 2 *N* hydrochloric acid (final *p*H 6). To the reaction mixture was added saturated aqueous sodium chloride solution (800 ml) and the reaction mixture was extracted into ether (3 x 800 ml). The combined organic extracts were washed with brine, 20% sodium thiosulfate solution, and brine. The organic phase was concentrated to a thick brown oil. The crude product was dissolved in ethanol (1.5 l) and was treated with 2.5 *N* sodium hydroxide solution (1 l). After stirring at 80° for 60 minutes, the ethanol was removed *in vacuo*. The residue was diluted with water (2 l) and was extracted into ether (3 x 500 ml). The organic phase was washed with brine (500 ml) and then with 1*N* hydrochloric acid (4 x 500 ml) to remove remaining 3-fluoroaniline. The organic phase was dried over magnesium sulfate, filtered through a pad of silica gel (2.5 cm x 13 cm; ether washed). The filtrate was then treated with excess hydrogen chloride gas to provide the title compound, mp 198° as a tan solid (162 g, 53% yield) which was pure enough to be used in the next reaction.

A sample of **17** (mp 55-56°) was obtained from a smaller metalation run and was isolated by hplc (Waters Prep 500 using 3% ethyl acetate in hexane elution) and crystallized from methylene chloride-hexane; R_f 0.53 (5% ether/petroleum ether); pmr (deuteriochloroform): δ 8.48 (bs, 1 H), 8.16 (dd, 1 H), 7.40 (m, 1 H) and 7.05 (dt, 1 H); ir (potassium bromide): 3300 and 1710 cm^{-1}; ms (m/e) 288, 285, 216, 218 and 69.

For analytical purposes, a small sample of **18** hydrochloride salt was recrystallized from an ethanol-ethyl acetate combination; mp 197° dec; pmr (DMSO-d_6): 400 MHz δ 7.45 (bs, 3 H), 7.03-7.09 (m, 1H), 6.64 (dt, 1 H, J = 8, 1 Hz), and 6.49 (td, 1 H, J = 8, 1 Hz; ir (potassium bromide): 3420 and 3480 cm^{-1}; ms: (m/e) 189 and 191.

Anal. Calcd. for $C_6H_6NBrClF$-0.4 H_2O: C, 30.84; H, 2.94; N, 6.00. Found: C, 31.21; H, 3.30; N, 6.25.

Aniline **18**, obtained as the free base; pmr (deuteriochloroform): 200 MHz δ 4.2 (bs, 2 H), 6.5-6.6 (m, 2 H), and 7.04 (q, 1 H).

7-Fluoroisatin (**20**) [9].

To 100 g (0.6 mole) of chloral hydrate in 1700 ml of water containing 675 g (4.75 moles) of sodium sulfate was added a solution of 60.3 g (0.54 mole) of 2-fluoroaniline in 300 ml of water containing 150 ml of concentrated hydrochloric acid. To the reaction mixture was then added 167.5 g (2.41 moles) of hydroxylamine hydrochloride. The reaction mixture was stirred at reflux for 10 minutes and cooled to room temperature. Further cooling to 0° and collection of the precipitate provided 95.5 g (96%) of a tan powder, mp 87-91° which was used as such in the next reaction.

To 100 ml of concentrated sulfuric acid was added portionwise 20 g (0.11 mole) of *N*-(2-fluorophenyl)-2-hydroxyiminoacetamide. The reaction mixture was then stirred at 70° for 45 minutes and then poured onto crushed ice (500 ml). The reaction mixture was extracted into ethyl acetate (4 x 150 ml), dried (magnesium sulfate), and concentrated to give 9.88 g (55%) of the crude isatin as an orange powder. This was used without further purification in the next reaction; R_f 0.28 (5% ether/petroleum ether); pmr (deuteriochloroform): 200 MHz δ 7.54 (t, 1 H), 7.38 (d, 1 H), and 7.07 (dt, 1 H); ms: (m/e) 165, 127.

3-Fluoroanthranilic Acid (**21**) [9].

To 20.7 g (126 mmoles) of crude isatin was added 200 ml (2 moles) of 10 *M* sodium hydroxide. The reaction mixture was stirred at 70° for 60 minutes. To the reaction mixture was added over a 30 minutes period 40 ml of 30% hydrogen peroxide solution. After stirring at 70° for 60 minutes, the reaction mixture was cooled to 0°, carefully treated with concentrated hydrochloric acid until *p*H 8-9 was obtained, diluted with ethyl acetate (200 ml), and further acidified with concentrated hydrochloric acid until *p*H 4-5 obtained. The aqueous phase was extracted into ethyl acetate (150 ml). The combined organic extracts were washed with water (3 x 100 ml) and dried over magnesium sulfate. Concentration gave 16.9 g (84%) of crude product as a brown powder which was used without further purification; pmr (DMSO-d_6): 200 MHz δ 7.55 (d, 1 H), 7.24 (t, 1 H), and 6.52 (bq, 1 H); ms (m/e) 155-137.

2-Bromo-3-fluorobenzoic Acid (**22**) using Isoamyl Nitrite.

The Doyle procedure was used [10]. At 0° to a solution of 2.00 g (2.9 mmoles) of **21** in 70 ml of acetonitrile was added 20 ml of 48% hydrobromic acid. To the resulting suspension was added 200 ml (14.9 mmoles) of isoamylnitrite. After 5 minutes at 0°, a solution resulted. To the reaction mixture was added 2.22 g (15.5 mmoles) of copper (I) bromide. The deep red reaction mixture was heated at 70° for 30 minutes. The reaction was quenched at room temperature with water (100 ml) and was extracted into

methylene chloride (3 x 70 ml). Drying (magnesium sulfate) and concentration gave 2.49 g of a solid which was dissolved in ethyl acetate (50 ml) and added to petroleum ether (200 ml). The mixture was filtered and the filtrate was evaporated *in vacuo* to provide 2.40 g (85%) of the title compound as a yellow powder, which was used without further purification. This material was identical to **22** as prepared below.

2-Bromo-3-fluorobenzoic Acid (**22**) using sodium nitrite.

At 0° to 16.8 g (0.105 mole) of **21** in acetonitrile (135 ml) was added 135 ml of 48% hydrobromic acid (precooled to 0°). After stirring for 30 minutes at 0° was added a solution of 8.4 g (0.122 mole) of sodium nitrite in water (16 ml) over a 20 minutes period.

After 1 hour at 0°, 18.4 g (0.126 mole) of copper (I) bromide was added portionwise over a 15 minutes period. The cold bath was removed and stirring was continued at ambient temperature for 30 minutes, then at 70° for 90 minutes. The reaction mixture was cooled to 0° and 405 ml of cold water was added over a 20 minute period. A precipitate resulted. After stirring for 60 minutes at 5-10°, the aqueous phase was decanted. The solid was washed with water (3 x 100 ml) in the same manner, the precipitate was collected and dried at 80° under high vacuum to provide 20.1 g (88%) of the title compound as beige crystals which were used in the next step without further purification.

An analytical sample, mp 157-158°, was obtained as a colorless powder by flash chromatography (silica gel pretreated with 1% phosphoric acid-methanol solution and then dried) using elutions of ether-petroleum ether (2:3); pmr (deuteriochloroform): 200 MHz δ 10 (bs, 1 H), 7.81 (bd, 1 H), and 7.2-7.5 (m, 2 H); ir (potassium bromide): 3000, and 1700 cm^{-1}; ms: (m/e) 218 and 220.

Anal. Calcd. for $C_7H_4BrFO_2$: C, 38.39; H, 1.84. Found: C, 38.69; H, 2.24.

2-Bromo-3-fluorobenzamide (**23**).

To a suspension of **22** (20.1 g, 91.8 mmoles) in methylene chloride (150 ml) was added thionyl chloride (25.4 g) over a period of 5 minutes. The reaction mixture was stirred at reflux for 1 hour (no **22** left as determined by tlc examination of a methanol quenched aliquot). The reaction mixture was cooled to 0° and added over a 2 hour period to a cold (-5 to -20°) solution of 16 g of ammonia gas in methylene chloride (250 ml). The cold bath was removed and the reaction was stirred for 1 hour. Methylene chloride was distilled from the reaction mixture. Toluene (100 ml) was added to the slurry and was then removed *via* distillation (50 ml of distillate collected). The reaction slurry was cooled to 0° and 100 ml of water was added. After 10 minutes, the slurry was filtered and the precipitate was washed sequentially was water (50 ml) and toluene (50 ml). Drying under high vacuum (80-85°) provided 18.8 g (91%) of **23** as white fine needles which were used without further purification. An analytical sample, mp 159-161°, was obtained from a smaller similar run and purified *via* recrystallization from a combination of methylene chloride, petroleum ether, and methanol; pmr (DMSO-d_6): 200 MHz δ 7.9 (bs, 1 H, NH), 7.67 (bs, 1 NH), 7.3-7.5 (m, 2 H), and 7.25 (bd, 1 H); ir (chloroform): 1685 cm^{-1}; ms: (m/e) 217 and 219.

Anal. Calcd. for C_7H_5BrNFO: C, 38.56; H, 2.31; N, 6.42. Found: C, 38.33; H, 2.61; N, 6.27.

2-Bromo-3-fluoroaniline (**18**) from **23**.

To 725 ml of 2 *N* sodium hydroxide at 0° was added dropwise over a 30 minute period 45.5 g (0.29 mole) of bromine. After stirring at 0° for 30 minutes was added portionwise over a 15 minutes period 51.4 g (0.23 mole) of 2-bromo-3-fluorobenzamide. The reaction mixture was stirred at 0° for 4 hours and then at 60° for 3 hours. The reaction mixture was cooled to 0° and acidified with concentrated hydrochloric acid (47 ml, final *p*H 6-7). The reaction mixture was extracted into methylene chloride (450 ml) and the combined organic extracts were washed with water. Removal of solvent *in vacuo* provided 42.5 g (79%) of a brown oil which solidified upon cooling to -10° and was used without further purification. This material was identical to that obtained by the lithiation route.

2-Bromo-3-fluorophenylhydrazine Hydrochloride (**24**).

A solution of sodium nitrite (9.7 g, 0.14 mole) in water (30 ml) was added dropwise over 45 minutes to a suspension of **18**·hydrogen chloride (28 g, 0.128 mole) in concentrated hydrochloric acid (70 ml) at -8°. A solution of stannous chloride dihydrate (90 g, 0.4 mole) in concentrated hydrochloric acid (100 ml) was added over a period of 1 hour. After stirring for 75 minutes at -10°, the reaction mixture was basified by adding dropwise 50% sodium hydroxide solution (150 ml) at -8°. The mixture was further diluted with water (100 ml) and treated with another 50 ml of 50% sodium hydroxide and then crushed ice (500 g). The reaction mixture was extracted into ether (3 x 500 ml) and the combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, and filtered. The filtrate was cooled to 0°, and hydrogen chloride gas was bubbled into the solution. The precipitate was collected and dried under reduced pressure to produce 24 g (78%) of the title compound as an off-white amorphous solid: pmr (DMSO-d_6): 400 MHz δ 8.20 (bs, 1 H), 7.36-7.42 (m, 1 H), and 6.90-6.97 (m, 2 H); ms: (m/e) 204 and 206.

6-Fluoro-7-bromotryptophol (**25**).

To 23.5 g (0.10 mole) of **24** in 10% aqueous tetrahydrofuran (300 ml) at -10° was added dropwise a solution of dihydrofuran (7.5 g, 0.11 mole) in tetrahydrofuran (40 ml). After 2 hours at -10° and 12 hours at ambient temperature, the reaction mixture was diluted with ether and then with brine (100 ml). The organic phase was separated, washed sequentially was saturated sodium bicarbonate solution and then brine, dried (magnesium sulfate) and concentrated. The residue was dissolved in ethylene glycol (130 ml), treated with zinc chloride (30 g), heated at 90° until homogeneous, and then at 170° for 3 hours. The reaction mixture was cooled to 70° and then poured onto a mixture of crushed ice (200 ml) and hydrochloric acid (200 ml). The reaction mixture was extracted into ether (3 x 100 ml) and the combined organic extracts were washed successively with 1 *N* hydrochloric acid (50 ml) and brine (2 x 50 ml). Drying (magnesium sulfate) and purification by flash chromatography (chloroform elution) gave 12.3 g (48%) of the title compound as an amber oil: pmr (deuteriochloroform): 400 MHz δ 8.26 (bs, 1 H), 7.45 (d, 1 H), 7.12 (d, 1 H), 6.94 (t, 1 H), 3.89 (t, 2 H), and 2.98 (t, 2 H); ir (chloroform): 3630 and 3480 cm^{-1}; ms: (m/e) 257 and 259, 226 and 229.

Methyl 1-Ethyl-7-fluoro-8-bromo-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetate (**26**).

To a solution of tryptophol **26** (12 g, 46 mmoles) in methylene chloride (400 ml) was added methyl 3-methoxy-2-pentenoate (7.1

g, 49 mmoles) and then boron trifluoride etherate (1 ml). After stirring at room temperature for 40 minutes, the mixture was diluted with 10% sodium bicarbonate solution. The organic phase was separated, dried (magnesium sulfate) and evaporated. The residue was crystallized from hexane (60 ml) to provide 12.9 g (71%) of the title compound as a pale yellow solid, mp 107-109°, which was used without further purification.

For analytical purposes, a sample was recrystallized from methylene chloride/hexane, mp 109-111°; pmr (deuteriochloroform): 400 MHz δ 9.32 (s, 1 H), 7.32 (dd, 1 H), 6.90 (t, 1 H), 3.98 (m, 2 H), 3.74 (s, 3 H), 2.99 (d, 1 H), 2.91 (d, 1 H), 2.75 (m, 2 H), 2.08 (m, 2 H), and 0.82 (t, 3 H).

Anal. Calcd. for $C_{16}H_{17}BrFNO_3$: C, 51.91; H, 4.63; N, 3.78. Found: C, 51.97; H, 4.92; N, 3.93.

1-Ethyl-7-fluoro-8-bromo-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid (**27**).

Ester **26** (1.5 g, 4.0 mmoles) in ethanol (14 ml) and 1 *N* sodium hydroxide (7 ml) was heated at reflux for 90 minutes. The ethanol was removed *in vacuo* and the residue was made acidic with 2 *N* hydrochloric acid. The reaction mixture was extracted into ether and the organic phase was washed with water, dried (magnesium sulfate), and concentrated. Recrystallization of the residue from hexane/methylene chloride gave 1.2 g (83%) of the title compound as colorless crystals, mp 185-186°; pmr (deuteriochloroform): 400 MHz δ 7.33 (dd, 1 H), 6.92 (t, 1 H), 4.02 (m, 2 H), 2.95 (d, 1 H), 3.00 (d, 1 H), 2.80 (m, 2 H), 2.10 (m, 3 H), and 0.86 (t, 3 H).

Anal. Calcd. for $C_{15}H_{15}BrFNO_3$: C, 50.58; H, 4.25; N, 3.93. Found: C, 50.49; H, 4.39; N, 4.04.

1-Ethyl-7-fluoro-8-(*n*-butyl)thio-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic acid (**28**).

Pyranoindole **26** (2.0 g, 5.3 mmoles), copper (I) oxide (0.773 g, 5.4 mmoles), *n*-butanethiol (1.46 g, 1.74 ml, 162 mmoles) and pyridine (1.5 ml) were dissolved in *N,N*-dimethylformamide (20 ml) and heated in a closed system at 150° for 3 days. The reaction mixture was cooled and treated with more copper (I) oxide (1 g, 7 mmoles), *n*-butanethiol (1.68 g, 2.0 ml, 186 mmoles) and pyridine (2 ml). After heating an additional 5 days, tlc analysis indicated complete reaction with some ester saponification. The reaction mixture was partitioned between ether (250 ml) and 2 *N* hydrochloric acid (200 ml). The mixture was stirred at room temperature for 1 hour and filtered through Celite. The organic phase was washed with brine (50 ml), dried (magnesium sulfate) and concentrated to an oil (2.6 g). The oil was dissolved in methanol (25 ml), treated with sodium hydroxide (0.5 g, 12.5 mmoles) and heated at reflux for 15 hours. The reaction mixture was cooled to room temperature, concentrated and partitioned between ether (100 ml) and 2 *N* hydrochloric acid (35 ml). The organic layer was dried (magnesium sulfate), concentrated, and chromatographed (silica gel treated with 2% phosphoric acid in methanol and dried; 3.9 x 15 cm column; 20% ethyl acetate in hexane elution) to give 1.24 g (63%) of the title compound as a clear oil, pmr (deuteriochloroform): 200 MHz δ 0.89 (6 H, 2 t), 1.45 (6H, m), 2.1 (2H, m), 2.8 (4H, m), 3.05 (2H, 2d), 4.1 (2H, m), 6.87 (1H, t), 7.4 (1H, dd), 8.95 (1H, br s).

1-Ethyl-7-fluoro-8-(2,2,2-trifluoroethyl)thio-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid (**29**).

Thioether **28** (1.2 g, 3.3 mmoles) was dissolved in tetrahydrofuran (25 ml) and added to liquid ammonia (*ca.* 60 ml) at -78°. Sodium metal (small chunks) was added until the purple color persisted and the ammonia was allowed to evaporate over the next 15 hours. The mixture was partitioned between ether (100 ml) and 2 *N* hydrochloric acid (50 ml). The ether phase was separated, washed with brine (50 ml), dried (magnesium sulfate) and concentrated to give 0.95 g (93%) of an oil, which was used without further purification.

The oil (0.95 g, 3.1 mmoles) was dissolved in benzene (50 ml), cooled to 0° in ice and was treated with trifluoroethyliodide (0.774 g, 364 μl, 7.7 mmoles) and 1,8-diabicyclo[5.4.0]undec-7-ene (1.17 g, 1.15 ml, 7.7 mmoles). Some *N,N*-dimethylformamide (10 ml) was then added to make the solution homogeneous and the reaction mixture was stirred at room temperature for 4 hours. The mixture was partitioned between ether (100 ml) and 2*N* hydrochloric acid (50 ml). The organic layer was washed with brine (50 ml), dried (magnesium sulfate), concentrated and chromatographed (silica gel treated with 2% phosphoric acid in methanol and dried; 3.9 x 15 cm column; 20% ethyl acetate in hexane elution) to give the product as a clear oil. Trituration of the oil in ethyl acetate-hexane gave 0.59 g (49%) of the title compound as a white solid, mp 88-89°; pmr (deuteriochloroform): 400 MHz δ 0.85 (3H, t, J = 7.4 Hz), 2.09 (2H, 2 dq), 2.78 (2H, m), 3.02 (1H, d, J = 16.6 Hz), 3.05 (1H, d, J = 16.6 Hz), 3.35 (2H, q, J = 9.7 Hz), 4.05 (2H, m), 6.92 (1H, dd, J = 8.6, 9.6 Hz), 7.44 (1H, dd, J = 4.9, 8.4 Hz), 9.04 (1H, br s); ir (potassium bromide): 1712, 2800-3500, 3400 cm^{-1}; ms: (m/e) 391, 362, and 332.

Anal. Calcd. for $C_{17}H_{17}NF_4SO_3$: C, 52.17; H, 4.38; N, 3.58. Found: C, 52.43; H, 4.42; N, 3.57.

Methyl 1-Ethyl-7-fluoro-8-(2-propenyl)-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetate (**30**).

A mixture of **26** (18.5 g, 50 mmoles), allyltributyltin (26 g, 78 mmoles), and tetrakis(triphenylphosphine)palladium (1 g) in benzene (40 ml) was divided between two 7 inch pressure vials and heated at 115° (3" immersion) with stirring for 65 hours. The reaction mixture was filtered (benzene washes) and the filtrate was evaporated to dryness to yield 47 g of an oil which was used in the next step. An analytical sample, mp 96-97°, was obtained by crystallization from ether/hexane; pmr (deuteriochloroform): 200 MHz δ 9.12, (s, 1 H), 7.3 (dd, 1 H), 6.9 (dd, 1 H), 6.0 (m, 1 H), 5.2 (dd, 2 H), 4.0 (m, 2 H), 3.72 (s, 3 H), 3.65 (d, 2 H), 2.98 (q, 2 H), 2.78 (q, 2 H), 2.10 (m, 2 H), and 0.82 (t, 3 H).

Anal. Calcd. for $C_{19}H_{22}FNO_3$: C, 68.87; H, 6.69; N, 4.22. Found: C, 69.15; H, 6.93; N, 4.20.

1-Ethyl-7-fluoro-8-(2-propenyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic Acid (**31**).

Crude ester **30** (47 g) in ethanol (400 ml) and 1 *N* sodium hydroxide (200 ml) was stirred at reflux for 90 minutes. The ethanol was removed *in vacuo*. Additional 1 *N*-sodium hydroxide (200 ml) was added and the reaction mixture was washed with hexane. The aqueous extract was acidified with 2 *N* hydrochloric acid and extracted into ether. The combined ethereal extracts were washed with brine, dried (magnesium sulfate), concentrated, and purified by passing through a 6" pad of flash silica gel (pretreated with 2% phosphoric acid in methanol and then dried) with 10% ether/hexane elution to yield 12.3 g of compound. Recrystallization from methylene chloride/hexane provided 11.7 g (74%) of pure title compound as colorless cyrstals, mp

122-124°; pmr (deuteriochloroform): 400 MHz δ 7.28 (m, 1 H), 6.85 (dd, 1 H), 5.9 (m, 1 H), 5.1 (dd, 2 H), 4.0 (m, 2 H), 3.6 (d, 2 H), 3.0 (dd, 2 H), 2.8 (m, 2 H), 2.0 (m, 2 H), and 0.85 (t, 3 H); ir (potassium bromide): 3440, and 1700 cm^{-1}.

Anal. Calcd. for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; N, 4.41. Found: C, 68.21; H, 6.37; N, 4.38.

3-(2-Fluoro-6-nitrophenyl)propanoic Acid (**33**).

Benzylic bromination of **32** was performed on a 98 g (0.63 mole) of **32** according to the procedure of Bentov *et al.* [14] to yield 121 g (82%) of product as a tan solid, mp 52-53° (lit 55-56°) [14].

To 15.08 g (0.62 mole) of magnesium turnings was added *ca.* 50 ml of ethanol and 1.5 ml of carbon tetrachloride. After hydrogen gas evolution ceased, an additional 200 ml of ethanol was added. The reation mixture was refluxed and to it was added dropwise over 2 hours, 100 g (0.625 mole) of diethyl malonate. The reaction mixture was refluxed until the magnesium turnings were consumed (*ca.* 21 hours). The reaction mixture was cooled to ambient temperature and then a solution of the benzylic bromide derivative of **32** (121 g, 0.517 mole) in 130 ml of hot absolute ethanol was added in one portion. After refluxing for 24 hours, the deep red reaction mixture was cooled to 0°, and then poured slowly into a solution of concentrated sulfuric acid (64.6 ml) in water (430 ml) at 0°. The ethanol was removed *in vacuo* and the residue was extracted into methylene chloride. The combined organic extracts were washed with water and then brine, dried (magnesium sulfate), and concentrated to yield 180 g of crude product which was used directly in the next reaction.

The crude product was refluxed in a mixture of glacial acetic acid (430 ml) and 20% hydrochloric acid (430 ml) for 16 hours. After removing solvent *in vacuo*, the residue was partitioned between ether (225 ml) and enough 2 *M* potassium carbonate to reach basic *p*H. The biphasic reaction was filtered to remove insoluble matter. The aqueous phase was acidified with concentrated hydrochloric acid (acidic to Congo red). The mixture was then extracted into ether, dried (magnesium sulfate), and concentrated to yield 101 g (92%) of the title compound as a tan solid, mp 97-98°, which was used as such in the next step; pmr (deuteriochloroform): 400 MHz δ 7.73 (d, 1H), 7.36 (m, 2 H), 3.20 (t, 2 H), and 2.77 (t, 2 H); ms: (m/e) 213, 167, and 154.

N,N-Dimethyl-3-(2-amino-6-fluorophenyl)propanamide (**34**).

To a suspension of crude acid **33** (9.0 g, 42 mmoles) in benzene (55 ml) containing 5 drops of *N,N*-dimethylformamide was added dropwise thionyl chloride (65 ml, 55 mmoles). After stirring at ambient temperature for 15 minutes a solution resulted. After 35 minutes, formation of the acid chloride was complete as determined by tlc (methanolic quenched aliquot; 1% phosphoric acid-methanol treated tlc plates; methylene chloride-methanol (95:5) solvent system). The reaction mixture was evaporated to dryness; pmr (deuteriochloroform): 200 MHz δ 7.8 (d, 1 H), 7.4 (m, 2 H), and 3.3 (m, 2 H).

To a saturated solution of dimethylamine gas in ether (50 ml) was added dropwise a solution of crude acid chloride (prepared from 5 mmoles of the acid as described above). After stirring for 90 minutes at ambient temperature, the reaction mixture was evaporated to dryness. The residue was diluted with water and extracted into ether (3 x). The combined organic extracts were then dried (magnesium sulfate) and evaporated to dryness to provide a pale brown oil (1.1 g, 92% yield) which was used as is in the next step; pmr (deuteriochloroform): 400 MHz, 7.67 (d 1 H), δ 7.26-7.38 (m, 2 H), 3.16 (t, 2 H), 2.97 (s, 3 H), 2.94 (s, 3 H), and 2.67 (t, 2 H); ms: (m/e) 240, 194 and 72.

A solution of the crude amide in ethanol (40 ml) was hydrogenated at normal pressure and ambient temperature in the presence of 0.2 g of 10% palladium on carbon. After 4 hours, the reaction mixture was filtered through Solka-Floc [27] (ethanol and methylene chloride rinses) and concentrated. Flash chromatography (methylene chloride-methanol-ammonium hydroxide (97.8:2.0:0.2)) provided 0.61 g (64%) of the title compound as an off-white solid; pmr (deuteriochloroform): 200 MHz δ 6.95 (q, 1 H), 6.4 (m, 2 H), 2.95 (m, 8 H), and 2.65 (t, 2 H); ms: (m/e) 210, 166 and 137.

N,N-Dimethyl-[7-[6-fluoro-3-(2-hydroxyethyl)]indolyl]propanamide (**35**).

To a mixture of aniline **34** (5.9 g, 28 mmoles) in 38 ml of concentrated hydrochloric acid at 0° was added dropwise a solution of sodium nitrite (1.94 g, 28 mmoles) in water (17 ml). The pale orange solution was stirred for 10 minutes and then treated with a solution of stannous chloride dihydrate (12.6 g, 56 mmoles) in 12 ml of concentrated hydrochloric acid. The yellow solution was stirred to room temperature over 2 hours and then poured into a mixture of ice and 50% sodium hydroxide. The mixture was extracted into ether. The organic extract was washed with 1 *N* sodium hydroxide (50 ml) and then brine (50 ml). The organic phase was dried (sodium sulfate), filtered, and treated with excess anhydrous hydrogen chloride. The solvent was removed *in vacuo* to afford 6.2 g (85% yield) of crude diazonium salt as an amorphour solid, which was used in the next step; pmr (DMSO-d_6): 400 MHz δ 10.3 (br s, 3 H), 8.7 (br s, 1 H), 7.22 (m, 1 H), 6.75-6.82 (m, 2H), 2.91 (s, 3 H), 2.82 (s, 3 H), 2.75 (t, 2 H), and 2.61 (t, 2 H); ms: (m/e) 225, 180, 83, and 72.

The crude material (6.2 g, 24 mmoles) and 2.3-dihydrofuran (1.68 g, 24 mmoles) in 50 ml of tetrahydrofuran-water (1:1) was stirred for 2 hours at ambient temperature. The reaction mixture was partitioned between ether (50 ml) and water (50 ml). The organic phase was dried (sodium sulfate) and concentrated to afford crude hydrazone (5.0 g, 71% yield) as a yellow oil.

Crude hydrazone (14 g, 47 mmoles) and zinc chloride (12.9 g, 94.1 mmoles) in ethylene glycol (125 ml) was heated at 160° for 3 hours. The reaction mixture was partitioned between 1 l of ethyl acetate and 1 l of water. The organic phase was washed with 1 *N* hydrochloric acid (250 ml) and then brine. The extract was then dried (sodium sulfate) and purified by flash chromatography (methylene chloride-methanol-ammonia 95:5:0.5) to afford 5.5 g (42% yield) of the title compound as an orange oil; pmr (deuteriochloroform): 200 MHz δ 9.87 (bs, 1 H), 7.36 (m, 1 H), 7.08 (s, 1 H), 6.84 (s, 1 H), 3.86 (t, 2 H), 3.27 (t, 2 H), 2.98 (m, 2 H), 2.92 (s, 6 H), and 2.68 (t, 2 H); ms: (m/e) 287 and 136.

8-[3-(Dimethylamino)-3-oxopropyl]-1-ethyl-7-fluoro-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid (**36**).

A solution of **35** (2.0 g, 7.2 mmoles) and methyl-3-methoxy-2-pentenoate (1.24 g, 8.6 mmoles) in methylene chloride (100 ml) containing a few drops of boron trifluoride etherate was stirred at room temperature for 5 hours. The reaction mixture was diluted with 100 ml of methylene chloride, washed successively with 5% sodium bicarbonate and brine, and dried (sodium sulfate). Purification by flash chromatography (methylene chloride-methanol 19:1) gave 2.65 g (95% yield) of the methyl ester of **36**.

An analytical sample was recrystallized from ether-hexane to provide a colorless solid, mp 86-88° (sintering at 58°); pmr (deuteriochloroform): 400 MHz δ 9.95 (s, 1 H), 7.24 (m, 1 H), 6.82 (dd, 1 H), 4.03 (m, 2 H), 3.7 (s, 3 H), 3.25 (m, 2 H), 2.93 (dd, 2 H), 2.91 (s, 3 H), 2.92 (s, 3 H), 2.64-2.82 (m, 4 H), 2.1 (q, 2 H), and 0.78 (t, 3 H); ir (potassium bromide): 1760, and 1620 cm^{-1}; ms: (m/e) 390, 361, and 317.

Anal. Calcd. for $C_{21}H_{27}FN_2O_4$: C, 64.60; H, 6.97; N, 7.17. Found: C, 64.25; H, 7.06; N, 6.80.

The ester (1.8 g, 4.6 mmoles) in a mixture of ethanol (15 ml) and 2.5 *N* sodium hydroxide (5 ml) was stirred at room temperature for 2 hours. The solvent was removed by distillation and the residue was dissolved in water (150 ml). The solution was washed with ether and the aqueous phase was then acidified with concentrated hydrochloric acid. The resulting solid was collected by filtration, washed successively with water and methanol, and dried to provide the title compound (0.91 g 53% yield) as an off-white solid, mp 218-219° dec; pmr (DMSO-d_6): 400 MHz δ 7.21 (dd, 1 H), 6.78 (dd, 1 H), 3.91 (m, 2 H), 3.01 (t, 2 H), 2.86 (dd, 1 H), 2.87 (s, 3 H), 2.84 (s, 3 H), 2.69 (d, 1 H), 2.48-2.66 (m, 4 H), 2.02 (q, 2 H), and 0.61 (t, 3 H); ir (potassium bromide): 1690 and 1600 cm^{-1}; ms: (m/e) 376, 317, and 72.

Anal. Calcd. for $C_{20}H_{25}FN_2O_4$: C, 63.81; H, 6.69; N, 7.44. Found: C, 63.77; H, 7.02; N, 7.29.

7-[3-(Dimethylamino)propyl]-6-fluorotryptophol (**37**).

To a solution of 3.5 g, 12.6 mmoles) of amide **35** in dry tetrahydrofuran (20 ml) was added portionwise lithium aluminum hydride (3.5 g, 92 mmoles) over 20 minutes. The slurry was stirred for 1 hour at room temperature. The reaction mixture was decomposed by the stepwise addition of water (3.5 ml), 1 *N* sodium hydroxide (3.5 ml) additional water (10.5 ml), and then sodium sulfate (44 g). After stirring for 20 minutes, the reaction mixture was filtered. The filtrate was concentrated to afford crude **37** (3.3 g) as an amber oil, which was pure enough to be used in the next step. Purification was also achieved by trituration of the product with ether to afford the title compound as an off white solid, mp 115-117°; pmr (deuteriochloroform): 400 MHz δ 10.9 (s, 1 H), 7.36 (dd, 1 H), 7.04 (d, 1 H), 6.84 (dd, 1 H), 3.89 (t, 2 H), 3.01 (t, 2 H), 2.95 (t, 2 H), 2.27 (s, 6 H), 2.17 (t, 2 H), and 1.88 (m, 2 H); ms: (m/e) 264, 233, and 188.

8-[3-(Dimethylamino)propyl]-1-ethyl-7-fluoro-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid Methyl Ester Hydrochloride (**38**).

A solution of **37** (3.3 g, 12.5 mmoles) and methyl 3-methoxy-2-pentenoate (2.34 g, 16.5 mmoles) in 100 ml of methylene chloride containing boron trifluoride etherate (1.54 ml, 12.5 mmoles) was stirred at room temperature for 2 hours. The turbid reaction mixture was diluted with 200 ml of methylene chloride, washed successively with 5% sodium bicarbonate and brine, and dried (sodium sulfate). Purification was accomplished by flash chromatography (methylene chloride-methanol-ammonium hydroxide (9:1:0.5)) to provide 3.1 g (66% yield) of the free base of the title compound as an amorphous solid. The compound was characterized as the hydrochloride salt by treating 1.0 g of free base with ethereal hydrogen chloride and resulting off-white solid was collected (0.46 g), mp 163-164°; pmr (deuteriochloroform): 400 MHz δ 10.74 (bs, 1 H), 7.25 (m, 1 H), 6.82 (dd, 1 H), 4.0 (m, 2 H), 3.6 (s, 3 H), 3.25-3.44 (m, 2 H), 3.23 (d, 1 H), 3.05 (d, 1 H), 2.9-2.8 (m, 2 H), 2.81 (s, 6 H), 2.72 (m, 2 H), 2.19 (m, 4 H), and 0.82 (t, 3 H); ir (potassium bromide): 1750 cm^{-1}; ms: (m/e) 376, 303, and 85.

Anal. Calcd. for $C_{21}H_{29}FN_2O_3 \cdot HCl$: C, 61.08; H, 7.32; N, 6.78. Found: C, 60.82; H, 7.17; N, 6.63.

8-[3-(Dimethylamino)propyl]-1-ethyl-7-fluoro-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid (**39**).

A solution of the ester (free base, 2.0 g, 5.3 mmoles) in ethanol (30 ml) containing 2.5 *N* sodium hydroxide (5 ml) was stirred at room temperature for 3 hours. The solvent was removed *in vacuo*. The residue was dissolved and adjusted to *p*H 7 with dilute hydrochloric acid. The reaction mixture was extracted into methylene chloride (3 x). The organic phase was washed with brine and then dried (sodium sulfate). The solvent was removed and the residue was triturated with ether to furnish 1.08 g (56% yield) of the title compound as an off-white solid, mp 159-161°; pmr (deuteriochloroform): 400 MHz δ 7.27 (m, 1 H), 6.82 (dd, 1 H), 4.03 (m, 2 H), 2.81-3.0 (m, 6 H), 2.76 (t, 2 H), 2.61 (s, 6 H), 2.16 (m, 4 H), and 0.88 (t, 3 H); ms: (m/e) 362, 318, 303, 289, and 85.

Anal. Calcd. for $C_{20}H_{27}FN_2O_3$: C, 66.28; H, 7.51; N, 7.73. Found: C, 65.95; H, 7.35; N, 7.42.

N,N,N-Trimethyl-3-[7,6-fluoro-3-(2-hydroxyethyl)indolyl]propylammonium Iodide (**40**).

A solution of amine **37** (5.0 g, 18.9 mmoles) in dry tetrahydrofuran (50 ml) was treated with methyl iodide (1.25 ml, 20 mmoles). After stirring for 1 hour at ambient temperature (complete reaction as judged by tlc) the solvent was removed *in vacuo* to afford 7 g of the title compound as a colorless foam which was used in the next reaction; pmr (DMSO-d_6): δ 10.98 (s, 1 H), 7.38 (m, 1 H), 7.20 (s, 1 H), 6.82 (t, 1 H), 4.61 (t, 1 H), 3.60 (m, 4 H), 3.05 (s, 9 H), 2.82 (m, 4 H), and 2.0 (m, 2 H).

7-Fluoro-5,6-dihydro-4*H*-pyrrolo[3,2,1-*if*]quinoline-1-ethanol (**41**).

A solution of **40** (5.2 g, 12.8 mmoles) in 150 ml of methanol was stirred with 50 g of Amberlite IRA 400 (OH) resin (prewashed with methanol according to the procedure of Kaiser [16]). The entire mixture was transferred to a column and the resin eluted with methanol until the eluant was no longer basic. The eluate was evaporated under reduced pressure. The residue was pyrolized at 125-140° for 1 hour (until gas evolution ceased) and then was purified by flash chromatography (methylene chloride-methanol (19:1)) to afford 2.1 g (75% yield) of the title compound. An analytical sample, mp 69-70°, was prepared by recrystallization from ether-petroleum ether; pmr (deuteriochloroform): 400 MHz δ 7.31 (dd, 1 H), 6.94 (s, 1 H), 6.8 (dd, 1 H), 4.08 (t, 2 H), 3.87 (br s, 2 H), 2.98 (m, 4 H), 2.21 (m, 2 H), and 1.49 (br, 2 H); ms (m/e) 219, 188, and 160.

Anal. Calcd. for $C_{13}H_{14}FNO$: C, 71.21; H, 6.44; N, 6.39. Found: C, 71.37; H, 6.27; N, 6.37.

8-Ethyl-3-fluoro-5,6,10,11-tetrahydro-4*H*,8*H*-pyrano[4',3':4,5]-pyrrolo[3,21-*ij*]quinoline-8-acetic Acid (**43**).

A solution of tryptophol **41** (0.91 g, 4.1 mmoles) and methyl 3-methoxy-2-pentenoate (0.65 g, 4.5 mmoles) in methylene chloride (20 ml) containing a trace of boron trifluoride etherate was stirred at room temperature for 1 hour. The reaction mixture was diluted with an equal portion of methylene chloride, washed with saturated bicarbonate solution and then brine, dried (sodium sulfate), and flash chromatographed (methylene

chloride-hexane (1:1)) to provide 0.87 g (64% yield) of the methyl ester of the title compound as a clear oil; pmr (deuteriochloroform): 400 MHz δ 7.2 (dd, 1 H), 6.8 (dd, 1 H), 4.03 (m, 4 H), 3.62 (s, 3 H), 2.68-3.05 (m, 6 H), 2.23 (m, 2 H), 2.06 (q, 2 H) and 0.76 (t, 3 H); ms: (m/e) 331, 302, and 258.

The ester (0.94 g, 2.8 mmoles) in 5 ml of ethanol and 5 ml of 1 *N* sodium hydroxide was stirred at room temperature overnight. The solvent was evaporated *in vacuo*, the residue diluted with water, and then washed with ether. The aqueous phase was acidified with concentrated hydrochloric acid and extracted into ether. The organic phase was dried (sodium sulfate) and concentrated. The oily residue was triturated from 1:1 ether petroleum ether to afford 0.65 g (73% yield) of the title compound as a colorless solid, mp 130-132°; pmr (deuteriochloroform): 400 MHz δ 7.21 (dd, 1 H), 6.81 (dd, 1 H), 4.11 (t, 2 H), 4.03 (m, 2 H), 2.84-3.4 (m, 6 H), 2.23 (m, 2 H), 2.05 (m, 2 H), and 0.86 (t, 3 H); ir (potassium bromide): 1740 cm^{-1}; ms: (m/e) 317, 288 and 258.

Anal. Calcd. for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; N, 4.41. Found: C, 68.12; H, 6.19; N, 4.79.

(*E*)-6-Fluoro-7-(1-propenyl)tryptophol (**44**).

A solution of **40** (7.0 g, 17.2 mmoles) in 120 ml of methanol was stirred for 2-3 minutes with 75 g of Amberlite IRA 400 (OH) resin (prewashed with methanol as described by Kaiser [16]). The entire mixture was transferred to a column and the resin was eluted with methanol until the eluent was no longer basic. The eluate was treated with 2 *N*-potassium hydroxide (17.2 ml) and then evaporated to dryness under reduced pressure. The residue was heated at 135° under reduced pressure (9 mm Hg) for 1 hour. The residue was purified by flash chromatography (methylene chloride-methanol (98:2 and 95:5)) to provide 0.69 g of pure **41** (less polar), 0.50 g of mixed fractions of **41** and **44**, and 0.77 g (20% yield) of title compound as a clear oil; pmr (deuteriochloroform): 200 MHz δ 8.28 (b, 1 H), 7.4 (dd, 1 H), 7.1 (d, 1 H), 6.9 (dd, 1 H), 6.68 (ds, 1 H), 6.35 (dq, 1 H), 3.9 (t, 2 H), 3.05 (t, 2 H), and 2.05 (d, 3 H).

(*E*)-1-Ethyl-7-fluoro-8-(1-propenyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid (**45**).

A solution of tryptophol **44** (0.77 g, 3.51 mmoles) and methyl 3-methoxy-2-pentenoate (0.66 g, 4.6 mmoles) in 30 ml of methylene chloride containing a few drops of boron trifluoride etherate was stirred at room temperature for 30 minutes. The reaction mixture was diluted with 30 ml of methylene chloride and was washed with 5% sodium bicarbonate and brine. The organic phase was dried (sodium sulfate) and concentrated. Purification by flash chromatography (methylene chloride) provided 0.90 g (78% yield) of the methyl ester of the title compound as an amber oil; pmr (deuteriochloroform): 2.00 MHz δ 9.4 (g, 1 H), 7.22 (m, 1 H), 6.55-6.9 (m, 2 H), 6.4 (m, 1 H), 3.85-4.1 (m, 2H), 3.7 (s, 3 H), 2.95 (dd, 2 H), 2.72 (m, 2 H), 1.9-2.2 (m, 5 H), and 0.81 (t, 3 H).

The ester (0.85 g, 2.6 mmoles) was stirred at room temperature in a solution of ethanol (10 ml) and 2.5 *N* sodium hydroxide (2 ml) for 3 hours. The solvent was removed under reduced pressure. The residue was diluted with water and washed with ether. The aqueous phase was acidified with concentrated hydrochloric acid and then extracted into ether. The organic phase was washed with brine, dried (sodium sulfate), and concentrated. The residue was crystallized from ether-petroleum ether to provide 0.67 g (82% yield) of pure title compound as a white solid, mp 164-166° dec; pmr (DMSO-d_6): 400 MHz δ 7.22 (dd, 1 H), 6.83 (dd, 1 H), 6.7 (d, 1 H), 6.45 (m, 1 H), 3.9 (m, 2 H), 2.91 and 2.74 (dd, 2 H), 2.55-2.65 (m, 2 H), 2.02 (m, 2 H), 1.96 (d, 3 H), and 0.6 (t, 3 H); ms: (m/e) 317, 288, and 258.

Anal. Calcd. for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; N, 4.41. Found: C, 67.87; H, 6.19; N, 4.35.

2-(2-Benzyloxyethyl)-3-fluoroaniline Hydrochloride (**46**).

A solution of potassium hydroxide (0.75 g) in ethanol (5 ml) was added to a mixture of **32** (77.5 g 0.5 mole) and paraformaldehyde (15 g, 0.5 mole) in dimethylsulfoxide (75 ml). After stirring for 3 days at room temperature, the dark solution was diluted with water (1.2 l), adjusted to *p*H 6.5 with 2.5 *N* hydrochloric acid, and was extracted into ether. The organic extracts were washed with brine, dried (magnesium sulfate), and evaporated to dryness. The solid was triturated with light petrol ether (removed small amount of **32**) to provide 82.3 g (89% yield) of pure alcohol as a pale yellow solid, mp 45-46°, which was used in the next step; pmr (deuteriochloroform): 400 MHz δ 7.72 (d, 1 H), 7.37 (m, 2 H), 3.93 (m, 2 H), 3.2 (t, 2 H), and 1.67 (t, 1 H); ms: (m/e) 138.

At 0° to a mechanically stirred solution of the alcohol (82 g, 0.44 mole) and benzyl chloride (300 ml) was added slowly 50% sodium hydroxide (133 ml). To the reaction mixture was then added tetrabutylammonium hydrogen sulfate (7.5 g). The cold bath was removed. After 15 minutes, the reaction mixture turned dark red and the temperature rose. The temperature was maintained at 30-35° using ice cooling. After 45 minutes, the reaction mixture was diluted with an ice-water mixture (300 ml) and was extracted into ether. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated under reduced pressure (water bath temperature was 45°). Purification was achieved by passing the residue through a pad of flash silica gel (4" thick x 5.5" diameter) using 1:1 hexane-methylene chloride and then 1:1 hexane-ethyl acetate elution to yield 116.8 g (96%) of benzyl ether product as a yellow oil which was used directly in the next step; pmr (deuteriochloroform): 400 MHz δ 7.68 (d, 1 H), 7.29 (m, 7 H), 4.50 (s, 2 H), 3.70 (t, 2 H), and 3.26 (t, 2 H); ms: (m/e) 276, 168, and 91.

To a stirred solution of sodium sulfide nonahydrate (67.2 g, 0.28 mole) and sulfur flowers (8.9 g, 0.28 mole) in 130 ml of water and 70 ml of ethanol was added a solution of the benzyl ether (38.5 g, 0.14 mole) in 60 ml of ethanol. The reaction mixture was refluxed for 3 hours. The ethanol was removed under reduced pressure. The residue was diluted with water and then extracted into ether. The organic phase was washed with brine, dried (sodium sulfate), and acidified with excess anhydrous hydrogen chloride to afford 37 g (94% yield) of the title compound as white needles, mp 148-150°; pmr (DMSO-d_6): 400 MHz δ 7.25 (m, 6 H), 6.96 (d, 1 H), 6.86 (t, 1 H), 4.48 (s, 2 H), 3.58 (t, 2 H), and 2.93 (t, 2 H).

Anal. Calcd. for $C_{15}H_{16}FNO{\cdot}HCl$: C, 63.94; H, 6.08; N, 4.97. Found: C, 63.51; H, 6.00; N, 5.29.

6-Fluoro-7-(2-benzyloxyethyl)tryptophol (**47**).

To a suspension of **46** (53.0 g, 0.188 mole) in water (30 ml), concentrated hydrochloric acid (127 ml) and glacial acetic acid (127 ml) at -10° was added dropwise a solution of sodium nitrite (14.27 g, 0.21 mole) in water (52 ml) at a rate such that the internal temperature of the reaction mixture was maintained at -10°. The resulting red solution was stirred at -10° for 75 minutes. To the reaction was then added dropwise a precooled solution of tin(II)

chloride dihydrate (84.8 g, 0.376 mole) in concentrated hydrochloric acid (97 ml) over a 30 minutes period. After stirring for 75 minutes at -10°, the reaction mixture was cooled to -15°, basified (to *p*H 14) with 50% sodium hydroxide (*ca.* 320 ml) at a rate such that the temperature was maintained at -8 to -10°. The reaction mixture was extracted into ether (3 portions) and the combined organic extracts were washed with brine, dried (potassium carbonate), and then carefully acidified with ethereal hydrogen chloride. The resulting solid was collected and washed with petroleum ether (to remove less polar impurities) to provide 48.4 g, 87% yield) of hydrazine hydrochloride derivative which was used directly in the next reaction; pmr (DMSO-d_6): 400 MHz δ 10.27 (br, 3 H), 8.12 (br, 1 H), 6.8 (m, 6 H), 4.48 (s, 2 H), 3.55 (t, 2 H), and 2.92 (t, 2 H); ms: (m/e) 260, 169, and 91.

To a solution of 48.4 g (0.163 mole) of the above hydrazine hydrochloride in tetrahydrofuran (440 ml) and water (60 ml) at -10° was added a solution of 2,3-dihydrofuran (11.4 g, 0.163 mole) in tetrahydrofuran (40 ml). The reaction mixture was stirred at room temperature overnight, diluted with ether (400 ml), washed and brine (2 x 150 ml), dried (magnesium sulfate), and concentrated in vacuo to produce crude hydrazone (*E*/*Z* mixture) as a thick red oil which was used directly in the next step.

A suspension of the crude hydrazone and zinc chloride (51 g, 0.37 mole) in ethylene glycol (210 ml) was heated slowly to 90° (oil bath). After 15 minutes at 90°, the reaction mixture became homogeneous. The reaction mixture was then heated at 155° for 2 hours. The room-cooled reaction mixture was poured into 1 *N* hydrochloric acid (330 ml) containing crushed ice (330 ml), and was extracted into ether and then ethyl acetate. The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. The residue was passed through a thick pad of flash silica gel (4" diameter) with elutions of methylene chloride and then hexane-ethyl acetate (1:1) to provide 23.4 g, 46% yield) of the title compound as a tan solid, mp 75-77° dec; pmr (deuteriochloroform): 400 MHz δ 9.1 (s, 1 H), 7.25-7.40 (m, 6 H), 6.92 (d, 1 H), 6.86 (d, 1 H), 4.51 (s, 2 H), 3.88 (t, 2 H), 3.83 (t, 2 H), 3.18 (t, 2 H), and 2.98 (t, 2 H); ms: (m/e) 313, 282, and 91.

Methyl 8-(2-Hydroxyethyl)-1-ethyl-7-fluoro-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetate (**48**).

To a solution of **47** (9.39 g, 30 mmoles) and methyl 3-methoxy-2-pentenoate (4.32 g, 30 mmoles) in methylene chloride (150 ml, dried over 4 A sieves) at 0° was added over 5 minutes boron trifluoride etherate (3.68 ml, 30 mmoles). The dark solution was stirred at 0° for 10 minutes and then at room temperature for 2 hours. The reaction mixture was cooled to 0° and neutralized with 5% sodium bicarbonate. The organic phase was washed with brine, (magnesium sulfate) and concentrated to afford crude title compound which was used directly in the next step; pmr (deuteriochloroform): δ 9.31 (s, 1 H), 7.27 (m, 6 H), 6.84 (d, 1 H), 4.54 (s, 2 H), 3.88-4.02 (m, 2 H), 3.80 (t, 2 H), 3.63 (s, 3 H), 3.18 (m, 2 H), 2.72 (m, 4 H), 1.86 (q, 2 H), and 0.71 (t, 3 H); ms: (m/e), 435, 396, 352, and 91.

Crude benzyl ether was hydrogenated over 10% palladium on carbon (4 g) in methanol (150 ml) and glacial acetic acid (50 ml) at atmospheric pressure (stirred overnight). The catalyst was removed by filtration over Solka Floc [28] and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether, neutralized with 5% sodium bicarbonate, washed with brine, dried (magnesium sulfate), and concentrated to yield crude title compound which was used directly in the next step. A sample was obtained as a white solid, mp 101-103°, by trituration from ether-petroleum ether; pmr (deuteriochloroform): 400 MHz δ 9.39 (br s, 1 H), 6.86 (d, 1 H), 3.98 (m, 4 H), 3.7 (s, 3 H), 3.13 (m, 2 H), 2.94 (d, 2 H), 2.74 (m, 2), 2.06 (m, 2 H) and 0.81 (t, 3 H); ms: (m/e) 335, 306, and 262.

1-Ethyl-7-fluoro-8-(2-hydroxyethyl)-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic Acid (**49**).

A solution of **48** (1.97 g, 5.9 mmoles) in ethanol (15 ml) and 2.5 *N* sodium hydroxide (10 ml) was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The residue was dissolved in water and then washed with ether. The aqueous phase was acidified with cold concentrated hydrochloric acid and extracted into ether. The combined organic extracts were dried (sodium sulfate) and concentrated. The residue was crystallized from hexane-ethyl acetate to provide 0.70 g, (37%) of pure title compound as an off-white solid, mp 176-178°; pmr (deuteriochloroform): 400 MHz δ 7.26 (dd, 1 H), 6.84 (dd, 1 H), 4.04 (m, 2 H), 3.87 (m, 2 H), 3.0-3.2 (m, 2 H), 2.94 (dd, 2 H), 2.7-2.8 (m, 2 H), 2.09 (m, 2 H), and 0.83 (t, 3 H); ms: (m/e) 321, 292, and 262.

Anal. Calcd. for $C_{17}H_{20}FNO_4$: C, 63.54; H, 6.27; N, 4.36. Found: C, 63.73; H, 6.17; N, 4.36.

Methyl 1-Ethyl-7-fluoro-8-(2-oxoethyl)-1,3,4,9-tetrahydropyran-[3,4-*b*]indole-1-acetate (**50**).

To a solution of Dess-Martin periodinane (11.9 g, 27.1 mmoles) in methylene chloride (100 ml, dried over 4 A sieves) was added dropwise a solution of crude **48** prepared above in methylene chloride (80 ml). After stirring at room temperature for 2 hours, the reaction mixture was diluted with ether (100 ml) and was poured into saturated sodium bicarbonate solution containing sodium thiosulfate (30 g, 190 mmoles). After 10 minutes, the organic phase was separated and washed successively with saturated sodium bicarbonate and brine, dried (magnesium sulfate), and concentrated to provide crude title compound as a brown foam which was used directly in the next reaction. An analytical sample, mp 94-96°, was obtained by trituration with ether; pmr (deuteriochloroform): δ 9.76 (t, 1 H), 9.2 (s, 1 H), 7.38 (dd, 1 H), 6.92 (dd, 1 H), 3.9-4.0 (m, 4 H), 3.74 (s, 3 H), 2.95 (dd, 1 H), 2.76 (m, 2 H), 2.0 (m, 2 H), and 0.81 (t, 3 H); ms: (m/e) 333, 304 and 260.

Anal. Calcd. for $C_{18}H_{20}FNO_4$: C, 64.85; H, 6.05; N, 4.20. Found: C, 64.48; H, 5.96; N, 4.12.

Methyl 1-Ethyl-7-fluoro-8-(2-propenyl)-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetate (**31**) from **50**.

To a mixture of zinc dust (6.477 g, 99 mmoles, 325 mesh) and dibromomethane (2.27 ml, 32.4 mmoles) in tetrahydrofuran at -40° was carefully added over 10 minutes via syringe titanium(IV) chloride (2.54 ml, 23.1 mmoles). The reaction mixture was stirred for 3 days at 0-2°. The dark grey slurry was then diluted at 0° with methylene chloride (20 ml). To the reaction mixture was added dropwise over 30 minutes crude **50** (prepared above) in methylene chloride. After stirring for 110 minutes at 0°, the reaction mixture was quenched carefully (over 30 minutes) with a slurry of sodium bicarbonate (32 g) in water (16 ml). The reaction mixture was adjusted to *p*H 8 with saturated sodium bicarbonate and was filtered to remove particulates (methylene chloride

rinse). The organic phase was separated and dried (magnesium sulfate and 5 g sodium bicarbonate). After 15 minutes, the organic extract was filtered, and concentrated under reduced pressure to provide a pale yellow syrup. The material was diluted with a little methylene chloride and passed through a thick pad of flash silica gel (methylene chloride rinse) to provide 4.64 g (67% yield) of the title compound as an off-white solid, which was identical (nmr spectrum and tlc mobility to **30** prepared above).

A mixture of **30** (2.1 g, 6.34 mmoles) in methanol (20 ml) and water (20 ml) containing 2.1 g (15 mmoles) of potassium carbonate was refluxed for 90 minutes. The methanol was removed under reduced pressure and the residue was diluted with additional water (50 ml). The mixture was acidified with cold concentrated hydrochloric acid (final *p*H 3), extracted into ether, dried (sodium sulfate), and concentrated to yield **31** as a pale yellow oil which crystallized upon standing. Recrystallization from hexane-methylene chloride provided 1.55 g (75% yield) of pure **31**, mp 123-124°, as a white solid. This material was spectrally identical to that prepared above.

Anal. Calcd. for $C_{18}H_{20}FNO_3$: C, 68.20; H, 6.36; N, 4.42. Found: C, 68.17; H, 6.42; N, 4.32.

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