buffer was prepared by dissolving 1.32 g of dibasic ammonium phosphate in 750 mL of distilled water, adjusting the pH to 2.5 with 85% aqueous H_3PO_4, and diluting the solution to 1000 mL with distilled water), flow rate 2.6 mL/min, detection UV at 210 nm. The yields of 18 and recovered 17 were determined by HPLC with an external standard. The results are summarized in Table IV.

Method C (by Formic Acid). A mixture of 99% HCOOH (2.5 mL) and 17 (0.5 g, 1.02 mmol) was heated at 40 °C. The reaction was monitored by HPLC until complete. The results are summarized in Table IV.

Method D (by $AlCl_3$). To a mixture of $ClCH_2CH_2Cl$ (2.5 mL), anisole (0.11 mL, 1.02 mmol), and 17 (0.5 g, 1.02 mmol) was added, drop by drop at 0 °C, a solution of $AlCl_3$ (0.41 g, 3.06 mmol) in CH_3NO_2 (2.5 mL). The reaction was monitored by HPLC until complete. The results are summarized in Table IV.

An Improved Synthesis of Dioxindole-3-propionic Acid and Some Transformations of the C-3 Hydroxyl Group[1]

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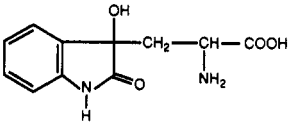
Dioxindole-3-propionic acid lactone (**3**) is obtained in 80% yield by oxidative cyclization of indole-3-propionic acid with t-BuBr/DMSO. In the presence of 18-crown-6 in DMSO, KCN opens the spirolactone ring of **3** at C-3 with the formation of 3-cyanooxindole-3-propionic acid (**4a**) in 14% yield. Methanolysis of the lactone is strongly promoted by DMAP, and the resulting 3-hydroxy ester (**5**) is converted into the 3-fluoro ester (**6**) with methyl DAST. Every attempt to isolate 3-fluorooxindole-3-propionic acid resulted in rapid intramolecular displacement of fluorine by the free carboxyl group to reform the spirolactone. The 3-hydroxy ester is converted into the 3-chloro ester (**9**) with $SOCl_2/Et_3N$. The halogen is readily displaced by nucleophiles (e.g., N_3^-, CN^-, NH_3, AcO^-, H_2O) to generate the corresponding methyl 3-X-oxindole-3-propionate. Saponification of the ester function provides the corresponding 3-X-oxindole-3-propionic acid. Acetylation of the 3-hydroxy ester provides a separable mixture of the *O*-acetyl (**16**) and *N*-acetyl (**17**) derivatives. As in the case of **3**, the *O*-acetyl derivative undergoes hydrogenolysis at C-3, while the 3-hydroxyl function is stable to removal by hydrogenolysis.

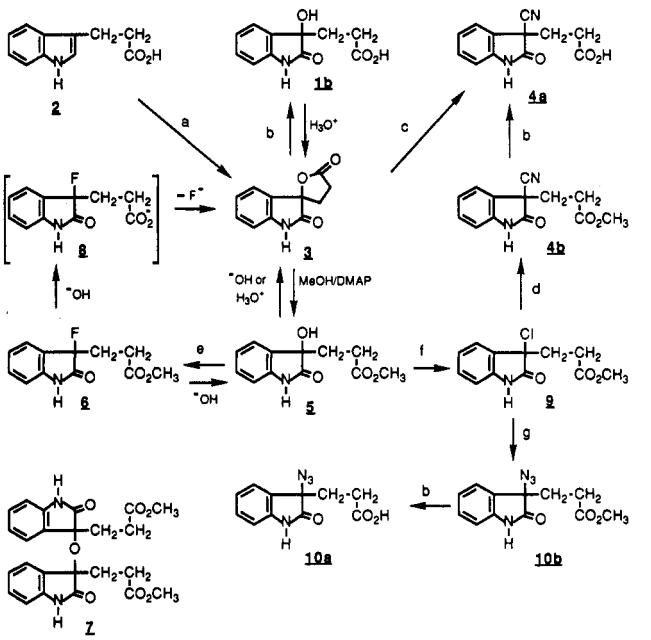
We have recently described the preparative separation of the diastereoisomers of dioxindolyl-L-alanine (**1a**) and the assignment of stereochemistry at C-3.[2] These diastereoisomers have the unique property of acting as "mirror-image enzyme inhibitors", since one isomer ($\alpha S,3R$) selectively inhibits the tryptophan-synthesizing enzyme, tryptophan synthase, while the other ($\alpha S,3S$) inhibits the tryptophan-degrading enzyme, tryptophanase.[3] Having found that these enzymes would tolerate not only hydrogen[4] but also hydroxyl[3] at C-3, we were drawn to extend the series of potential inhibitors to oxindolyl-L-alanines containing yet other substituents at C-3. Thus, we wished to evaluate the generality of the mirror-image phenomenon, the size limit of the C-3 substituents, and the possibility of creating both chemical affinity and photoaffinity labels for the enzymes through appropriate choice of substituents.



1a

Although dioxindolylalanine has been known since 1956,[5] we are unaware of any efforts to effect transformations of the C-3 hydroxyl group in the amino acid or its derivatives. Thus, we could only speculate on the possibility of effecting S_N2 displacements at the tertiary carbon or S_N1 displacements at this position adjacent to the carbocation-destabilizing oxindole carbonyl group;[6] furthermore, an N^{α}-acyl function may behave as a competitive internal nucleophile in displacing a leaving group at C-3.[7] In order to avoid the consumption of valuable dioxindolyl-L-alanine

Scheme I[a]



[a] a = *t*-BuBr/DMSO; b = ^-OH, followed by H_3O^+; c = KCN/18-crown-6, followed by H_3O^+; d = KCN/18-crown-6; e = Me DAST/$CHCl_3$; f = $SOCl_2/Et_3N/CH_2Cl_2$; g = NaN_3/15-crown-5.

(1) Taken in part from the Ph.D. dissertation (1990) of Rita B. Labroo, George Washington University, Washington, D.C.
(2) Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, *55*, 4901.
(3) Labroo, R. B.; Labroo, V. M.; Cohen, L. A., manuscript in preparation.

[†] George Washington University.
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0022-3263/91/1956-3637$02.50/0

in exploratory chemistry, we turned to the simpler model compounds, dioxindole-3-propionic acid (**1b**) and its spirolactone **3** (Scheme I). The propionic acid series offers specific interests of its own, since some inhibition of the tryptophan enzymes has been observed even without the α-amino group[8] and since we had already found that certain members of the propionic acid series are potent inhibitors of totally different enzymes.[9]

Results and Discussion

Dioxindole-3-propionic acid has been obtained by a lengthy total synthesis from dioxindole,[10] by iodine oxidation of oxindole-3-propionic acid,[10,11] or by acid hydrolysis of the spirolactone **3**.[12] The spirolactone had been obtained by direct oxidation of indole-3-propionic acid (**2**) with *N*-bromosuccinimide in 22% yield[13] or with thallium trinitrate (TTN) in 54% yield.[14] Any attempt to improve the yield by use of excess NBS would result in bromination of the benzene ring;[15] oxidation with TTN seemed unattractive not only because of the toxicity of thallium salts but because we had already experienced low yields by the use of TTN as an oxidizing agent in other cases. With t-BuBr/DMSO as oxidant,[16] however, we have effected the same oxidative cyclization to **3** in 80% yield. Despite the use of a large excess of reagent, no bromination of the benzene ring was observed.[17]

The possibility was first explored of the direct ring opening of **3** at C-3 by nucleophiles less likely to react at the lactone carbonyl group. Although the ester function is a relatively poor leaving group[18] and C-3 is a tertiary carbon, we hoped that the combination of S_N2 enhancement[19] (by the oxindole carbonyl and the benzene ring) and γ-lactone ring strain[20] might overcome such obstacles. Furthermore, an S_N1 pathway must also be considered.[21] Indeed, the reaction of **3** with KCN/18-crown-6 in DMSO at ambient temperature gave a 14% yield of **4a**, although no product was detected in comparable reactions with sodium azide or with tetra-*n*-butylammonium fluoride/silica. Tertiary halide has been found to undergo facile displacement by azide ion in somewhat comparable dihydroindole systems.[22]

The alternative approach involved alcoholysis of the lactone and further manipulation of the resulting hydroxy ester **5**. Although **3** undergoes slow, uncatalyzed methanolysis, addition of 4-(dimethylamino)pyridine (DMAP) accelerated the reaction considerably. It proved necessary to perform the methanolysis at ambient temperature, since heat was found to promote relactonization. As a crystalline solid, **5** was found to be stable at ambient temperature; however, solutions of the hydroxy ester **5** should be prepared as needed. The catalytic effect of DMAP may depend (a) on its function as a general base in facilitating the addition of methanol to the carbonyl group of spirolactone or (b) on its behavior as a nucleophile in forming an acylpyridinium intermediate. While the former role of DMAP has been demonstrated in at least one case[23] and implied in others,[24] we are unaware of any precedents for the generation of an acylpyridinium ion from an unactivated ester or lactone.[25] Nevertheless, the relief of significant bond angle strain[20] may be sufficient inducement for DMAP to add to the lactone carbonyl group.

Reaction of **5** with (diethylamino)sulfur trifluoride (DAST) in chloroform gave a 42% yield of the fluoro ester **6**, together with a significant amount of a side product, presumably **7**. Since **6** is relatively unreactive in intermolecular displacements (see below), **7** is probably formed by reaction of **5** with an intermediate formed from **5** and DAST. By use of (dimethylamino)sulfur trifluoride (methyl DAST), a reverse order of addition (**5** added to methyl DAST in anhydrous chloroform) and a more dilute reaction mixture, the yield of **6** was increased to 80% and the formation of **7** was essentially eliminated. Efforts to obtain the fluoro acid by saponification of **6** and acidification of **8** were unsuccessful and led solely to the hydroxy acid **1b**. Since **5** and **3** are both detected as intermediates by TLC, we infer that fluorine is lost by a combination of direct displacement by hydroxide ion to form **5**, and intramolecular displacement by the carboxylate anion in **8** to form **3**; in alkaline medium, both **3** and **5** hydrolyze readily to **1b**. Acid hydrolysis (0.1 N H_2SO_4 for 7 d at 25 °C) of **6** provided a mixture of **6**, **1b**, **3**, and **5**; other than the starting material **6**, no fluorine-containing products could be detected.

The fluoro ester **6** proved to be a substrate for α-chymotrypsin,[3] but the hydrolysis product **8** recyclized to **3** too rapidly (at pH 7) to be isolated. The conversion of **8** to **3** is apparently faster than that of 4-fluorobutyrate acid to γ-butyrolactone; for the latter reaction, $t_{1/2}$ = 40 h at 25 °C (a value estimated from literature data at higher temperatures).[26] Presumably, the intramolecular displacement of the fluorine atom in **8** is enhanced by the adjacent phenyl and carbonyl functions.[19] Despite our inability to obtain the conjugate acid of **8** by enzymatic hydrolysis, the reaction proved gratifying in that both the lactone **3** and the unreacted fluoro ester **6** were found to be optically active.[3]

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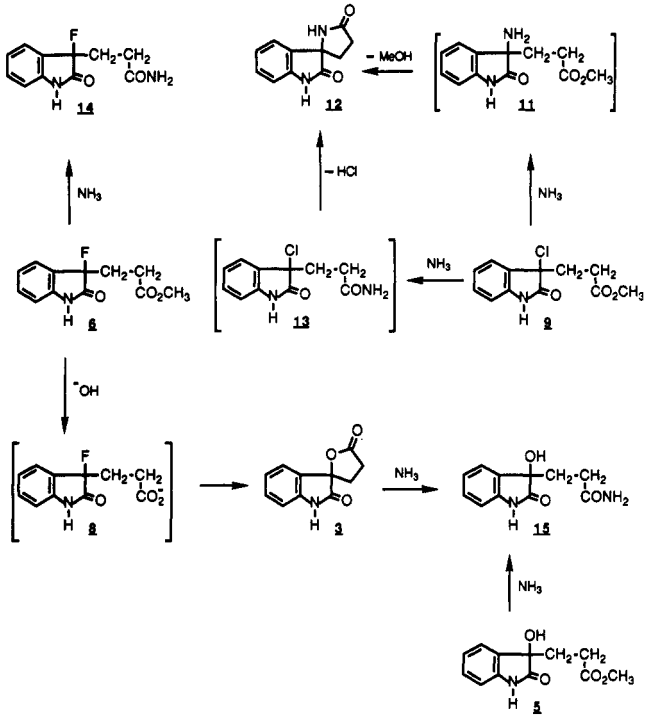
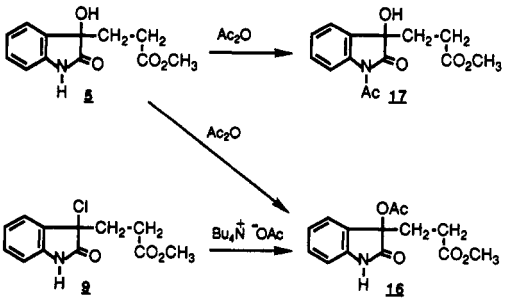
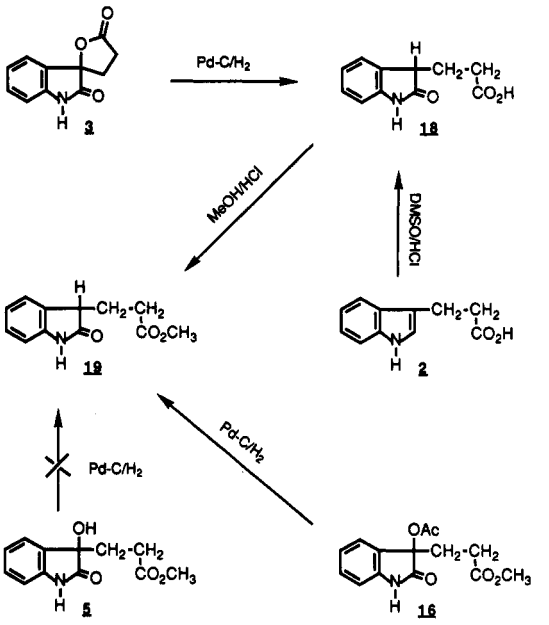
Scheme II



Scheme III



Scheme IV



Although the fluorine atom in **8** proved to be very reactive toward intramolecular displacement by carboxylate ion, it was considerably less reactive toward intermolecular displacement in **6**, even by such effective nucleophiles as azide and cyanide ions. Accordingly, the use of chlorine as a better leaving group was explored. Reaction of **5** with thionyl chloride in dichloromethane gave only **3**, the acid-catalyzed relactonization of **5** being faster than the reaction of the C-3 hydroxyl group with thionyl chloride. In the presence of 1 equiv of triethylamine, however, the chloro ester **9** was obtained in 70% crude yield; the high reactivity of the halogen precluded further purification of **9**. With sodium azide and 15-crown-5, **9** was converted almost quantitatively to **10b** in 3 h at ambient temperature. Saponification of **10b** at pH 12 proceeded rapidly; the azido acid **10a** showed no tendency to regenerate **3** or to undergo loss of the azido chromophore by intramolecular addition of the carboxylate ion according to TLC, HPLC, IR, and NMR. The greater reactivity of **9** over **6** was further evident in its rapid reaction with cyanide ion to give **4b** in 77% yield. Saponification of **4b** to **4a** proceeded normally. At present, this four-step procedure for the conversion of **3** to **4a** seems preferable to the slow, one-step direct displacement on the lactone; on the other hand, direct displacement may be more stereospecific,[27] a consideration in the case of chiral **3**.

The various transformation products of **1b**, as illustrated by some exploratory studies, can themselves serve as starting materials for conversion to other oxindoles of both chemical and medicinal interest. Ammonolysis of **9** produced lactam **12** directly (Scheme II). The product may have been formed by cyclization of the intermediate 3-amino ester **11** or of the 3-chloro amide **13**. An intermediate was detected by TLC, but it was not identified by its mass spectrum since **11** could form **12** while **13** could also form **12** or eliminate HCl in the mass spectrometer. An examination of solvent effects revealed that, while the intermediate is formed with almost equal ease in methanol, ethanol, and 2-propanol, its conversion to **12** was slowest in 2-propanol (TLC evidence). This variation in solvent polarity should affect carbonyl reactions more than intramolecular nucleophilic displacements;[28] hence, we suggest that **11** is the more likely intermediate in the conversion of **9** to **12**. In the case of the less reactive fluoro ester, however, ammonolysis occurs preferentially at the ester function to give the fluoro amide **14**. This compound did not cyclize spontaneously in the presence of ammonia or in the mass spectrometer. The stable hydroxy amide **15** is formed by direct ammonolysis of **3** or **5** (Scheme II).

For certain mechanistic studies,[3] we also required the acetate **16** of **5** (Scheme III). Direct acetylation of **5** produced a separable mixture of the *O*-acetyl- (**16**) and *N*-acetyloxindole (**17**). Structure assignment was based on ^{1}H NMR spectra and on the tendency of **16** to undergo loss of acetic acid in the mass spectrometer, while **17** loses water. Furthermore, **16** was also obtained by reaction of **9** with tetra-*n*-butylammonium acetate.

In the course of these studies, we confirmed earlier observations[5,15] that oxindole spirolactones undergo catalytic hydrogenolysis at C-3, while the corresponding 3-hydroxy esters or acids do not (Scheme IV). This difference may be attributed to the better leaving ability of the ester (lactone) function than that of the hydroxyl group[29] or to ring strain in the γ-lactone. Since **16** also undergoes hydrogenolysis under comparable conditions, it would appear

(27) Studies of ring opening of **3** with trimethylsilyl azide and cyanide are in progress: cf. Groutas, W. C.; Felkes, D. *Synthesis* **1980**, 861.

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that ring strain is less important than leaving ability. Alternatively, we consider that hydrogenolysis might be a homolytic process,[30] in which case the departure of a resonance-stabilized acyloxy radical should certainly be more facile than that of the higher energy hydroxyl radical.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL 300 or on a Varian 220 spectrometer; δ values are reported relative to internal TMS or H_2O (δ 4.78) as reference. Chemical ionization mass spectra were obtained on a Finnigan 1015 D gas chromatograph/mass spectrometer with ammonia as the reagent gas. Normal thin-layer (TLC) or reverse-phase (RPTLC) chromatography was performed using silica plates. Amino acids were detected by use of 0.2% ninhydrin in methanol.

Dioxindole-3-propionic Acid Lactone (3). A solution of indole-3-propionic acid (**2**, 11.34 g, 0.06 mol) in anhydrous DMSO (35 mL) was added dropwise, over a period of 30 min, to a stirred solution of t-BuBr (69.12 mL, 0.6 mol) in anhydrous DMSO (10 mL). The reaction mixture was stirred at 45–50 °C for 24 h, at which point the solution had become dark red and TLC indicated all starting material had reacted. DMSO was removed under high vacuum, and the dark syrupy residue was dissolved in ethyl acetate (700 mL). The solution was washed with water (3 × 100 mL), and the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue crystallized from ethyl acetate/hexanes as a light brown solid. The mixture was refrigerated overnight, and the solid was collected (8 g). The filtrated showed a substantial amount of **3** by TLC, which could not be recovered by further crystallization. The remaining product was recovered by flash column chromatography with 50% ethyl acetate/hexanes as the eluting solvent, an additional 1.7 g of **3** being obtained as a light brown solid. Total product recovery was 9.7 g (80% yield): mp 130–132 °C (lit.[13] mp 134 °C); MS (CI, NH_3) m/z (%) 221 (100) $(M + 18)^+$, 204 (15) $(M + 1)^+$; UV (50% EtOH/H_2O) λ_{max} 250.4 nm; ^{1}H NMR ($CDCl_3$) δ 2.40–3.25 (m, 4 H, two CH_2's), 6.90–7.40 (m, 4 H, aromatic). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.43; N, 6.89. Found: C, 64.76; H, 4.50; N, 6.81.

Dioxindole-3-propionic Acid (1b). To a solution of lactone **3** (1.218 g, 6 mmol) in ethanol (20 mL) was added 1 N sodium hydroxide (9 mL, 9 mmol). After 30 min, the only TLC spot was found at the origin. Ethanol was evaporated, and the aqueous solution was neutralized with 1 N hydrochloric acid to pH 3 in an ice–water bath. The product was removed completely by saturating the aqueous solution with sodium chloride and extracting exhaustively with ethyl acetate. The organic extract was dried (sodium sulfate) and concentrated in vacuo. During concentration, white crystals separated. The solid was collected and dried to give 684 mg of **1b**, mp 185–188 °C (lit.[10] mp 195–196 °C). A second crop was recovered from the filtrate for a total yield of 1.068 g (80.5% yield): MS (CI, NH_3) m/z (%) 222 (42) $(M + 1)^+$, 204 (96) $(M + 1 - H_2O)^+$, 221 (100) $(M + NH_3 - H_2O)^+$, 239 (5) $(M + 18)$; ^{1}H NMR (CD_3OD) δ 2.13–2.32 (m, 4 H, two CH_2's), 6.87–7.34 (m, 4 H, aromatic).

3-Cyanooxindole-3-propionic Acid (4a) from 3. Lactone **3** (2.03 g, 0.01 mol) was dissolved in anhydrous DMSO (100 mL). Potassium cyanide (1.95 g, 0.03 mol) was added, followed by 18-crown-6 (7.9 g, 0.03 mol), and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC (chloroform/methanol/acetic acid, 90:9:1 v/v), and essentially complete disappearance of lactone was observed after 10 days. The reaction mixture was brought to pH 3 with 1 N hydrochloric acid and was extracted with ethyl acetate (3 × 250 mL). The organic layer was washed with water (100 mL), dried (sodium sulfate), and concentrated in vacuo. The product was isolated by flash column chromatography with chloroform/methanol/acetic acid, 90:9:1 (v/v), as the eluting solvent. The fractions containing **4a** were pooled, and the solvent was removed in vacuo. The product was crystallized from ethyl acetate/hexanes as a pale brown powder (0.33 g, 14% yield): mp 158–160 °C; MS (CI, NH_3) m/z (%) 231 (55) $(M + 1)^+$, 248 (80) $(M + 18)^+$; ^{1}H NMR (D_2O) δ 2.26–2.55 (m, 4 H, two CH_2's), 7.02–7.48 (m, 4 H, aromatic). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.35; N, 12.17. Found: C, 62.37; H, 4.47; N, 12.10.

Methyl Dioxindole-3-propionate (5). Lactone **3** (4.06 g, 20 mmol) was dissolved in methanol (100 mL), and DMAP (2.68 g, 22 mmol) was added. According to TLC (50% ethyl acetate/hexanes), most of the starting material had been consumed after 24 h at room temperature. An attempt to force the reaction to completion by heating resulted in increased regeneration of **3**. The methanol was removed in vacuo to yield a yellow solid. A variety of attempts to obtain **5** free of **3** and DMAP proved unsuccessful. Eventually, all three compounds were separated by flash column chromatography, using 66% ethyl acetate/hexanes as the eluting solvent. Fractions containing **5** were pooled, solvent was removed in vacuo, and colorless crystals separated. The mixture was refrigerated overnight, and the crystals were collected to give a colorless solid (4.08 g, 87% yield), mp 120–122 °C. Unreacted **3** was also recovered (0.43 g): MS (CI, NH_3) m/z (%) 236 (40) $(M + 1)^+$, 218 (100) $(M + 1 - H_2O)^+$, 253 (2) $(M + 18)^+$; UV (50% EtOH/H_2O) λ_{max} 248.8 nm; ^{1}H NMR ($CDCl_3$) δ 2.20–2.57 (m, 4 H, two CH_2's), 3.62 (s, 3 H, OCH_3), 6.87–7.37 (m, 4 H, aromatic), 8.28 (s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 29.07, 34.02, 52.13, 76.81, 111.31, 123.68, 125.17, 130.68, 132.31, 142.67, 174.91, 181.57. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.53; N, 5.96. Found: C, 61.29; H, 5.58; N, 5.92.

The separation procedure was simplified by the use of DMAP/polystyrene, since the polymer-bound catalyst can be removed from the reaction mixture by a simple filtration step.

Methyl 3-Fluorooxindole-3-propionate (6). Method A (DAST). To a chilled solution (−60 to −70 °C) of DAST (0.762 mL, 5.7 mmol) in pentene-stabilized anhydrous chloroform (0.5 mL) was added a solution of **5** (1.35 g, 5.7 mmol) in pentene-stabilized anhydrous chloroform (2 mL). After 30–45 min, TLC (50% ethyl acetate/hexanes) showed almost complete disappearance of the starting material. The mass spectrum of the crude product showed, in addition to ion peaks for **6** and its fragments, significant signals corresponding to those of a dimer, such as **7**. The reaction mixture was diluted to 10 mL with chloroform and was washed with water (2 × 10 mL). The organic layer was dried (sodium sulfate) and the solvent evaporated. The product was separated by flash column chromatography with 66% ethyl acetate/hexanes as the eluting solvent. The fractions containing **6** were pooled, and the solvent was removed in vacuo. During removal of the solvent, crystals started to separate. Most of the compound was crystallized by diluting the solution with hexanes and refrigerating it for 2–3 h. Colorless crystals were collected (570 mg, 42% yield): mp 84–87 °C; MS (CI, NH_3) m/z (%) 238 (65) $(M + 1)^+$, 218 (100) $(M + 1 - HF)^+$, 225 (32) $(M + 18)^+$, 235 (20) $(M + 18 - HF)^+$; ^{1}H NMR ($CDCl_3$) δ 2.45–2.53 (m, 4 H, two CH_2's), 3.63 (s, 3 H, OCH_3), 6.89–7.41 (m, 4 H, aromatic), 8.13 (s, 1 H, NH); ^{19}F NMR (CD_3CN, TFA) −80.5 (t, C-3 F). Anal. Calcd for $C_{12}H_{12}NO_3F$: C, 60.76; H, 5.06; N, 5.91; F, 8.02. Found: C, 60.60; H, 4.93; N, 5.76; F, 8.46.

Method B (Methyl DAST). Compound **5** (0.796 g, 3.39 mmol) was added in small portions to an ice-cold solution (0–4 °C) of methyl DAST (0.488 mL, 5 mmol) in anhydrous pentene-stabilized chloroform (30 mL) over 2 h. The reaction mixture was stirred at 0–4 °C for an additional 2 h and was diluted with chloroform (25 mL). The solution was washed with water (2 × 10 mL), dried (sodium sulfate), and concentrated. The product was isolated by flash column chromatography with 50% ethyl acetate/hexanes as the eluting solvent. Fractions containing the product were pooled and concentrated to a viscous yellow oil. The oil was scratched and left to crystallize. It was triturated with hexanes, and the white crystalline solid was filtered (637 mg, 79.3% yield). The product was characterized by comparing its mass, ^{1}H NMR, ^{19}F NMR spectra, and R_f value with those of **6** already synthesized by the DAST method and fully characterized.

Base Hydrolysis of 6. A solution of **6** (12 mg, 0.05 mmol) in methanol (0.3 mL) was diluted with water (0.1 mL). Sodium hydroxide (1 N) was added dropwise at room temperature, maintaining the reaction mixture at pH 8–9. The immediate reaction products were identified as lactone **3** and ester **5** from mass and ^{1}H NMR spectra; both products were ultimately con-

(30) (a) Bonner, W. A. *J. Am. Chem. Soc.* **1952**, *74*, 1934. (b) Hauptmann, H.; Wladislaw, B. *J. Am. Chem. Soc.* **1950**, *82*, 707, 711. (c) Busch, M.; Schmidt, W. *Ber.* **1929**, *62*, 2612.

verted to dioxindole-3-propionic acid (**1b**) at pH 8–9 (TLC evidence). The final product was identified as **1b** by comparing its ^{1}H NMR and mass spectra and R_f value with those of **1b**, synthesized separately by alkaline hydrolysis of **3** and characterized. ^{19}F NMR spectra failed to give any response for the presence of a carbon–fluorine bond in the product.

Methyl 3-Chlorooxindole-3-propionate (9). Compound **5** (0.47 g, 2 mmol) was dissolved in anhydrous dichloromethane (20 mL). The solution was cooled in an ice–water bath, and anhydrous triethylamine (1.67 mL, 12 mmol) was added, followed by slow addition of thionyl chloride (0.729 mL, 10 mmol). The reaction was exothermic, and the color of the reaction mixture changed from yellow to orange to red and, finally, to dark red with the evolution of white fumes. The fumes were acidic to pH paper. The reaction was complete in 15 min, and TLC indicated the formation of a major spot less polar than the starting material. The reaction mixture was diluted to 100 mL with dichloromethane and was washed with water (3 × 50 mL). The organic layer was dried (magnesium sulfate), and the filtrate was concentrated in vacuo. The major spot was separated by flash column chromatography, with 50% ethyl acetate/hexanes as the eluting solvent. The fractions containing the major spot were pooled and concentrated in high vacuum to a viscous oil (360 mg, 70% yield): MS (CI, NH_3) m/z (%) 254 (100) $(M + 1)^+$, 256 (35) $(M + 1)^+$, 220 (60) $(M + 1 - HCl)^+$, 218 (25) [$(M + 1 - H_2O)^+$, SM] (SM refers to **5**); ^{1}H NMR (CD_3CN) δ 2.24–2.54 (m, 4 H, two CH_2's), 3.53 (s, 3 H, OCH_3), 6.93–7.40 (m, 4 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 29.13, 34.10, 51.81, 64.29, 110.74, 123.52, 124.65, 129.28, 130.48, 139.75, 172.29, 175.52; high-resolution mass spectrum, M^+ calcd for $C_{12}H_{12}NO_3(^{35}Cl)$ m/e 253.0506, found m/e 253.0510; high-resolution mass spectrum, M^+ calcd for $C_{12}H_{12}NO_3(^{37}Cl)$ m/e 255.0476, found m/e 255.0470.

Methyl 3-Cyanooxindole-3-propionate (4b) from 9. Compound **5** (50 mg, 0.213 mmol) was converted to **9** as described above. After the complete removal of dichloromethane, the residue was dissolved in anhydrous acetonitrile (2 mL) and potassium cyanide (83.22 mg, 1.278 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, but no apparent reaction was observed by TLC (50% ethyl acetate/hexanes). 18-Crown-6 (337.8 mg, 1.278 mmol) was introduced, and the reaction mixture was stirred at room temperature. The reaction was complete after 1 h. The acetonitrile was evaporated in vacuo, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (2 × 5 mL) and saturated brine solution (5 mL). TLC of the organic layer indicated a clean, single spot with a very faint tail (R_f of **9** = 0.61; R_f of **4b** = 0.51). The organic layer was dried (sodium sulfate) and concentrated to a pale oil (40 mg, 77% yield): MS (CI, NH_3) m/z (%) 245 (100) $(M + 1)^+$, 262 (85) $(M + 18)^+$; ^{1}H NMR (CD_3OD) δ 2.34–2.43 (m, 4 H, two CH_2's), 3.52 (s, 3 H, OCH_3), 6.89–7.38 (m, 4 H, aromatic); ^{13}C NMR (CD_3OD) δ 29.52, 32.86, 47.41, 52.33, 112.02, 118.09, 124.51, 125.51, 126.71, 131.74, 142.78, 173.39, 173.54; high-resolution mass spectrum, M^+ calcd for $C_{13}H_{12}N_2O_3$ m/e 244.0848, found m/e 244.0848.

Saponification of 4b to 4a. A portion of the oil **4b** was dissolved in methanol, and the ester was hydrolyzed with sodium hydroxide (pH 12). The reaction was monitored by TLC (chloroform/methanol/acetic acid, 9:0.0:0.1 v/v) and was complete in 0.5 h. The solvent was evaporated, and the residue was dissolved in water. The aqueous solution was neutralized to pH 4 with acetic acid and was extracted with ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated. The R_f value of the product was identical with that obtained from the reaction of **3** with potassium cyanide/18-crown-6. The product was further characterized by its mass spectrum as **4a**: MS (CI, NH_3) m/z (%) 231 (40) $(M + 1)^+$, 248 (100) $(M + 18)^+$.

Methyl 3-Azidooxindole-3-propionate (10b). Compound **9** (0.36 g, 1.42 mmol), freshly synthesized from **5**, was dissolved in anhydrous acetonitrile (10 mL), and sodium azide (0.455 g, 7 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, but the mass spectrum showed mainly starting material. An equivalent amount of 15-crown-5 (1.354 mL, 7 mmol) was then introduced into the reaction mixture, and its color changed rapidly to light orange. After 1 h, TLC (50% ethyl acetate/hexanes) showed only a spot corresponding in R_f to that of **9**; however, the spot gave an intense bright fluorescence in the long wavelength region of the UV lamp, whereas the starting material did not fluoresce in this region. Thus, starting material and product could not be differentiated by their R_f values on TLC. The completion of the reaction was monitored by storing aliquots of the reaction mixture in water for about 1 h and checking for the hydrolysis of residual **9** to **5** by TLC. After 3 h, acetonitrile was removed completely in vacuo. The residue was dissolved in dichloromethane (25 mL), and the solution was washed with water (3 × 20 mL). The organic layer was dried (magnesium sulfate) and concentrated in vacuo to give a dark reddish oil. Flash column chromatography (silica gel) was used to remove the crown ether: following elution with 300 mL of 20% ethyl acetate in hexanes, the product was collected by elution with 30% ethyl acetate in hexanes (25-mL fractions). The pale red oil showed a mass spectrum expected for the azido ester **10b** (314 mg, 84.8% yield): MS (CI, NH_3) m/z (%) 261 (10) $(M + 1)^+$, 233 (76) $(M + 1 - N_2)^+$, 218 (45) $(M + 1 - N_3H)^+$; ^{1}H NMR (CD_3OD) δ 2.16–2.33 (m, 4 H, two CH_2's), 3.55 (s, 3 H, OCH_3), 6.94–7.32 (m, 4 H, aromatic); ^{13}C NMR (CD_3OD) δ 29.24, 31.50, 52.33, 68.14, 111.80, 124.09, 125.54, 127.89, 131.63, 142.92, 174.18, 177.29; high-resolution mass spectrum, M^+ calcd for $C_{12}H_{12}N_4O_3$ m/e 260.0909, found m/e 260.0912; IR (thin film) 2100, 1735, 1620, 1470, 1120 cm^{-1}.

3-Azidooxindole-3-propionic Acid (10a). A portion of compound **10b** was dissolved in methanol, and the solution was maintained at pH 12 with 1 N sodium hydroxide. Ester hydrolysis was complete in about 2 h, and a more polar spot was observed on TLC. The solvent was evaporated in vacuo. The residue was dissolved in water and the solution was extracted with ethyl acetate. The aqueous layer was neutralized to pH 3 with 1 N hydrochloric acid and was extracted with ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated in vacuo. The oily residue showed a single UV positive spot on TLC, which was more polar than the corresponding ester **10b** (developing solvent; chloroform/methanol/acetic acid, 9:0.9:0.1 v/v); in an iodine chamber, however, a slower moving spot was observed due to the crown ether. The oil was dissolved in 2 N NaOH, the solution was extracted exhaustively with ether, and the alkaline layer was acidified to pH 3 with 1 N HCl. The separated oil was extracted with 3 × 75-mL portions of ethyl acetate, and the combined organic extracts were dried (sodium sulfate) and concentrated to a pale yellow oil: MS (CI, NH_3) m/z (%) 247 (5) $(M + 1)^+$, 219 (100) $(M + 1 - N_2)^+$; ^{1}H NMR (CD_3OD) δ 2.13–2.30 (m, 4 H, two CH_2's), 6.95–7.35 (m, 4 H, aromatic); ^{13}C NMR (CD_3OD) δ 29.18, 31.60, 68.18, 111.79, 124.16, 125.47, 128.04, 131.60, 142.84, 175.63, 177.44; high-resolution mass spectrum, M^+ calcd for $C_{11}H_{10}N_4O_3$ m/e 246.0752, found m/e 246.0752; IR (thin film) 2080, 1725, 1610, 1460, 1230, 1100 cm^{-1}.

Dioxindole-3-propionamide (15). Compound **5** (100 mg) was dissolved in methanol (10 mL), and ammonia gas was bubbled slowly through the solution for 5 min. In about 1 h, a new TLC spot, slightly more polar than dioxindole-3-propionic acid, began appearing. The reaction mixture was stirred overnight at room temperature, when the reaction was essentially complete. The solvent was evaporated to give a white solid, which was more polar than compound **5** and was chromatographically pure on TLC (chloroform/methanol/acetic acid, 9:0.8:0.2 v/v): MS (CI, NH_3) m/z (%) 221 (100) $(M + 1)^+$, 203 (20) $(M + 1 - H_2O)^+$; ^{1}H NMR (CD_3OD) δ 2.07–2.28 (m, 4 H, two CH_2's), 6.87–7.35 (m, 4 H, aromatic); ^{13}C NMR (CD_3OD) δ 30.31, 34.71, 77.01, 111.24, 123.73, 125.17, 130.60, 132.56, 142.63, 177.85, 181.83; high-resolution mass spectrum, M^+ calcd for $C_{11}H_{12}N_2O_3$ m/e 220.0848, found m/e 220.0849.

The same product was obtained in quantitative yield by ammonolysis of lactone **3**.

3-Fluorooxindole-3-propionamide (14). Compound **6** (50 mg) was dissolved in methanol (5 mL), and ammonia gas was bubbled through the solution for about 5 min. Reaction was almost complete in 24 h, and TLC showed the formation of a major new spot, in addition to a trace of **5**. The solvent was evaporated and the major band was separated on a 2 mm preparative silica plate with chloroform/methanol/acetic acid, 90:9:1 (v/v), as the developing solvent. The product was crystallized from methanol/ethyl acetate as a white solid, which was collected by filtration (40 mg, 86% yield), mp 140–142 °C. The R_f value of the product fell between those of compounds **5** and **1b**: MS (CI, NH_3) m/z (%) 223 (100) $(M + 1)^+$, 203 (65) $(M + 1 - HF)^+$, 240 (60) $(M + 18)^+$; ^{1}H NMR (CD_3OD) δ 2.18–2.44 (m, 4 H, two CH_2's), 6.89–7.44

(m, 4 H, aromatic); ^{19}F NMR (CD_3OD, TFA) -81.88 (t, benzylic); high-resolution mass spectrum, M^+ calcd for $C_{11}H_{11}N_2O_2F$ m/e 222.0805, found m/e 222.0797.

3-Aminooxindole-3-propionic Acid Lactam (12). Portions of **9** (3 mg each), prepared freshly from **5**, were dissolved in anhydrous methanol, ethanol, and 2-propanol (0.5 mL each). Anhydrous ammonia gas was bubbled through each solution for about 3 min, and the reaction mixtures were stirred at ambient temperature. After 2 h, TLC (silica, chloroform/methanol/acetic acid, 9:0.9:0.2 v/v) showed that all the starting material had disappeared and two new products, both more polar than the starting material, had formed. The relative intensities of the products were 2:1, 1:1, and 1:2 in methanol, ethanol, and 2-propanol, respectively. The R_f of the more polar product (presumably **11**) is slightly higher than that of **15**. After 18 h, TLC of two reaction mixtures (in methanol and ethanol) showed complete conversion of the more polar product to the less polar product, whereas the reaction mixture in 2-propanol showed incomplete conversion to the same product. The R_f of this final product (**12**) is slightly lower than that of **5**: MS (CI, NH_3) m/z (%) 203 (100) $(M + 1)^+$, 220 (5) $(M + 18)^+$ (M refers to **12**).

The same mass spectra were obtained for the products of reactions in ethanol and 2-propanol.

Preparative-Scale Synthesis of 12 from 5. Compound **5** (0.235 g) was converted to compound **9** by the procedure described earlier. The product was purified by flash column chromatography, with 50% ethyl acetate/hexanes as the eluting solvent. Removal of the solvent in vacuo afforded the product (194 mg, 76.4% yield) as a pale, viscous oil.

The oil was dissolved in 5 mL of methanolic ammonia solution, and the solution was stirred at room temperature for 6 h. The solvent was removed under nitrogen, and the mixture was fractionated by flash column chromatography, with chloroform/methanol/acetic acid (9:0.9:0.1 v/v) as the eluting solvent. Fractions containing **12** were pooled and the solvent was removed in vacuo. The product was crystallized from methanol to give off-white crystals (90 mg, 44.6% yield): mp 227–230 °C: MS (CI, NH_3) m/z (%) 203 (100) $(M + 1)^+$, 220 (40) $(M + 18)^+$; ^1H NMR (CD_3OD) δ 2.28–2.78 (m, 4 H, two CH_2's), 6.89–7.37 (m, 4 H, aromatic); ^{13}C NMR (CD_3OD) δ 30.96, 33.56, 66.06, 111.44, 124.21, 124.81, 130.93, 131.87, 142.58, 181.37, 181.64; high-resolution mass spectrum, M^+ calcd for $C_{11}H_{10}N_2O_2$ m/e 202.0742, found m/e 202.0741. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.35; H, 4.95; N, 13.86. Found: C, 64.71; H, 4.81; N, 13.70.

Acetylation of 5. Compound **5** (0.233 g) was dissolved in pyridine (0.72 mL), acetic anhydride (0.72 mL) was added, and the reaction mixture was stirred at room temperature. After 20 h, all of the starting material had reacted with the formation of two new, less polar spots. The solvent was evaporated in high vacuum, and the residue was dissolved in ethyl acetate. The two products were separated by flash column chromatography with 50% ethyl acetate/hexanes as the eluting solvent and collection of 15-mL fractions. The two new products were identified as methyl *N*-acetyldioxindole-3-propionate (eluting first) and methyl *O*-acetyldioxindole-3-propionate (eluting later) from their mass and ^1H NMR spectra.[31] The *N*-acetyl derivative was obtained as an oil (0.09 g), whereas the *O*-acetyl derivative was obtained as a white solid (0.114 g), mp 100–102 °C.

***O*-Acetyl derivative 16**: MS (CI, NH_3) m/z (%) 278 (10) $(M + 1)^+$, 218 (100) $(M + 1 - AcOH)^+$; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, $OCOCH_3$), 2.30–2.53 (m, 4 H, two CH_2's), 3.62 (s, 3 H, OCH_3), 6.85–7.30 (m, 4 H, aromatic), 8.12 (s, 1 H, NH). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.41; N, 5.05. Found: C, 60.75; H, 5.48; N, 4.98.

***N*-Acetyl derivative 17**: MS (CI, NH_3) m/z (%) 278 (2) $(M + 1)^+$, 260 (100) $(M + 1 - H_2O)^+$, 277 (15) $(M + 18 - H_2O)$; ^1H NMR ($CDCl_3$) δ 2.30–2.48 (m, 4 H, two CH_2's), 2.67 (s, 3 H, $NCOCH_3$), 3.63 (s, 3 H, OCH_3), 7.20–7.41 (m, 4 H, aromatic). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.41; N, 5.05. Found: C, 60.25; H, 5.35; N, 4.53.

When **5** was treated with excess acetic anhydride in dichloromethane in the absence of base, no reaction occurred. Addition of excess DMAP, however, induced a rapid reaction which yielded **16** and **17**, the latter being the major product.

Reaction of 9 with Tetra-*n*-butylammonium Acetate. Compound **9** (10 mg, 0.039 mmol) was dissolved in anhydrous DMF (1 mL), tetra-*n*-butylammonium acetate (117.59 mg, 0.39 mmol) was added to the solution, and the reaction mixture was stirred at room temperature. The mixture turned pale yellow, and the reaction was complete in about 10 min, as shown by TLC (50% ethyl acetate/hexanes). A single product was obtained with R_f corresponding to that of **16**. The product was also characterized as **16** by mass spectrum.

Hydrogenolysis of 16. Compound **16** (10 mg, 0.036 mmol) was dissolved in ethyl acetate (2 mL) and was hydrogenated in the presence of 10% Pd/C on a Parr shaker at 40 psi. After 69 h, TLC (50% ethyl acetate/hexanes) showed reaction to be complete with the formation of a single product with the same R_f and mass spectrum as those of methyl oxindole-3-propionate (**19**).

Oxindole-3-propionic Acid (18). DMSO (0.18 mL, 2.5 mmol) was added slowly to concentrated hydrochloric acid (1 mL) followed by phenol (18.8 mg, 0.2 mmol). To this mixture was added a solution of indole-3-propionic acid (**2**, 189 mg, 1 mmol) in glacial acetic acid (10 mL). The reaction mixture turned orange, and the reaction was complete in 30 min, as monitored by TLC (chloroform/methanol/acetic acid, 9:0.9:0.1 v/v). Most of the solvent was removed in vacuo. The residual material was purified by flash column chromatography with chloroform/methanol/acetic acid, 90:9:1 (v/v), as the eluting solvent and collection of 15-mL fractions. The fractions containing pure product were pooled and concentrated in vacuo. A yellow solid separated during concentration. The solvent was removed completely, and the solid was dissolved in methanol. The solution was decolorized with charcoal, and the filtrate was concentrated to a colorless solid. The product was crystallized from methanol as a white solid (60 mg, 30% yield): mp 164–166 °C (lit.[32] mp 165–167 °C); MS (CI, NH_3) m/z (%) 206 (100) $(M + 1)^+$; ^1H NMR (CD_3OD) δ 2.07–2.31 (m, 4 H, two CH_2's), 3.43–3.47 (t, C-3 H), 6.81–7.21 (m, 4 H, aromatic); ^{13}C NMR (CD_3OD) δ 26.75, 30.92, 46.21, 110.85, 123.39, 125.19, 129.18, 130.41, 143.55, 176.59, 181.86; high-resolution mass spectrum, M^+ calcd for $C_{11}H_{11}NO_3$ m/e 205.0739, found m/e 205.0733.

Methyl Oxindole-3-propionate (19). Oxindole-3-propionic acid (**18**) (30 mg) was dissolved in methanol (15 mL), which had been saturated with dry hydrogen chloride, and the solution was stirred at room temperature. The reaction was complete in 15 min, with the formation of a major product less polar than the starting material (chloroform/methanol/acetic acid, 9:0.9:0.1 v/v). The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (3 × 20 mL) and saturated brine (5 mL), dried (sodium sulfate), and concentrated in vacuo. The product was purified on a silica gel plate with 50% ethyl acetate/hexanes as the eluting solvent. The major band was scraped off and eluted with ethyl acetate. The silica was filtered and the filtrate was concentrated to yield an off-white solid. Crystallization from ether/petroleum ether gave white crystals (25 mg, 76% yield): mp 75–78 °C (lit.[32] mp 79–80 °C); MS (CI, NH_3) m/z (%) 220 (100) $(M + 1)^+$; ^1H NMR (CD_3CN) δ 2.10–2.41 (m, 4 H, two CH_2's), 3.56 (s, 3 H, OCH_3), 6.85–7.25 (m, 4 H, aromatic), 8.4 (br s, 1 H, NH).

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Supplementary Material Available: Proton and carbon NMR spectra for compounds **4b**, **9**, **15**, **10a**, **10b**, and **18** (12 pages). Ordering information is given on any current masthead page.

(31) The δ value for the *N*-acetyl protons of **20** is consistent with that found for 1-acetyltryptophan: Ohki, S.; Nagasaka, T. *Chem. Pharm. Bull.* **1971**, *19*, 545.

(32) Julian, P. J.; Printy, H. C. *J. Am. Chem. Soc.* **1953**, *75*, 5301.