A Practical, Nenitzescu-Based Synthesis of LY311727, the First Potent and Selective s-PLA$_2$ Inhibitor

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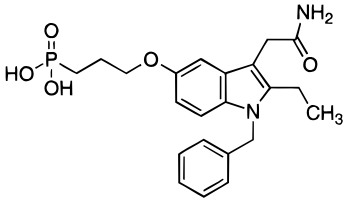
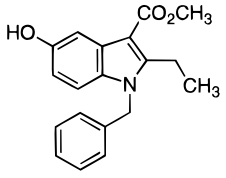
Received July 30, 1996

Introduction

Patients with acute pancreatitis, bacterial peritonitis, adult respiratory distress syndrome (ARDS), septic shock, and arthritis all display extraordinarily high blood levels of secretory phospholipase A_2 (s-PLA$_2$).[1] The *in vivo* trigger for s-PLA$_2$ release under such conditions is mediated by a number of mechanisms, all of which have been investigated as a primary site for drug discovery. However, it is believed that potent and selective inhibitors of s-PLA$_2$ itself will provide important clinical therapies. A significant study on the structure of human nonpancreatic s-PLA$_2$ revealed the native crystal form,[2] as well as that complexed with a phosphonate transition state analogue.[3] The former structural information afforded an elegant example of a contemporary structure-based search for selective s-PLA$_2$ inhibitors, optimally resulting in exciting clinical candidates. From that study, LY311727 (**1**) emerged as the first potent and selective inhibitor of human nonpancreatic s-PLA$_2$.[1] The exciting *in vitro* activity of LY311727 signified that an effective synthesis was warranted to support further *in vivo* studies.



1, LY311727



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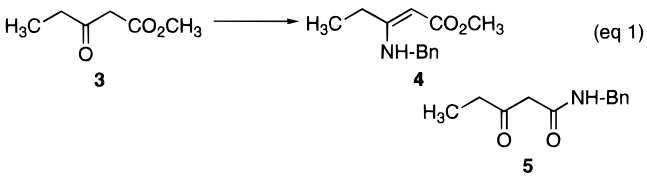
The Nenitzescu reaction is a highly regioselective synthetic entry into 1,2,3-trisubstituted 5-oxyindoles, affording the requisite 5-hydroxy moiety and 3-(methoxycarbonyl) substitution pattern (cf. **2**) for compounds such as **1**.[4] Nenitzescu precursors are the readily available β-keto esters which after being transformed into the enamino ester are reacted selectively with *p*-benzoquinone to afford this desired selectivity pattern.[5] Although the reaction has been reviewed, several new advances have since been made,[6] including new quinone surrogates[7] and solvent optimization studies.[8] The Nenitzescu reaction efficiency is highly dependent upon substituent effects and reaction medium. The utility of the Nenitzescu adducts has been somewhat limited, however, by the highly reactive β-(hydroxymethyl)indole nucleus. This report describes the Nenitzescu reaction with specific substrates and the practical incorporation of their products into LY311727.

Results and Discussion

Nentizescu reaction precursors were prepared from reaction of readily available methyl propionylacetate (**3**) with benzylamine to afford the corresponding enamino esters **4** (eq 1). Catalytic *p*-TsOH·H_2O ensured complete



(eq 1)

formation of the enamino esters **4** as a 13:1 *Z*:*E* mixture under azeotropic conditions, whereas clean formation of the amide **5** was the dominant pathway without acid catalysis.[9]

For the reaction of enamino ester **4** with *p*-benzoquinone (**6**) to produce indole **2**, a survey was conducted using solvents of widely varying dielectric constants. The results shown in Table 1 (Scheme 1) demonstrate that the yields of **2** are highly variable and virtually independent of dielectric constant. Optimal yields in CH_3NO_2 required 48 h reaction time at ambient temperature, whereas reaction in 1,2-dichloroethane showed optimal performance within 3−6 h. Other solvents provided similarly moderate yields but involved more tedious workups. The less efficient reaction in 1,2-dichloroethane was preferred on a small scale due to the short reaction time, especially since these inexpensive starting materials were readily available. However, CH_3NO_2 was the preferred solvent on a larger scale based upon the higher chemical efficiency and ease of product isolation by simple filtration directly from the crude reaction mixture. The mother liquors were shown to contain an assortment of the typical Nenitzescu reaction byproducts as the mass balance.[5]

The Nenitzescu reaction is an interesting process presumed to involve an internal oxidation−reduction sequence.[5,6] Since electron transfer characterized by deep burgundy reaction mixtures may be an important mechanistic aspect, the outcome should be sensitive to the reaction medium. Patrick reported on the use of nitromethane (CH_3NO_2) as an optimal Nenitzescu reaction solvent with methyl enamino esters as substrates.[8] Although empirically this solvent was the most efficient medium, the rationale was more complex than dielectric

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S0022-3263(96)01445-4 CCC: $12.00

Scheme 1

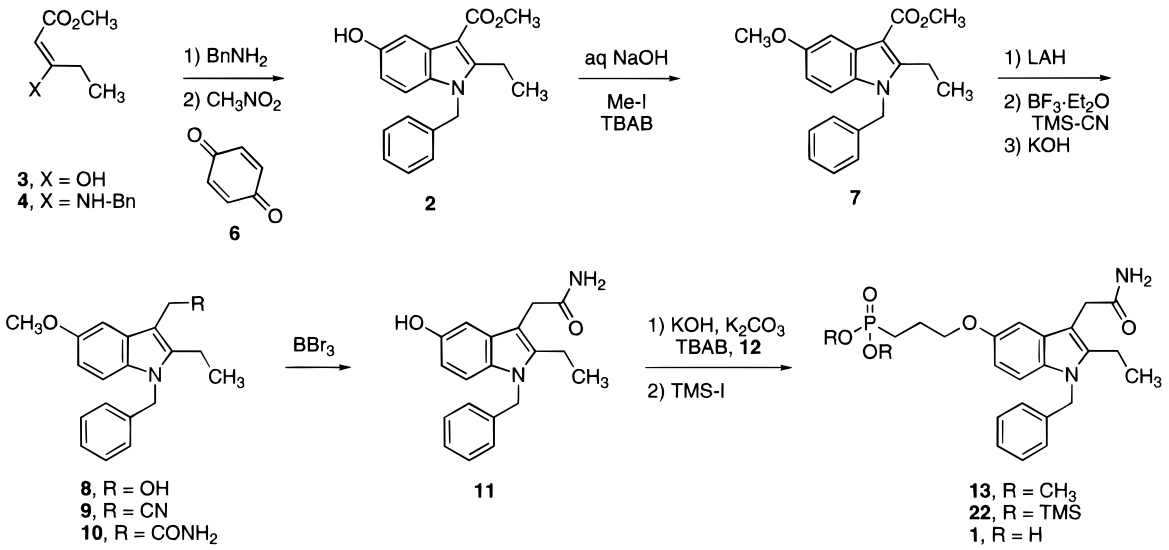


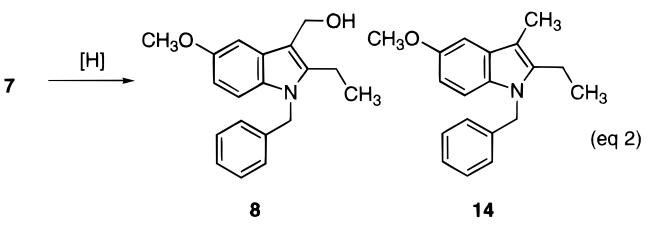
Table 1. Reaction Media for 4 + 6 → 2

solvent	ϵ	yield of **2** (%)
PhMe	2.38	25
$CHCl_3$	4.70	49
PhMe/HOAc 2/1[6g]	6.19	50
$ClCH_2CH_2Cl$	10.4	47
Acetone	20.7	22
MeOH	32.6	30
CH_3NO_2	38.6	83

constant considerations alone. Initial charge-transfer complexation has been implicated, thereby warranting the use of such polar media. With CH_3NO_2 as the reaction medium, however, direct product crystallization occurred as the reaction progressed.

Protection of the 5-hydroxyl moiety of indole **2** was accomplished in reasonable yield by reaction with MeI and K_2CO_3 in acetone or MEK at reflux. Reaction times were typically long (3 days), with incomplete conversion even when an enormous excess of reagents was employed. Alkylation could also be accomplished in H_2O under phase transfer conditions (aqueous NaOH, MeI, *n*-Bu_4N^+-Br^-, reflux) in good yield (78%). The alkylation of 5-hydroxyindoles is known to be problematic, and C-alkylation can be the dominant by-product; however, this was not observed.[10] Alternatively, appendage of the requisite β-propyl phosphonate moiety could be accomplished, although this strategy was abandoned due to its limited compatibility with subsequent elaborations, specifically reduction of the C-3 ester (*vide infra*).

Having established an access to quantities of **7**, attention was next turned to the reduction of indole-3-carboxylic esters.[11] It became readily apparent that overreduction of ester **7** to irreversibly afford the 3-methyl product **14** was a predominant pathway under a variety of conditions (eq 2, Table 2). In fact, the literature



(eq 2)

suggested that overreduction might not be controllable, although the problem appears to be more significant

Table 2. Reduction of 7 To Afford Methylindole 14:(Hydroxymethyl)indole 8[a]

[H]	solvent	*T* (°C)	**14:8**
LAH·bis-THF	THF	ambient	>4:1
LAH·bis-THF	CH_2Cl_2	0	>4:1
LAH	THF	0	8:1
LAH	CH_2Cl_2	0 → ambient	8:1
$NaBH_4$	Tol/THF	reflux	0
$NaBH_4$	MeOH	reflux	0
$LiBH_4$	Et_2O	reflux	0
$LiBH_4$	Tol/THF	22 → 70	trace
DIBAL	THF	0	3:1
DIBAL	CH_2Cl_2	0	3:1
DIBAL	CH_2Cl_2	−78 → ambient	1:0
LAH (solid)	THF	ambient	0:1
LAH (soln)	THF	reflux	1:0
$LiAl(O\text{-}t\text{-}Bu)_3H$	THF	reflux	trace
Red-Al	toluene	reflux	trace

[a] Ratios determined by NMR analysis.

without *N*-substitution.[12] Most conditions afforded the 3-methylindole when the reducing agent was added to the substrate. However, addition of ester **7** to LAH in THF at ambient temperature afforded very clean reduction to the desired alcohol **8** as determined by chromatographic analysis. Quench to precipitate the aluminum salts,[13] filtration, and concentration afforded the alcohol **8** in nearly quantitative yield. Crystallization was accomplished from a mixture of EtOAc/hexanes, and the crystalline product was stored indefinitely at refrigerator temperatures.

NMR analysis of the product, however, revealed a second component containing vinylic protons. Chromatographic analysis of the NMR sample still in $CDCl_3$ showed the appearance of a new material at slightly higher R_f that was not present prior to initial sampling. Spectroscopic analysis of the crude product in $CDCl_3$ freshly eluted over basic alumina showed only the alcohol **8**. Over the next 24 h, however, the solution became reddish in color concomitant with the appearance of the new product proposed to have the structure **16**. The acid-

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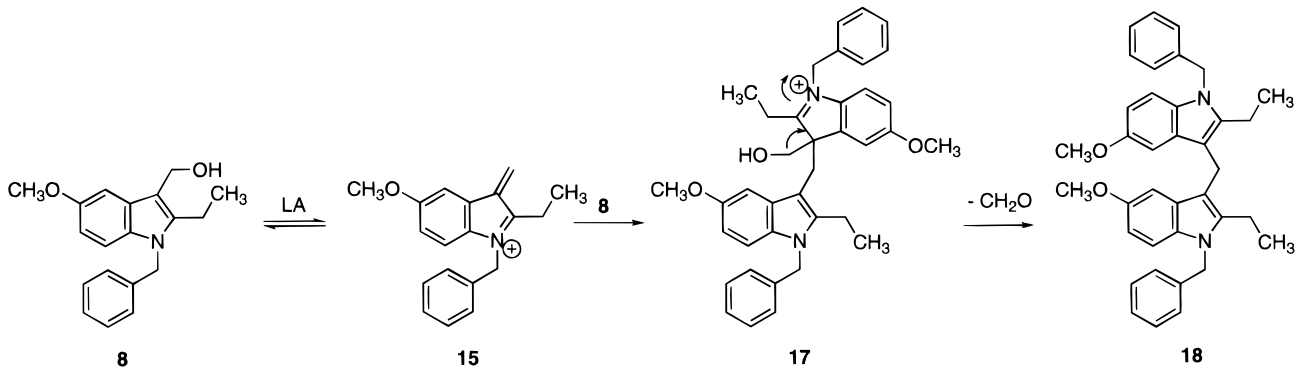
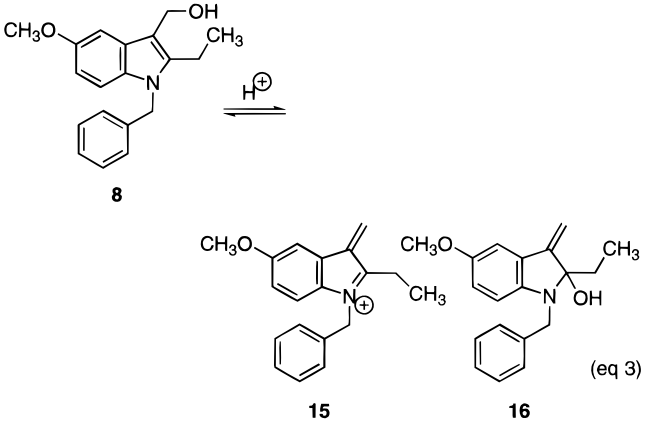
Scheme 2



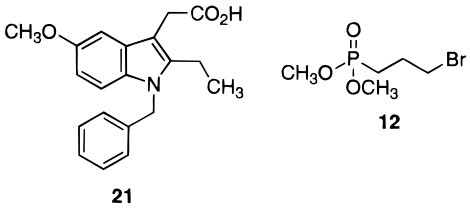
catalyzed equilibrium shown in eq 3 could explain these results; however, attempts to isolate and fully characterize **16** have thus far been unsuccessful.



With many of the reductions shown in Table 2, a variable product profile resulted depending upon the workup conditions. The rate of quench and the resulting temperature (upon quench) were critical to control undesired reaction pathways. In some instances, rapid quench afforded a new reducing agent concomitant with an exotherm to provide overreduction of alcohol **8**, furnishing byproduct **14**. Formation of unidentified products also occurred in some instances (*vide infra*).

On the basis of the ease of overreduction and the hypothesized acid-catalyzed alcohol rearrangement (eq 3), we were encouraged that it would be possible to generate and trap the proposed immonium species **15**. Addition of Et_2AlCN to the alcohol **8** in toluene at 0 °C rapidly afforded two products that were characterized as the desired nitrile **9** and the 3,3′-methylbis(indole) **18** (Scheme 2). The formation of the 3,3′-methylbis(indole) **18** was envisioned by a mechanism involving reaction of **8** with the Lewis acid (LA) to afford **15**, which underwent subsequent attack by another molecule of **8** followed by eventual loss of CH_2O.[14] Inverse addition of the reaction mixture to Et_2AlCN resulted in an improved yield of nitrile **9**, but concomitant formation of **18** also occurred. These results suggested the use of a better, more soluble, and nucleophilic source of cyanide. A number of cyanide-containing reagents were examined that provided nitrile **9** in moderate yield: ZnI_2/TMSCN; Et_2AlCN/TMSCN; TsCl/NaCN; $BF_3{\cdot}Et_2O$/NaCN; $ZnCl_2$/NaCN; Et_3Al/TMS−CN. However, addition of the alcohol **8** to a solution of $BF_3{\cdot}Et_2O$/TMSCN in CH_2Cl_2 provided the best yield of nitrile **9** (83%). Optimization for formation of the 3,3′-methylbis(indole) **18** was found to occur by reaction of **8** with Et_3Al in CH_2Cl_2 without added cyanide nucleophile. Formation of 3,3′-methylbis(indole)s from 3-unsubstituted indoles is also known to occur in acidic medium in the presence of CH_2O.[14]

Nitrile hydrolysis to afford the amide **10** was most efficiently accomplished with powdered KOH in *t*-BuOH at reflux (Scheme 1).[15] The amide **10** was crystallized from *i*-PrOH in excellent yield (95%) with this protocol. Typically, nitrile hydrolysis is reported to occur with basic peroxide,[16] but many of these conditions also produced the corresponding acid **21** as an unwanted byproduct.



Cleavage of the methoxy protecting group at C-5 with BBr_3 in CH_2Cl_2 afforded **11**, which was purified over silica gel.[17] Alkylation with **12**[18] under phase-transfer conditions provided the penultimate phosphonate ester **13**. Once again, incomplete alkylation and a more complex impurity profile were observed with NaH or *t*-BuOK/DMF, even with excess reagents. Finally, ester cleavage was effected with excess TMSI in CH_2Cl_2 at ambient temperature for 2 h to yield the trimethylsilyl phosphonic acid **22**, which upon alcoholytic workup afforded **1**.

The versatility of the approach summarized in Scheme 1 was further demonstrated through the preparation of LY311727 and analogues.[19] The regiochemical outcome of the Nenitzescu reaction is well documented[5] and allows for the selective incorporation of a variety of substituents in the indole ring. Controlled reduction of the ester moiety afforded a reactive intermediate alcohol, also providing insight for hydroxide displacement. The Lewis acid-mediated cyanide reaction provided smooth conversion of the alcohol to the nitrile. The Nenitzescu reaction and the subsequent functional group modification has

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(19) A detailed study of these analogues will be disclosed in a future report.

afforded a powerful means to synthesize potent and selective s-PLA_2 inhibitors. Some of these agents are currently being investigated clinically.

Experimental Section

Melting points were determined on a hot stage microscope and are uncorrected. All experiments were conducted under an inert atmosphere of nitrogen unless otherwise noted and monitored by thin-layer chromatography using Merck F254 silica gel plates. All solvents and reagents were used as obtained. ^{1}H, ^{13}C NMR, and HETCOR spectra were obtained on either a GE QE-300 or a Bruker ACP-300 spectrometer. Microanalyses were conducted by the Physical Chemistry Department of Lilly Research Laboratories.

3-(Carbomethoxy)-2-ethyl-1-(phenylmethyl)-1*H*-5-hydroxyindole (2). Methyl propionylacetate (131.0 g, 1.0 mol) and benzylamine (112.0 g, 1.05 mol) were dissolved in toluene (500 mL), to which was added *p*-TsOH·H_2O (9.5 g, 0.05 mol). The resulting solution was stirred under reflux for 4 h using a Dean−Stark trap to remove H_2O (18.9 mL, 1.05 mol). The reaction mixture was cooled to 10 °C, filtered to remove insoluble materials, and concentrated to a crude oil (220 g) that was used directly in the subsequent transformation. 1,4-Benzoquinone (149.0 g, 1.38 mol) was dissolved in nitromethane (500 mL) and cooled to 20 °C under N_2. The freshly prepared crude enamino ester (220 g) was dissolved in nitromethane (250 mL) and added dropwise to the benzoquinone solution over 30 min. An additional rinse of nitromethane (100 mL) was employed to ensure complete transfer. A slight endotherm caused the internal temperature to drop to 17 °C initially. The initial dark green solution became dark brown red, and a precipitate was formed within several hours. After 48 h at ambient temperature, the reaction mixture was cooled in an ice bath, filtered, and washed with fresh, cold nitromethane to afford a slightly reddish solid (214 g, 69%) after drying. The material thus obtained could be used without further purification. However, the crude solid suspended in 1,2-dichloroethane (400 mL) was stirred at reflux for 30 min and then filtered hot to provide 159 g (52%) as a light yellow solid: mp 194−5 °C; TLC (hexane/EtOAc (1:1)) R_f 0.64; IR ($CHCl_3$, cm^{-1}) 3019, 1689, 1464, 1454, 1145; UV (EtOH) 291 (11 900), 246 (17 800), 216 (33 300); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (t, 3H, J = 7.4 Hz), 3.04 (q, 2H, J = 7.4 Hz), 3.77 (s, 3H), 5.40 (s, 2H), 6.60−7.40 (m, 8H), 8.98 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 19.2, 46.3, 51.0, 102.3, 106.0, 106.1, 111.7, 112.4, 126.5, 127.7, 129.2, 130.8, 138.1, 151.1, 153.5, 165.7; MS m/z (M^+) 309. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.57; H, 6.08; N, 4.57.

3-(Carbomethoxy)-2-ethyl-1-(phenylmethyl)-1*H*-5-methoxyindole (7). Indole **2** (106 g, 0.35 mol) and (*n*-Bu)$_4$NBr (11.3 g, 0.035 mol) were placed in H_2O (1 L) to which was then added 50% aqueous NaOH (333 mL) followed by MeI (148 g, 1.04 mol). The resulting heterogeneous mixture was brought to reflux, whereupon a dark brown solution was obtained. After 30 min at reflux, the reaction was cooled to ambient temperature and extracted with EtOAc (3 × 900 mL). The combined organic phase was washed with brine and dried ($MgSO_4$) to yield methoxyindole **7** as a crude tan solid (115.4 g). Recrystallization from *i*-PrOH afforded a colorless crystalline solid (90.5 g, 80%): mp 102−3 °C; TLC (hexane/EtOAc (3:1)) R_f 0.58; IR ($CHCl_3$, cm^{-1}) 3013, 1690, 1479, 1462, 1169; UV (EtOH) 289 (12 000), 244 (19 600), 216 (34 100); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (t, 3H, J = 7.4 Hz), 3.12 (q, 2H, J = 7.4 Hz), 3.80 (s, 3H), 3.86 (s, 3H), 5.52 (s, 2H), 6.80−7.56 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 19.3, 46.4, 51.1, 55.8, 102.7, 103.7, 103.9, 111.9, 126.5, 127.4, 127.8, 129.2, 131.5, 138.0, 151.4, 155.8, 165.9; MS m/z (M^+) 323. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.61; H, 6.73; N, 4.51.

3-(Hydroxymethyl)-2-ethyl-1-(phenylmethyl)-1*H*-5-methoxyindole (8). The indole ester **7** (130 g, 0.40 mol) was dissolved in THF (300 mL) and added dropwise to a slurry of LAH (46 g, 1.2 mol) in THF (900 mL) at 0 °C under N_2. After the mixture was stirred for 4 h at 0 °C, water (46 mL) was added slowly with efficient stirring, followed by 15% NaOH (46 mL) and then water (138 mL). After filtration of the aluminum salts, the filtrate was dried and concentrated to yield (hydroxymethyl)-indole **8** as a colorless solid (93 g, 78%): mp 69−70 °C; TLC (hexane/EtOAc (3:1)) R_f 0.20; IR ($CHCl_3$, cm^{-1}) 3010, 1485, 1454, 1158; UV (EtOH) 280 (8600), 215 (29 500); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (t, 3H, J = 7.5 Hz), 2.71 (q, 2H, J = 7.5 Hz), 3.72 (s, 3H), 4.40 (s, 3H), 5.32 (s, 2H), 6.62−7.24 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.7, 17.9, 46.3, 54.4, 55.9, 101.2, 110.8, 112.0, 126.5, 127.5, 128.5, 128.8, 129.0, 131.7, 139.3, 141.2, 154.0; MS m/z (M^+) 295. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.56; H, 7.20; N, 4.88.

3-(Cyanomethyl)-2-ethyl-1-(phenylmethyl)-1*H*-5-methoxyindole (9). BF_3·Et_2O (57.8 g, 0.407 mol) and TMSCN (54.0 g, 0.544 mol) were added to CH_2Cl_2 (800 mL) at 0 °C under N_2. A solution of the (hydroxymethyl)indole **8** (40.0 g, 0.136 mol) in CH_2Cl_2 (200 mL) was then added dropwise at a rate to maintain the temperature ≤7 °C, forming a deep red reaction mixture. After the solution was stirred for 1 h at 0 °C, saturated aqueous $NaHCO_3$ solution (300 mL) was added with continued stirring for 40 min. The layers were separated, and the organic phase was washed successively with 1 N HCl (300 mL), saturated $NaHCO_3$ (300 mL), and brine (300 mL) and dried (Na_2SO_4). The resulting brown oil (46.5 g) was filtered over SiO_2, eluting with CH_2Cl_2, to afford 34.3 g (83%) as a light amber semisolid: TLC (hexane/EtOAc (3:1)) R_f 0.46; IR ($CHCl_3$, cm^{-1}) 2251, 1486, 1454, 1157; UV (EtOH) 279 (7600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 3H, J = 7.6 Hz), 2.75 (q, 2H, J = 7.6 Hz), 3.79 (s, 2H), 3.88 (s, 3H), 5.31 (s, 2H), 6.79−7.27 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.6, 14.7, 17.8, 46.4, 55.9, 100.2, 100.5, 111.3, 111.4, 120.1, 126.4, 127.5, 127.6, 129.0, 131.6, 139.0, 141.2, 154.4; MS m/z (M^+) 304. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.77; H, 6.86; N, 8.91.

3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-1*H*-5-methoxyindole (10). The (cyanomethyl)indole **9** (14.0 g, 0.046 mol) and powdered KOH (15.0 g, 0.23 mol) were added to *t*-BuOH (180 mL) and stirred at reflux under N_2 for 1 h. After cooling, the reaction mixture was partitioned between saturated brine solution (400 mL) and EtOAc (400 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Purification was accomplished by chromatography over SiO_2 with CH_2Cl_2/EtOAc (1:1) to afford 12.6 g (85%) of a colorless solid: mp 169−170 °C; TLC (CH_2Cl_2/EtOAc (1:1)) R_f 0.26; IR ($CHCl_3$, cm^{-1}) 3008, 1673, 1573, 1485, 1454, 1154; UV (EtOH) 283 (8600), 224 (26000); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (t, 3H, J = 7.5 Hz), 2.68 (q, 2H, J = 7.5 Hz), 3.43 (br s, 2H), 3.40 (s, 2H), 3.70 (s, 3H), 5.32 (s, 2H), 6.61 (dd, 1H, J = 2.3, 8.7 Hz), 6.89−7.25 (m, 7H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.1, 18.0, 32.0, 46.4, 56.0, 101.5, 105.9, 110.5, 110.7, 126.5, 127.4, 128.8, 129.0, 131.7, 139.4, 141.0, 154.0, 173.4; MS m/z (M^+) 322. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.47; H, 7.01; N, 8.55.

3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-1*H*-5-hydroxyindole (11). The amide **10** (50.0 g, 0.16 mol) was dissolved in CH_2Cl_2 (500 mL) and treated dropwise with 1.0 M BBr_3 in CH_2Cl_2 (470 mL, 0.47 mol) at 0 °C under N_2. After being stirred for 2 h, the mixture was diluted with CH_2Cl_2, washed successively with water, saturated aqueous NH_4Cl solution, and brine, and dried (Na_2SO_4). After removal of the volatiles, 39.3 g of a light tan semisolid was obtained in 80.2% yield: TLC (EtOAc) R_f 0.41; IR ($CHCl_3$, cm^{-1}) 3010, 2973, 1668, 1574, 1481, 1376; UV (EtOH) 283 (8200); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (t, 3H, J = 7.5 Hz), 2.72 (q, 2H, J = 7.5 Hz), 3.43 (s, 2H), 5.32 (s, 2H), 6.54−7.29 (m, 10H), 8.66 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.3, 18.0, 32.1, 46.4, 103.4, 105.3, 110.4, 111.0, 126.6, 127.4, 127.6, 129.2, 131.1, 139.5, 140.7, 151.3, 173.6; MS m/z (M^+) 308; HRMS calcd for $C_{19}H_{20}N_2O_2$ 309.1603, found: 309.1610. Anal. Calcd for $C_{19}H_{20}N_2O_2$·H_2O: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.94; H, 7.02; N, 8.18.

Dimethyl [3-[[3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonate (13). The 5-hydroxyindole **11** (7.5 g, 0.023 mol), powdered KOH (4.0 g, 0.070 mol), (*n*-Bu)$_4$NBr (0.45 g, 0.0014 mol), and K_2CO_3 (2.5 g, 0.019 mol) were combined in DMF (60 mL) at ambient temperature under N_2 for 15 min. A solution of dimethyl (3-bromopropyl)phosphonate[18] (7.3 g, 0.028 mol) in DMF (25 mL) was added dropwise and the resulting mixture stirred at ambient temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2, washed successively with H_2O and brine, and dried (Na_2SO_4) to afford 10.4 g as a light tan solid (89.2%): mp 118−120 °C; TLC (CH_2Cl_2/*i*-PrOH (9:1)) R_f 0.29; IR ($CHCl_3$, cm^{-1}) 3007, 1673, 1485, 1040; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21 (t, 3H, J = 7.8 Hz), 1.90 (m, 4H), 2.72 (q, 2H, J = 7.8 Hz), 3.44 (s, 2H), 3.62 (s, 3H), 3.66 (s, 3H), 3.98 (m, 2H), 5.34 (s, 2H), 6.62−7.31 (m, 10H); MS

m/*z* (M^+) 458. Anal. Calcd for $C_{24}H_{31}N_2O_5P$: C, 62.87; H, 6.82; N, 6.11. Found: C, 62.72; H, 6.97; N, 6.29.

[3-[[3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid (1). The phosphonate ester **13** (8.75 g, 17.6 mmol) was dissolved in CH_2Cl_2 (200 mL) and treated dropwise with TMSI (7.5 mL, 52.7 mmol) at ambient temperature. After 1.5 h, the volatiles were removed and the residue was digested in MeOH. After removal of the volatiles, 7.2 g (92.3%) of an off-white solid was obtained. The residue could be recrystallized from a mixture of EtOAc/CH_3CN/HOAc/H_2O (21/7/7/9) to afford 7.0 g as a colorless solid: mp 194−6 °C; IR (KBr, cm^{-1}) 2962, 1658, 1487, 1226, 1154; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (t, 3H, J = 7.8 Hz), 1.75 (m, 2H), 2.00 (m, 2H), 2.81 (q, 2H, J = 7.8 Hz), 3.42 (br s, 2H), 3.98 (m, 2H), 5.33 (s, 2H), 6.57−7.41 (m, 10H); MS *m*/*z* (M^+) 430. Anal. Calcd for $C_{22}H_{27}N_2O_5P$: C, 61.39; H, 6.32; N, 6.51. Found: C, 61.35; H, 6.38; N, 6.35.

3,3′-Methylbis-[2-ethyl-1-(phenylmethyl)-1*H*-5-methoxyindole] (18). The alcohol **8** (0.30 g, 1 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated dropwise with Et_3Al (1 mL, 1 mmol, 1 M in hexane) at 0 °C under N_2. After 1 h, the reaction was carefully quenched with 1N HCl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with 1 N HCl and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography over SiO_2 (5:1 hexanes:EtOAc) afforded 263 mg (87%) of the desired symmetrical dimer as a foam: TLC (hexane/EtOAc (3:1)) R_f 0.50; IR (KBr, cm^{-1}) 3007, 2936, 1618, 1484, 1453; UV (EtOH) 288 (12 600), 228 (36 500); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz), 2.77 (q, 2H, J = 7.4 Hz), 3.62 (s, 3H), 4.21 (s, 1H), 5.31 (s, 2H), 6.67−7.26 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 18.2, 20.1, 46.6, 55.7, 101.1, 110.0, 110.3, 110.7, 125.9, 127.2, 128.8, 128.9, 131.8, 138.6, 139.2, 153.8; MS *m*/*z* (M^+) 542; HRMS calcd for $C_{37}H_{38}N_2O_2$ 542.7276, found: 542.7271.

Acknowledgment. The authors would like to thank Professor Leo Paquette, Professor Ted Taylor, Dr. Ed Mihelich, and Mr. Nick Bach for helpful discussions.

JO9614452