Photocyclization Strategy for the Synthesis of Antitumor Agent CC-1065: Synthesis of Dideoxy PDE-I and PDE-II. Synthesis of Thiophene and Furan Analogues of Dideoxy PDE-I and PDE-II

Viresh H. Rawal, Robert J. Jones, and Michael P. Cava*†

Departments of Chemistry, University of Alabama, Tuscaloosa, Alabama 35486-9671, and University of Pennsylvania, Philadelphia, Pennsylvania 19104

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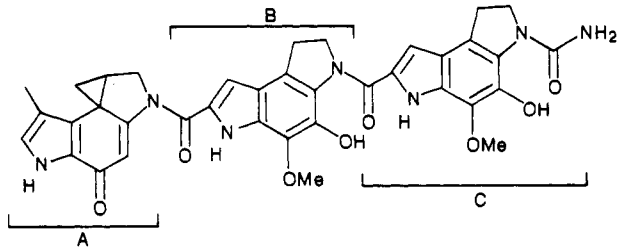
The total synthesis of dideoxy PDE-I and PDE-II and their thiophene and furan congeners is described. The key step is a "Mallory-type" photocyclization of the stilbenoid heterocycles, which are synthesized in a few steps from simple heterocyclic compounds, to yield the tricyclic framework. The photocyclization products are converted to the title compounds in a straightforward manner.

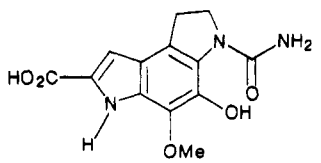
The extremely potent antitumor antibiotic CC-1065 (1) was first isolated from cultures of *Streptomyces zelensis*, by workers at Upjohn in 1978,[1] and its structure was subsequently determined by spectroscopic and crystallographic techniques.[2] As compared to other antineoplastic



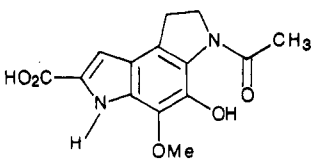
CC-1065 (1)

agents, CC-1065 is about 400 times more potent than adriamycin,[3] 10 times more potent than actinomycin D, xanthomycin, or quinomycin C, and about 2 times as potent as maytansine[4] against L1210 leukemia cells in vitro. In vivo examination has shown this substance to be active against a variety of murine and human tumors.[5] CC-1065 exhibits highly sequence-specific binding to the minor groove of DNA via alkylation of the cyclopropyl dienone moiety of the A unit with the N3 of adenine.[6] The biological and potential clinical importance of this antitumor agent, along with its unique, architecturally interesting structure, has initiated a great deal of research effort directed toward its synthesis.[7-9] Unfortunately, the clinical potential of CC-1065 will never be realized due to an unusual delayed lethality.[10] With judicious structural modification, we reasoned it should be possible to develop synthetic analogues of CC-1065 with reduced toxic properties, making them more suitable for use in chemotherapy.[11]

It is noteworthy that units B and C are essentially the same as the *Streptomyces* metabolites PDE-I (2) and PDE-II (3), which were isolated[9a,b] and synthesized[9c,d] by



PDE-I (2)



PDE-II (3)

Umezawa and co-workers in 1978 and were found to be potent inhibitors of cyclic adenosine 3′,5′-monophosphate (cAMP) phosphodiesterase. This substrate-specific enzyme is important for regulating the intracellular concentration of the "secondary messenger" cAMP. Dideoxy analogues of PDE-I and PDE-II may also function as in-

† To whom inquiries should be sent to at the University of Alabama.

(1) Hanka, L. J.; Dietz, A.; Gerpheide, S. A.; Kuentzel, S. L.; Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211.

(2) (a) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizak, S. A. *J. Antibiot.* **1980**, *33*, 902. (b) Chidester, C. G.; Krueger, W. C.; Mizak, S. A.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629.

(3) Swenson, D. H.; Krueger, W. C.; Lin, A. H.; Schpok, S. L.; Li, L. H. *Proc. Am. Assoc. Cancer Res.* **1981**, *22*, 857.

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(5) Bhuyan, B. K.; Newell, K. A.; Adams, E. G.; Crampton, S. L.; Von Hoff, D. D. *Proc. Am. Assoc. Cancer Res.* **1981**, *22*, 224. Bhuyan, B. K.; Newell, K. A.; Crampton, S. L.; Von Hoff, D. D. *Cancer Res.* **1982**, *42*, 3532. Martin, D. G.; Biles, C.; Gerpheide, S. A.; Hanka, L. J.; Krueger, W. C.; McGovren, J. P.; Mizak, S. A.; Neil, G. L.; Stewart, J. C.; Visser, J. *J. Antibiot.* **1981**, *34*, 1119.

(6) Needham-VanDevanter, D. H.; Hurley, L. H.; Reynolds, V. L.; Theriault, N. Y.; Krueger, W. C.; Wierenga, W. *Nucleic Acids Res.* **1984**, *12*, 6159. Hurley, L. H.; Reynolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science (Washington, D.C.)* **1984**, *226*, 843. Reynolds, V. L.; Molineux, I. J.; Kaplan, D. J.; Swenson, D. H.; Hurley, L. H. *Biochemistry 1985*, *24*, 6228.

(7) Studies directed toward unit A: (a) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621. (b) Magnus, P.; Or, Y-S. *J. Chem. Soc., Chem. Commun.* **1983**, 26. (c) Kraus, G. A.; Yue, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1198. (d) Magnus, P.; Gallager, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389. (e) Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 284. (f) Sundberg, R. J.; Nishigushi, T. *Tetrahedron Lett.* **1983**, *24*, 4473.

(8) Studies directed toward units B and C: (a) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240. (b) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1985**, *50*, 425. (c) Magnus, P.; Halazy, S. *Tetrahedron Lett.* **1984**, *25*, 1421. (d) Magnus, P.; Halazy, S. *Tetrahedron Lett.* **1985**, *26*, 2985. (e) Rawal, V. H.; Cava, M. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1526; (f) Rawal, V. H.; Jones, R. J.; Cava M. P. *Tetrahedron Lett.* **1985**, *26*, 2423. (g) Samsoniya, S. A.; et al. *Khin. Geterotsikl. Soedin.* **1982**, *4*, 504; *Chem. Abstr.* **1973**, *97*(3), 23660g. *Notes added in proof*: (h) Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1986**, *27*, 2735. (i) Bryson, T. A.; Roth, G. A. *Tetrahedron Lett.* **1986**, *27*, 3685, 3689.

(9) PDE-I and PDE-II. *Isolation*: (a) Enomoto, Y.; Furutani, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *Agric. Biol. Chem.* **1978**, *42*, 1331. (b) Nakamura, H.; Enomoto, Y.; Takeuchi, T.; Umezawa, H.; Litaka, Y. *Agric. Biol. Chem.* **1978**, *42*, 1337. *Synthesis*: (c) Komoto, N; Enomoto, Y.; Miyagaki, M.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 555. (d) Komoto, N.; Enomoto, Y.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 559. (e) Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1775. (f) Rawal, V. H.; Cava, M. P. *J. Am. Chem. Soc.* **1986**, *108*, 2110. *Thiophene analogue of PDE-I and PDE-II*: (g) Jones, R. J.; Cava, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 826. *Note added in proof* (PDE-II): (h) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3520.

(10) McGovren, J. P.; Clarke, G. L.; Pratt, E. A.; Dekoning, T. F. *J. Antibiot.* **1984**, *37*, 63.

(11) Reviewer's Note: Structural modification had already yielded less toxic, highly active analogues. Warpehoski, M. A.; Kelly, R. C.; McGovren, J. P.; Wierenga, W. *Rec. Adv. Chemother. (Proc. 14th Int. Cong. Chemother., Kyoto, 1985)* **1985**, 570. Wierenga, W.; Bhuyan, B. K.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Swenson, D. H.; Warpehoski, M. A. *Adv. Enzyme Regul.* **1986**, *25*, 141. Warpehoski, M. A. *Tetrahedron Lett.* **1986**, *27*, 4103.

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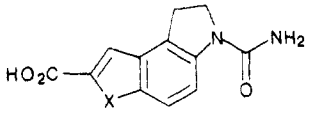
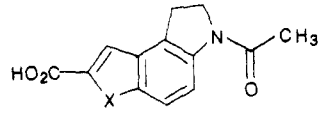
hibitors of cAMP phosphodiesterase.

In selecting the criteria for the structural variations that would provide potentially active analogues of CC-1065, we relied on the structural and circular dichroism studies carried out by Chidester et al., at Upjohn.[2b] CC-1065 is characterized by a pronounced right-handed twist along the long axis; while the individual units (A, B, C) of CC-1065 are planar, *the whole molecule has an unusual shape and curvature that mimics that of the DNA helix* and has a hydrophilic outer periphery and a hydrophobic interior.[2b] The cyclopropane ring in unit A appears to serve only to irreversibly bind the molecule to DNA by an alkylation reaction with the N3 of adenine;[6] some other alkylating function should suffice. Numerous analogues should show antitumor properties provided that they have an overall structure similar to CC-1065 and an appropriate site for covalent binding with DNA.[11]

With such considerations, we have developed a photochemical cyclization-based strategy[8e,f] that is sufficiently flexible so as to allow the rapid construction of not only the individual units of CC-1065 but also numerous and varied analogues, and this methodology has resulted in the syntheses of PDE-I and PDE-II[9f] and their thiophene congeners.[9g] Herein we report the first syntheses of dideoxy analogues of units B and C of CC-1065—that is, of dideoxy PDE-I (**4**) and dideoxy PDE-II (**5**),[8h] along with their thiophene (**6**, **8**) and furan (**7**, **9**) analogues. The key



4, X = NH
6, X = S
7, X = O

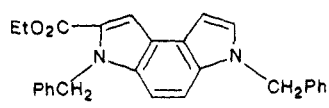


5, X = NH
8, X = S
9, X = O

step is the photocyclization of heterostilbenoid compounds. The syntheses begin with simple heterocyclic derivatives and proceed through a short, convergent route, in high overall yield. Also the syntheses illustrate a useful application of the (*tert*-butyloxy)carbonyl (BOC) group for pyrrole and indole chemistry and demonstrate to some extent the scope of the Wittig reaction as it pertains to pyrroles. These dideoxygenated analogues themselves may have interesting activity in the PDE series as well as being useful precursors of synthetic CC-1065 hybrids.

Results and Discussion

I. Synthesis of Dideoxy PDE-I and PDE-II. In a preliminary report we described the photocyclization-based synthesis of a benzyl-protected dideoxy analogue **10** of the PDE type.[8e] We have since examined, without success, a number of procedures for removing these benzyl groups. Although a method was eventually found for debenzylating the indoline nitrogen, deprotection of the indole ester nitrogen remained problematic.



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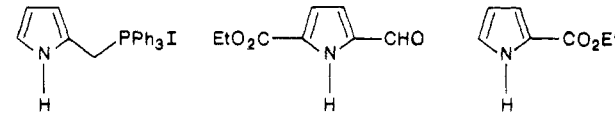
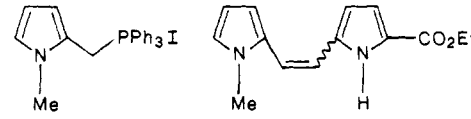
We first attempted to circumvent this problem of deprotection by using no protecting groups altogether, fully aware of the potential side reactions resulting from abstraction of the NH protons. The required phosphonium salt **11** was prepared in 94% yield from the readily available Mannich salt of pyrrole,[12] and the required aldehyde **12**, by a Vilsmeier reaction of ethyl pyrrole-2-carboxylate (**13**).[13]



11 **12** **13**

The Wittig reaction between **11** and **12**, carried out in DMF using NaH as the base, gave rise to the characteristic burgundy color of an ylide. As anticipated, however, a complex mixture of products resulted, with the desired olefin being present in only trace amounts. Also present in the mixture was much of the starting aldehyde **12** along with triphenylphosphine. Although some ylide appeared to have formed, the majority of the phosphonium salt was evidently destroyed by elimination of the triphenylphosphine. A similar process is believe to occur in the gramine-type fragmentation of an indole-derived phosphonium iodide.[14]

To prevent the elimination reaction we decided to block the problematic nitrogen. In the model case, Wittig reaction of the *N*-methylpyrrole-derived phosphonium salt **14** with aldehyde **12** gave in good yield a cis–trans mixture of the olefin **15**. The reaction worked equally well when

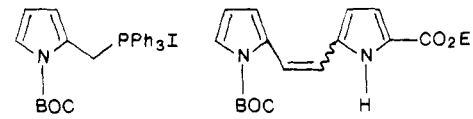


14 **15**

the base was *t*-BuOK. Although fluoride anion also functioned as a base, the reaction proceeded very slowly and in appreciably lower yield. On the other hand, the equally mild base K_2CO_3 worked remarkably well (89%), provided the reaction mixture was heated.

Having established the need for only one protecting group, we then looked into various protecting groups for the pyrrole bearing the phosphonium salt moiety and found the BOC group to be ideal. This group was introduced directly onto phosphonium salt **11** under the remarkably mild conditions of Grehn and Ragnarsson [$(BOC)_2O$, acetonitrile, DMAP, 97%].[15] The success of this reaction appears to indicate that the pyrrole anion of **11** undergoes acylation much more rapidly than the undesirable fragmentation process mentioned above.

Wittig reaction of this BOC-protected phosphonium salt **16** with aldehyde **12** proceeded in good yield under heterogeneous conditions as before (K_2CO_3, DMF, Δ, 92%) to afford olefin **17** as a mixture of cis and trans isomers.



16 **17**

These conditions allowed the preparation of multigram quantities of the olefin. Deprotection of this olefin proved to be difficult under the standard acidic conditions (i.e., CF_3CO_2H–CH_2Cl_2); however, under basic conditions (NaOEt, EtOH, Δ) this group could be removed in good yield.[16] An interesting observation led to what we consider

(12) Herz, W.; Rogers, J. L. *J. Am. Chem. Soc.* **1951**, *73*, 4921.

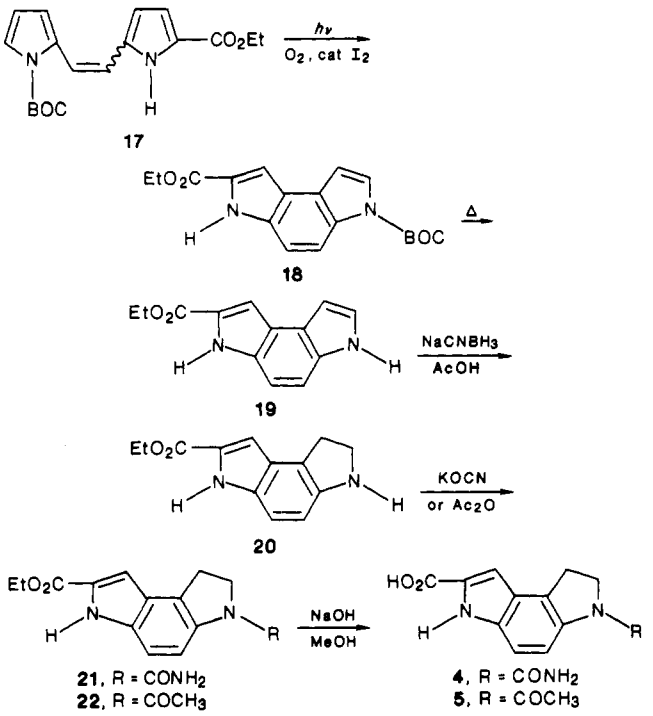
(13) Fournari, P.; Farnier, M.; Fournier, C. *Bull. Soc. Chim. Fr.* **1972**, 283.

(14) de Silva, S. O.; Snieckus, V. *Can. J. Chem.* **1974**, *52*, 1294.

(15) Grehn, L.; Ragnarsson, V. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296.

(16) Hasan, I.; Marinelli, E. R.; Lin, L. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.

Scheme I



an even better procedure for removing this group.[17] Simply heating a neat sample of the olefin effected the deprotection in high yield. This thermolytic deprotection procedure has been used successfully on 1–2 mM scale.

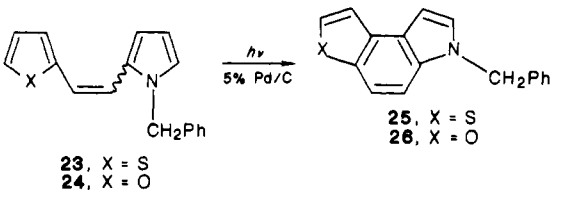
As anticipated, photocyclization of the olefin **15** proceeded in low yield under the standard conditions [*hν* (Pyrex), air, I_2(cat), EtOH, 15–20%].[24] Surprisingly, the reaction worked poorly even with the Pd/C protocol, which we have shown to be effective for cyclizing electron-rich, heterocyclic analogues of stilbene.[8f] Air-mediated photocyclization of the BOC-protected olefin **17**, on the other hand, proceeded in acceptable yield, even on preparative scales (55–65%, 0.5–1.5 g) (Scheme I). The improved yield in this case was not entirely unexpected, since the deactivating effect of the electron-withdrawing groups "protects" both of the pyrroles—and, likewise, the resulting indoles—from oxidative destruction. In this sense the BOC group is again functioning as a protecting group. As before, whereas acidic conditions were unsatisfactory (20–40%), and basic conditions superior (85%), thermolysis proved to be the method of choice for deprotecting **18** (97%).

With a good procedure for preparing the tricyclic unit **19**, what remained was selective reduction of the indole not bearing the withdrawing group, acylation of the resulting indoline, and hydrolysis of the ester. Selective reduction was effected smoothly using $NaCNBH_3$ in acetic acid[18] and afforded the indoline **20** as a bright yellow solid that was somewhat sensitive to air. Treatment of **20** with either aqueous KOCN at 60 °C or acetic anhydride at room temperature gave in high yield the desired urea **21** and amide **22**, respectively.

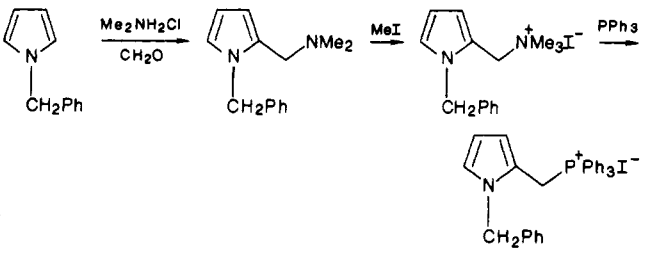
It was later found that since the thermolytic deprotection procedure required no solvent or reagents, i.e. no workup, and gave essentially a quantitative yield, and since the two subsequent steps were performed in acetic acid, all three steps could be performed in one pot. Thus, after a sample of **18** was thermolyzed, the cooled reaction product was dissolved in acetic acid and treated with $NaCNBH_3$ and, after TLC indicated no starting material, with acetic anhydride. This three-step, one-pot procedure required about 2 h and afforded the ethyl ester of dideoxy PDE-II **22** in excellent yield (94%). A similar one-pot sequence gave the urea **21** in 92% yield along with a small amount of the amide **22**, 3%. Basic hydrolysis gave in good yield the deoxygenated analogues of PDE-I **4** and of PDE-II **5**.

The photocyclization-based synthesis of dideoxy PDE-I and PDE-II required 10 chemical steps from pyrrole; however, as the deprotection, reduction, and acylation are performed in one flask, the synthesis actually *proceeds in only eight steps* and *goes in better than 30% overall yield.* We are presently investigating the use of **20** and **22** as the B and C units, respectively, for preparing the complete deoxy analogue of CC-1065.

II. Synthesis of Thieno and Furo PDE-I and PDE-II. Our general strategy centers around our palladium-mediated photocyclization[8f] of the stilbenoid heterocycles **23** and **24**, which can be prepared by the Wittig reaction of simple precursors. We then proceed to explore the regioselective lithiation of the photocyclization products **25** and **26** and later show how the benzyl group can be successfully used as protecting group for the pyrrole/indole nitrogen in this series by finally removing it with β,β,β-trichloroethyl chloroformate.



The synthesis, as shown for the thiophene series, began with pyrrole and 2-thiophenecarboxaldehyde. Pyrrole was reacted with sodium hydride and benzyl chloride in dimethylformamide to give *N*-benzylpyrrole in 87% yield.

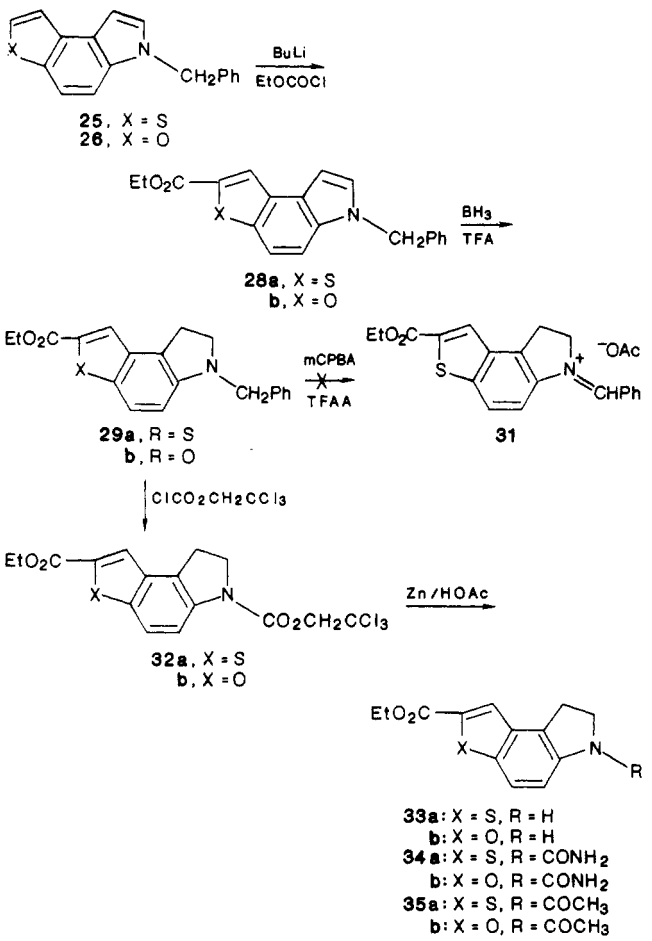


The Mannich product[12] from *N*-benzylpyrrole was treated with iodomethane in ethanol at 0 °C and then with triphenylphosphine in refluxing acetonitrile to give the phosphonium iodide **27** in 90% yield for the three steps. The pyrrole phosphonium iodide **12** was reacted in Wittig fashion with 2-thiophenecarboxaldehyde and potassium *tert*-butoxide in DMF to give the stilbenoid heterocycles **23**, as a mixture of a cis–trans isomers in 85% yield. Since cis–trans olefins are photochemically interconvertible, separation was unnecessary. Although air-mediated photocyclization was not suitable for these compounds, our palladium-mediated procedure worked expediently. Thus, the isomers **23** were photocyclized with palladized carbon in refluxing acetonitrile with triethylammonium *p*-nitrobenzoate as the hydrogen acceptor in 48 h to give the thienoindole **25** in 85% yield.[8f]

At this point we required a regioselective lithiation on the thiophene ring. Chadwick and Willbe have reported studies on the lithiation of thiophene, furan, and N-substituted pyrroles and indoles and have found that N-sub-

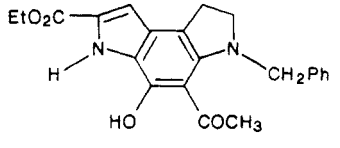
(17) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *25*, 6141.
(18) Gribble, G. W.; Hoffman, J. H. *Synthesis.* **1977**, 859.

Scheme II



stituted pyrroles and indoles that do not contain electron-withdrawing groups require relatively vigorous lithiation conditions (0 °C to reflux in ether), whereas thiophene, furan, and their benzo congeners are lithiated rapidly at −78 °C.[19] Therefore, we anticipated exclusive lithiation of the benzothiophene ring over the indole ring, and this proved to be the case. Thus, the cyclization product **25** was selectively lithiated on the thiophene ring with *n*-butyllithium in tetrahydrofuran at −78 °C; subsequent with ethyl chloroformate afforded ester **28a** in 96% yield (Scheme II).

Indole **28a** can be selectively reduced to the indoline **29a** with sodium cyanoborohydride in acetic acid[18] or borane in tetrahydrofuran at 0 °C.[20] Both procedures give the indoline in 85–90% yield. Although seemingly trivial, we expected the removal of the benzyl group to be problematic. Sundberg et al. had tried various catalytic hydrogenation procedures to debenzylate the oxygenated compound **30** but were unsuccessful and finally resorted to



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cyanogen bromide.[8b] We also tried various catalytic methods unsuccessfully. Employment of the modified Polonovsky reaction (*m*-chloroperbenzoic acid at 0 °C followed by trifluoroacetic anhydride),[21] which was elegantly utilized in the partial synthesis of vinblastine-type alkaloids,[22] we hoped to give the imine **31**, which would hydrolyze to the indoline **33a** and benzaldehyde. Unfortunately, it gave the rearomatized indole **28a** in 75–80% yield; actually, this appears to be a good procedure for oxidizing *N*-alkyl indolines to indoles. Debenzylation was finally achieved with β,β,β-trichloroethyl chloroformate[23] in acetonitrile to give the pleasant-smelling carbamate **32a** in excellent yield. The trichloro carbamate was then removed with zinc in acetic acid to give the indoline **33a**, which was generally not isolated but reacted directly with an aqueous solution of potassium cyanate or acetic anhydride to give the analogues **34a** and **35a** in 80 and 85% yields, respectively, for the two steps. The esters were saponified to the acids **6** and **8** in 80% yield. The furan compounds **7** and **9** were constructed in an analogous manner to **6** and **8** with one minor exception. The photocyclization of furan-containing analogues **24** proceeded at a slower rate than their respective thiophene congeners and required 4 days to go to completion. In general, we have found that furan-containing heterostilbenes require longer reaction times than other heterostilbenes under comparable conditions.[8f] In summary, the reaction sequence requires 11 steps from pyrrole and thiophenecarboxaldehyde or furfural and goes in better than 30% overall yield. The precursors of these thiophene and furan analogues of dideoxy PDE-I and PDE-II are currently being investigated for the synthesis of new analogues of CC-1065.[26]

Experimental Section

General Data. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on either a Bruker WM-250, an IBM 200, or a Nicolet 200 NMR spectrometer, and chemical shifts are reported in δ values relative to internal standard Me_4Si (0.00). The following abbreviations are used in reporting the NMR data: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; a, apparent (one of the peaks not clearly resolved); *J*, coupling constant. Infrared spectra (IR) were recorded on a Perkin-Elmer 781 infrared spectrophotometer as KBr pellets (for solids) or thin films (for liquids) and are uncorrected. Mass spectra were obtained through the Mass Spectrometry Center of the Chemistry Department of either the University of Pennsylvania or the University of Alabama. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalytical data was obtained through either Galbraith Laboratories, Knoxville, TN, or Atlantic Microlab, Atlanta, GA. Unless indicated otherwise, all reactions were performed in a flame-dried flask using dry distilled solvents and maintained under a positive pressure of argon or nitrogen (balloon). Tetrahydrofuran was distilled from sodium–benzophenone ketyl. Other distilled solvents were stored over either 3A or 4A molecular sieves. Solvents used for extraction and chromatography were reagent grade. Reactions were heated in silicone oil baths, the stated reaction temperature being the temperature of the bath, within ±5 °C. All column chromatography was performed by the method of Still et al.[25] using Merck silica gel 60 (230–400 mesh).

Photolyses were performed in a water-cooled quartz or borosilicate immersion well available from Ace Glass Co. The light source was a Hanovia 450-W, medium-pressure mercury vapor lamp, which was used in connection with a Pyrex filter. The photolyses were carried out in a specially constructed Pyrex

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Dewar[8f] in spectrograde acetonitrile.

***N,N*,1-Trimethyl-1*H*-pyrrole-2-methanamine.** This compound was prepared by Herz's method.[12] Thus, a solution of Me_2NH_2Cl (51.0 g, 0.62 mol) in aqueous 37% formalin (51.0 g, 0.63 mol) was added dropwise to *N*-methylpyrrole at such a rate that the temperature did not exceed 55 °C. After addition was complete, the reaction was stirred for 6 h, then poured into 10% aqueous NaOH (200 mL), and extracted repeatedly with ether (4 × 150 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and distilled at reduced pressure to afford a clear liquid: 58.0 g (70%); bp 35–37 °C (3 torr) [lit.[12] mp 53–54 °C (6 torr)]; ^1H NMR ($CDCl_3$) δ 2.19 (s, 6 H, NMe_2), 3.32 (s, 2 H, CH_2N), 3.63 (s, 3 H, NCH_3), 5.98 (m, 1 H, Ar-H), 6.03 (m, 1 H, Ar-H), 6.58 (m, 1 H, Ar-H).

***N,N,N*,1-Tetramethyl-1*H*-pyrrole-2-methanaminium Iodide.** Methylation was carried out by a modification of Herz's procedure.[12] Thus, a solution of the Mannich product (30.0 g, 0.217 mol) in absolute ethanol (175 mL) was chilled in an ice bath (ca. 5 °C, internal) and treated dropwise with a solution of methyl iodide (35.0 g, 0.247 mol) in absolute ethanol (25 mL). After addition was complete, the solution was stirred further for 2 h. Over this period a large amount of a white solid precipitated. The reaction mixture was allowed to warm to room temperature for 1 h and then placed in a freezer. After several hours, ether (150 mL) was added and the white mass was broken up and filtered to afford the product as white, powdery crystals: 60.1 g (99%); mp 140–146 °C dec (lit.[12] mp 140–150 °C dec); ^1H NMR ($CDCl_3$) δ 3.40 (s, 9 H, NMe_3I), 3.89 (s, 3 H, NCH_3), 4.98 (s, 2 H, CH_2N), 6.18 (t, 1 H, Ar-H), 6.48 (m, 1 H, Ar-H), 6.78 (m, 1 H, Ar-H).

[(1-Methyl-1*H*-pyrrol-2-yl)methyl]triphenylphosphonium Iodide (14). The methiodide (8.40 g, 30.0 mmol) and triphenylphosphine (8.70 g, 34.0 mmol) was added to acetonitrile (30 mL), and the mixture was heated to reflux for 5 h. Most of the solvent was evaporated under reduced pressure (until approximately 5 mL remained), and 1:1 ethyl acetate–benzene (50 mL) was added. The resulting solid was separated by filtration, washed twice with 1:1 ethyl acetate–benzene, and dried to give a white solid: 13.35 g (92%); mp 197–200 °C. Recrystallization from methylene chloride–ethyl acetate afforded an analytically pure sample as small colorless needles: mp 203–205 °C dec; ^1H NMR ($CDCl_3$) δ 3.11 (s, 3 H, NCH_3), 5.05 (d, 2 H, J = 11.7 Hz, CH_2N), 5.61 (m, 1 H, Ar-H), 5.94 (m, 1 H, Ar-H), 6.50 (m, 1 H, Ar-H), 7.55–7.87 (m, 15 H, PPh_3); IR (KBr, cm^{-1}) 3015, 2860, 1595, 1490, 1450, 1440, 1310, 1130, 1117, 1003, 850, 800; mass spectrum, m/e (relative intensity) because of the nonvolatility of this salt a good mass spectrum could not be obtained. Anal. Calcd for $C_{24}H_{23}INP$: C, 59.36; H, 4.77; N, 2.88. Found: C, 59.59; H, 4.82; N, 2.88.

***N,N,N*-Trimethyl-1*H*-pyrrole-2-methanaminium Iodide.** Herz's procedure[12] was modified as follows: To a stirred, ice bath chilled solution of the pyrrole Mannich product (24.83 g, 0.20 mol) in absolute ethanol (200 mL) was added dropwise over 15 min a solution of CH_3I (32.0 g, 0.225 mol) in absolute ethanol (50 mL). After 1 h the reaction mixture, which had become a white solid mass, was stopped and placed in a refrigerator overnight. Ether (150 mL) was added, and the product was isolated by vacuum filtration, giving a white powder which slowly became yellow: 50.1 g (94%); mp 155–165 °C dec (lit.[12] mp >160 °C dec; ^1H NMR ($CDCl_3$) δ 3.20 (s, 9 H, NCH_3), 4.93 (s, 2 H, CH_2), 6.20 (m, 1 H, Ar-H), 6.41 (m, 1 H, Ar-H), 6.94 (m, 1 H, Ar-H), 9.65 (brs, 1 H, NH).

(1*H*-Pyrrol-2-ylmethyl)triphenylphosphonium Iodide (11). To a flame-dried 1-L flask, fitted with a condenser and a magnetic stir bar, was added the aforementioned methiodide (45.0 g, 0.169 mol), PPh_3 (46.0 g, 0.175 mol), and acetonitrile (200 mL). The stirred reaction mixture was vacuum purged with nitrogen (3×) and then heated to reflux in an oil bath. A slow stream of nitrogen was passed through the system to remove the trimethylamine that was evolved. After 24 h, the cooled reaction mixture was diluted with ether (100 mL) and the product, an off-white powdery solid, was collected by vacuum filtration; 74.8 g (94%). Crystallization from acetonitrile afforded analytically pure, colorless crystals: mp 213–216 °C; ^1H NMR ($CDCl_3$) δ 5.35 (d, 2 H, J = 12.3, CH_2), 5.54 (br s, 1 H, J = 5.96, 2.7 Hz, Ar-H), 6.68 (m, 1 H, Ar–H), 7.50–7.82 (m, 15 H, PPh_3). 10.56 (br s, 1 H, NH); IR (cm^{-1} KBr) 3280 (NH), 2900, 1590, 1485, 1435, 1115, 755, 745, 735. Anal. Calcd for $C_{23}H_{21}INP \cdot 1.5\ H_2O$: C, 55.40; H, 4.81. Found: C, 55.40; H, 4.73.

5-[2-(1-Methyl-1*H*-pyrrol-2-yl)ethenyl]-1*H*-pyrrole-2-carboxylic Acid, Ethyl Ester (15). A stirred mixture of aldehyde **12** (0.34 g, 2.0 mmol), anhydrous K_2CO_3 (2.0 g, powdered), and the *N*-methylpyrrole-derived phosphonium salt **14** (1.06 g, 2.1 mmol) in dry DMF (20 mL) was heated (80 °C, bath temperature). Progress of the reaction was followed by TLC. After complete disappearance of the starting material, the cooled reaction mixture was diluted with ether (100 mL) and water (100 mL), stirred vigorously for 10 min, and then filtered through a pad of Celite. The organic phase separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic phase was washed with water (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude was chromatographed (methylene chloride) to afford **15** [0.57 g (85%)], a pale yellow sticky solid, as a mixture of cis and trans isomers: ^1H NMR ($CDCl_3$) δ 1.28–1.38 (2 t, 3 H, CH_3), 3.54 + 3.65 (2 s, 3 H, NCH_3), 4.24–4.37 (2 q, 2 H, OCH_2), 6.13–6.95 (complex m, 7 H, pyrrole + olefinic H), 9.57 + 9.65 (2 br s, 1 H, NH); IR (KBr) 3290 (NH), 1680 (C=O), 1485, 1425, 1320, 1245, 1210, 1155; mass spectrum (isobutane), m/e (relative intensity) 245 (62, M + 1), 244 (100, M^+), 198 (14), 197 (13), 170 (16), 157 (6), 145 (15), 140 (15), 117 (9), 91 (17), 85 (36), 83 (50), 79 (26), 77 (23); exact mass determination for $C_{14}H_{16}N_2O_2$ (M+1) calcd 245.1290, found 245.1286, (M^+) calcd 244.1211, found 244.1240.

[[1-[[(1,1-Dimethylethyl)oxy]carbonyl]-1*H*-pyrrol-2-yl]-methyl]triphenylphosphonium Iodide (16). To a flask was added $(BOC)_2O$ (6.55 g, 30.0 mmol), acetonitrile (100 mL), and the dried phosphonium salt **11** (11.72 g, 225 mmol). The reaction flask was flushed several times with argon. Addition of a catalytic amount of DMAP (0.12 g, 1.0 mmol) initiated the reaction (gas evolution). After the mixture was stirred overnight at room temperature, the solvent was removed in vacuo, and ethyl acetate (50 mL) was added, causing a brown oil to separate. Crystallization was effected by dropwise addition of methylene chloride (ca. 5 mL) to the swirled reaction mixture. The resulting suspension was warmed briefly (1–2 min) on a steam bath and then chilled in an ice bath. The product, a tan solid, was separated by vacuum filtration and washed with ether (100 mL). The filtrate was chilled to give a second crop of crystals, 2.05 g, pure by NMR. The combined yield was 13.76 g (97%). Product was dried under a vacuum over P_2O_5. Recrystallization from methylene chloride–ethyl acetate afforded an analytically pure sample as colorless microcrystals: mp 163–165 °C (effervescence); ^1H NMR ($CDCl_3$) δ 1.29 (s, 9 H, CH_3), 5.57 (d, 2 H, J = 12.8 Hz, CH_2), 6.11 (t, 1 H, J = 3.45 Hz, Ar-H), 6.37 (br s, 1 H, Ar-H), 7.08 (m, 1 H, Ar-H), 7.52–7.85 (m, 15 H, PPh_3); IR (KBr, cm^{-1}) 3020, 2995, 1725 (C=O), 1495, 1485, 1440, 1350, 1330, 1130. Anal. Calcd for $C_{28}H_{29}INO_2P$: C, 58.78; H, 5.11; N, 2.45. Found: C, 58.90; H, 5.16; N, 2.44.

5-[2-[1-[[(1,1-Dimethylethyl)oxy]carbonyl]-1*H*-pyrrol-2-yl]ethenyl]-1*H*-pyrrole-2-carboxylic Acid, Ethyl Ester (17). To a flask fitted with a magnetic stirring bar were added aldehyde **11** (12.5 g, 22.0 mmol), phosphonium salt **16** (12.53 g, 22.0 mmol), anhydrous K_2CO_3 (20 g, powdered), and DMF (100 mL). The stirred reaction mixture was vacuum purged with argon (3×) and then heated in an oil bath for 8 h (80 °C, bath temperature). The cooled reaction mixture was diluted with water (500 mL) and ether (200 mL), stirred vigorously for 30 min, and then filtered through a pad of Celite. The organic phase was separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic phase was washed with water (100 mL) and brine (25 mL), dried (Na_2SO_4 and silica gel), and concentrated under reduced pressure. Purification by chromatography (methylene chloride:hexanes = 4:1) afforded the product, a mixture of cis and trans isomers, as a gummy, cream-colored solid, 6.08 g (92%). The trans isomer was separated by recrystallizing from ether–hexanes, affording an analytically pure sample as white, fibrous needles: mp 151–152 °C; ^1H NMR ($CDCl_3$) δ (trans isomer) 1.36 (t, 3 H, J = 7.1 Hz, CH_3), 1.62 (s, 9 H, CH_3), 4.33 (q, 2 H, J = 7.1 Hz, CH_2), 6.18 (t, 1 H, J = 3.4 Hz, Ar-H), 6.33 (m, 1 H, Ar-H), 6.51 (m, 1 H, Ar-H), 6.72 (d, 1 H, J = 16.5 Hz, CH), 6.88 (m, 1 H, Ar-H), 7.26 (m, 1 H, Ar-H), 7.57 (d, 1 H, J = 16.5 Hz, CH), 9.28 (br s, 1 H, NH); IR (KBr, cm^{-1}) 3305 (NH), 2990, 1735 (C=O), 1680 (C=O), 1490, 1480, 1375, 1330; mass spectrum, m/e (relative intensity) 330 (35, M^+), 275 (11), 274 (62), 231 (6), 230 (51), 185 (21), 184 (100), 183 (48), 157 (25), 158 (70), 157 (40), 140 (10), 130

(10), 101 (6). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.61; N, 8.48. Found: C, 65.35; H, 6.81; N, 8.36.

5-[2-(1*H*-Pyrrol-2-yl)ethenyl]-1*H*-pyrrole-2-carboxylic Acid, Ethyl Ester. a. Thermal Deprotection. A 0.33-g (1.0-mmol) sample of the trans olefin **18**, which was obtained by crystallization from ether–hexanes, was heated (185 °C, bath) in a flask. The solid melted quickly and began to effervesce. After 20 min, the bubbling had ceased. The resulting yellow oil was heated further for 5–10 min and then cooled to give a crystalline solid. Chromatography (methylene chloride:ether = 20:1 to 10:1) gave a white crystalline product [0.21 g (91%)] that was quite light sensitive and darkened to gray-green. A clear solution of this substance quickly becomes blue-green: mp 157–159 °C; ^{1}H NMR ($CDCl_3$) δ (slower fraction, trans) 1.36 (t, 3 H, J = 7.1 Hz, CH_3), 4.33 (q, 2 H, J = 7.1 Hz, CH_2), 6.23–6.29 (m, 2 H, pyrrole H), 6.35 (m, 1 H, pyrrole H), 6.48 (d, 1 H, J = 16.6 Hz, C=CH), 6.77 (d, 1 H, J = 16.6 Hz, C=CH), 6.83 (m, 1 H, pyrrole H), 6.88 (m, 1 H, Ar-H), 8.31 (br s, 1 H, NH), 9.01 (br s, 1 H, NH); IR (cm^{-1}) 3370 (NH), 3290, 1680 (C=O), 1485, 1450, 1440, 1320, 1225; mass spectrum, m/e (relative intensity) 231 (14, M + 1), 230 (89, M$^+$), 200 (1), 185 (19), 184 (80), 183 (100), 182 (22), 157 (29), 156 (84), 155 (40), 141 (11), 130 (11), 104 (6), 102 (8), 78 (13); exact mass determination for $C_{13}H_{14}N_2O_2$ (M + 1) calcd 231.1133, found 231.1136, (M$^+$) calcd 230.1055, found 230.1048.

b. Base-Mediated Deprotection. To a suspension of the protected olefin **18** (1.30 g, 3.93 mmol) in absolute ethanol (40 mL) was added 5.0 mL of a 1.0 M solution of sodium ethoxide (prepared from 0.24 g Na and 10 mL of absolute ethanol). Progress of the reaction was monitored by TLC. After it had gone to completion (overnight), the reaction solution was diluted with 10% aqueous NH_4Cl (20 mL) and extracted with methylene chloride (4 × 50 mL). The combined extracts were dried and concentrated in vacuo to give a brown solid that was purified by chromatography (methylene chloride:ether = 20:1) to give the product in two fractions (cis and trans) in a combined yield of 0.77 g (85%). This product was identical with that obtained from the thermal deprotection.

3,6-Dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2,6-dicarboxylic Acid, 6-(1,1-Dimethylethyl) 2-Ethyl Ester (18). A stirred solution of olefin **17** (1.0 g, 3.0 mmol) in absolute ethanol (375 mL) containing a catalytic amount of I_2 (50 mg) was irradiated. Air was slowly bubbled into the reaction during the irradiation. Progress of reaction was monitored every 15 min by TLC (silica gel plate, methylene chloride). Upon disappearance of the starting material (ca. 1 h), the solvent was removed in vacuo, and the residue purified by chromatography (methylene chloride) to afford the cyclized product **18** as a clear oil that crystallized to cream-colored needles, 0.54–0.64 g (55–65%). Recrystallization from ethanol afforded an analytically pure sample as fine, cream-colored needles: mp 162–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.1 Hz, CH_2), 1.69 (s, 3 H, CH_2), 4.43 (q, 2 H, J = 7.1 Hz, CH_2), 6.83 (d, 1 H, J = 3.6 Hz, Ar-H), 7.33 (d, 1 H, J = 9.1 Hz, Ar-H), 7.44 (m, 1 H, Ar-H), 7.66 (d, 1 H, J = 3.6 Hz, Ar-H), 8.22 (d, 1 H, J = 9.1 Hz, Ar-H), 9.13 (br s, 1 H, NH); IR (KBr, cm^{-1}) 3400 (NH), 2990, 1720 (C=O), 1685 (C=O), 1515, 1445, 1365, 1340, 1150; mass spectrum, m/e (relative intensity) 328 (3, M$^+$), 272 (14), 226 (8), 211 (21), 182 (11), 166 (13), 139 (44), 129 (13), 122 (18), 111 (42), 95 (45), 94 (100), 93 (96). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.01; H, 6.18; N, 8.54.

3,6-Dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic Acid, Ethyl Ester (19). To a flask was added the indole **18** (328 mg, 1.0 mmol), and the flask was flushed several times with argon. The flask was placed in an oil bath (ca. 185 °C, bath temperature), causing evolution of gas, as evidenced by slow bubbling. A positive pressure of argon was maintained during the reaction. After gas evolution ceased (ca. 20–30 min), the flask was cooled to afford the product as an off-white solid impregnated with traces of a darker material, sufficiently pure for the next step; 227 mg (100%). Chromatography (methylene chloride) gave a colorless crystalline solid, 221 mg (97%). Recrystallization from methylene chloride–hexanes afforded an analytically pure sample as shiny, colorless needles: mp 184.5–185.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.1 Hz, CH_2), 4.42 (q, 2 H, J = 7.1 Hz, CH_2), 6.80 (m, 1 H, Ar-H), 7.22 (d, 1 H, J = 8.7 Hz, Ar-H), 7.24 (m, 1 H, Ar-H), 7.37 (dd, 1 H, J = 0.7, 8.8 Hz, Ar-H), 7.47 (m, 1 H, Ar-H), 8.37 (br s, 1 H, NH), 9.10 (br s, 1 H, NH); IR (KBr, cm^{-1}) 3410 (NH), 3320 (NH), 1690 (C=O), 1525, 1485, 1385, 1285, 1220; mass spectrum, m/e (relative intensity) 228 (61, M$^+$), 183 (20), 182 (100), 155 (12), 154 (43), 128 (20), 127 (12); exact mass determination for $C_{13}H_{12}N_2O_2$ (M + 1) calcd 229.0977, found 229.0997, (M$^+$) calcd 228.0899, found 228.0880. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30.14; N, 12.27. Found: C, 68.47; H, 5.32; N, 12.25.

3,6,7,8-Tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic Acid, Ethyl Ester (20). A purified sample of the deprotected indole **13** (0.114 g, 0.5 mmol) was dissolved in acetic acid (3.0 mL) and cooled in a water bath (17–20 °C). Small portions of $NaCNBH_3$ (ca. 15 m) were added every 5–10 min, and progress of the reaction was monitored by TLC. After the fifth or sixth addition, very little starting material remained. The reaction solution was stirred further for 15 min, then carefully poured into 10% Na_2CO_3 (25 mL), and extracted repeatedly with ether (4 × 25 mL). The combined ether portion was washed with water (25 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification through a short column (methylene chloride:THF = 10:1) gave a bright yellow powdery solid, 0.11 g (96%). This material is somewhat air sensitive. In solution it is a highly fluorescent yellow-green in long-wave UV: mp 162–164 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3 H, J = 7.1 Hz, CH_3), 3.22 (t, 2 H, J = 8.5 Hz, Ar-CH_2), 3.66 (t, 2 H, J = 8.4 Hz, CH_2N), 4.40 (q, 2 H, J = 7.1 Hz, OCH_2), 6.84 (d, 1 H, J = 8.6 Hz, Ar-H), 7.03 (dd, 1 H, J = 0.8, 2.0 Hz, indole H), 7.11 (dd, 1 H, J = 0.8, 8.6 Hz, Ar-H), 9.05 (br s, 1 H, NH); IR (cm^{-1}, KBr) 3330 (NH), 1685 (C=O), 1530, 1450, 1330, 1255, 1210; mass spectrum, m/e (relative intensity) 230 (32, M$^+$), 228 (21), 201 (5), 197 (8), 184 (100), 155 (68), 128 (68), 101 (56), 92 (29), 87 (18), 85 (48), 77 (67); exact mass determination for $C_{13}H_{14}N_2O_2$ (M$^+$) calcd 230.1055, found 230.1057.

6-Acetyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic Acid, Ethyl Ester (22). To a water bath (15–20 °C) cooled solution of the indole **19** (114 mg, 0.5 mmol) in acetic acid (5 mL) was added, over ca. 1 h, small portions of $NaCNBH_3$ (ca. 6 × 15 mg). After the disappearance of starting material (TLC), the reaction mixture was stirred for 1 h, then quenched with an excess of acetic anhydride (0.5 mL), and stirred further for 30 min. Addition of water (50 mL) gave a cloudy suspension that, after allowing to stir overnight, was filtered to give the product as a fine white powder, 125 mg. Extraction of the filtrate (methylene chloride, 2 × 10 mL), afforded additional 6 mg of the product, combined yield 131 mg (96%). Crystallization from ethanol afforded an analytically pure sample as colorless crystals: mp 281–282.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz, CH_2), 2.26 (s, 3 H, CH_2), 3.38 (t, 2 H, J = 8.5 Hz, CH_2), 4.18 (t, 2 H, J = 8.6 Hz, CH_2), 4.41 (q, 2 H, J = 7.1 Hz, OCH_2), 7.10 (m, 1 H, Ar-H), 8.40 (d, 1 H, J = 8.9 Hz, Ar-H), 8.93 (br s, 1 H, NH); IR (KBr, cm^{-1}) 3300 (NH), 1710 (C=O), 1630 (C=O), 1530, 1445, 1385, 1330, 1255; mass spectrum, m/e (relative intensity) 272 (69, M$^+$), 230 (22), 226 (21), 185 (18), 184 (100), 183 (17), 157 (20), 156 (48), 155 (30), 128 (29), 102 (11), 101 (11), 77 (10). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.26; H, 6.11; N, 10.26.

6-(Aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic Acid, Ethyl Ester (21). The reaction was carried out as described above, except a solution of KOCN (250 mg in 3 mL water) was added after the reduction was complete. After being warmed in an oil bath (60 °C) for 1 h, the reaction mixture was diluted with water (15 mL), stirred overnight, and then filtered to give the urea **21** as a white powder, 114 mg. Extraction of the filtrate (methylene chloride, 2 × 10 mL), followed by chromatographic purification (methylene chloride:THF = 10:1 to 3:1) afforded a small amount of the amide **22** [8 mg (3%)], along with the urea **21**; 12 mg; combined yield 126 mg (92%). The whole sequence was carried out on 1-mmol scale, and the crude product was recrystallized directly to afford the product in identical yield; 251 mg (92%). Recrystallization from ethanol afforded shiny, pale yellow plates: mp 260–262 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H, J = 7.1 Hz, CH_3), 3.26 (t, 2 H, J = 8.7 Hz, Ar-CH_2), 3.97 (t, 2 H, J = 8.8 Hz, CH_2N), 4.33 (q, 2 H, J = 7.1 Hz, OCH_2), 6.14 (br s, 2 H, NH_2), 6.98 (d, 1 H, J = 1.2 Hz, indole H), 7.20 (d, 1 H, J =9.1 Hz, Ar-H), 8.02 (d, 1 H, J = 9.0 Hz, Ar-H), 11.77 (br s, 1 H, NH); IR (KBr, cm^{-1}) 3300 (br, NH), 1700 (C=O), 1670 (C=O), 1610, 1585, 1455, 1335, 126; mass spectrum, m/e (relative intensity) 273 (56, M$^+$), 230 (9), 227 (18), 227 (18), 184 (100), 156

(53), 155 (33), 128 (20), 101 (11), 92 (10). Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.37. Found: C, 61.40; H, 5.55; N, 15.30.

6-(Aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic Acid (4). A solution of ester **21** (50 mg, 0.18 mmol) in methanol (25 mL) was treated with aqueous NaOH (200 mg in 2 mL of water) and warmed gently on a steam bath. Progress of the reaction was monitored by observing the disappearance of the starting ester (TLC, silica gel; methylene chloride:acetone = 3:1). After hydrolysis was completed (ca. 20 min), the reaction solution was cooled and acidified to pH 1 by dropwise addition of concentrated HCl. Cooling overnight in a freezer precipitated the product **4** as colorless needles, which were separated by filtration; 34 mg. An additional crop was obtained by diluting the filtrate with water and cooling: combined yield 37 mg (80%); mp >250 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.25 (t, 2 H, J = 8.8 Hz, Ar-CH_2), 3.96 (t, 2 H, J = 8.8 Hz, NCH_2), 6.13 (br s, 2 H, NH_2), 6.92 (d, 1 H, J = 1.0 Hz, indole H), 7.18 (d, J = 9.0 Hz, Ar-H), 7.99 (d, 1 H, J = 8.9 Hz, Ar-H). 11.64 (br s, 1 H, NH), 11.8 (br s, 1 H, COOH); IR (KBr, cm^{-1}) 3500, 3350 (NH), 1695 (C=O), 1690 (C=O), 1610, 1520, 1475; mass spectrum, m/e (relative intensity) 245 (5, M^+), 202 (10), 184 (28), 156 (15), 155 (14), 132 (37), 128 (8), 113 (49), 92 (9), 85 (33), 64 (15), 44 (100). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.69; H, 4.53; N, 17.07.

6-Acetyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic Acid (5). This reaction was performed exactly as described for preparing urea **4**. Thus, 50 mg (0.18 mmol) of the ester gave 39 mg of the acid: 87%; mp >275 °C dec; ^{1}H NMR (Me_2So-d_6) δ 2.15 (s, 3 H, $COCH_3$), 3.29 (t, 2 H, J = 8.4 Hz, Ar-CH_2), 4.16 (t, 2 H, J = 8.4 Hz, NCH_2), 6.99 (s, 1 H, indole H), 7.24 (d, 1 H, J = 8.9 Hz, Ar-H), 8.18 (d, 1 H, J = 8.9 Hz, Ar-H), 11.78 (s, 1 H, NH), 12.98 (br s, 1 H, COOH); IR (KBr, cm^{-1}) 3270 (NH, OH), 1665 (C=O), 1600, 1575, 1535, 1455, 1330; mass spectrum, m/e (relative intensity) 245 (10, M + 1), 244 (56, M^+), 226 (10), 202 (25), 201 (6), 185 (12), 184 (100), 183 (18), 157 (16), 156 (36), 155 (30), 130 (10), 128 (25), 101 (13), 101 (13), 77 (10); exact mass determination for $C_{13}H_{12}N_2O_3$ (M^+) calcd 244.0848, found 244.0851.

1-(Phenylmethyl)-1*H*-pyrrole. In a 500-mL flask, maintained under a positive pressure of argon, a mineral oil dispersion of NaH (50%; 10.6 g, 0.22 mol) was washed once with hexane, dried, and resuspended in DMF (200 mL). A solution of pyrrole (13.4 g, 0.20 mol, 13.9 mL) in dimethylformamide (50 mL) was then added dropwise over 30 min (*CAUTION*! moderately exothermic reaction; water bath recommended). After the mixture was stirred further for 30 min, benzyl chloride was added dropwise over 15 min. After 1 h the reaction mixture was poured into water (500 mL) and extracted with 1:1 ether–hexanes (3 × 150 mL). The combined organic phase was washed with water, dried (Na_2SO_4), and concentrated. Vacuum distillation gave the product, a pleasant-smelling, colorless liquid that solidified in the refrigerator: 27.3 g (87%); bp 90–95 °C (ca. 2 torr) [lit.[12] bp 140 °C (16 torr)]; ^{1}H NMR ($CDCl_3$) δ 5.07 (s, 2 H, NCH_2), 6.19 (d, 2 H, J = 2.1 Hz, pyrrole *H*), 6.69 (d, 2 H, J = 2.1 Hz, pyrrole *H*), 7.09–7.13 (m, 2 H, Ar-*H*), 7.25–7.36 (m, 3 H, Ar-*H*).

***N*,*N*-Dimethyl-1-(phenylmethyl)-1*H*-pyrrole-2-methanamine.**[12] To a solution of Me_2NH_2Cl (4.13 g, 50.6 mmol) in aqueous 37% formalin (3.91 g, 48.0 mmol) was added *N*-benzylpyrrole (6.56 g, 45.0 mmol), and the resulting two-phase mixture was stirred overnight. Aqueous 10% NaOH (50 mL) was added, and the product was extracted with ether (3 × 75 mL). The combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification by Kugelrohr distillation gave the product, a colorless liquid that contained a small amount (5–10% by NMR) of the 3-isomer: 9.13 g (93%); bp 85–90 °C (ca. 0.1 torr); ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 6 H, NMe_2), 3.21 (s, 2 H, pyrrole CH_2N), 5.21 (s, 2 H, NCH_2-Ar), 6.04–6.09 (m, 2 H, pyrrole *H*), 6.64–6.65 (m, 1 H, pyrrole *H*), 7.01–7.04 (m, 2 H, Ar-*H*), 7.25–7.30 (m, 3 H, Ar-*H*); MS (EI) m/e (relative intensity) 214 (M^+, 2.2), 170 (18.2), 169 (15.8), 91 (100.0), 65 (21.5); IR (KBr, cm^{-1}) 3030, 2930, 2780, 1605, 1495, 1485, 1455, 1360, 1300, 1300, 1180, 1160, 1135; HRMS (CI) m/e (M^+) 214.1464 (calcd for $C_{14}H_{18}N_2$ 214.1471).

***N*,*N*,*N*-Trimethyl-1-(phenylmethyl)-1*H*-pyrrole-2-methanaminium Iodide.** The above-mentioned Mannich compound (5.50 g, 25.5 mmol) in ethanol at 0 °C was treated with methyl iodide (4.52 g, 31.9 mmol, 1.25 equiv) dropwise. The solution was allowed to warm to room temperature and filtered to afford the trimethylammonium salt as a white powder, 9.0 g (99%). Crystallization from ethyl acetate afforded an analytically pure sample as colorless crystals: mp >205 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.02 (s, 9 H, NMe_3), 4.56 (s, 2 H, pyrrole CH_2N), 5.33 (s, 2 H, NCH_2Ph), 6.23 (dd, 1 H, J = 2.9, 3.4 Hz, pyrrole *H*), 6.48 (dd, 1 H, J = 1.6, 3.6 Hz, pyrrole *H*), 7.03–7.06 (m, 3 H, Ar-*H*), 7.29–7.39 (m, 3 H, Ar-*H*); IR (cm^{-1}, KBr) 3000, 1500, 1485, 1455, 1415, 1375, 1305, 1085, 745. Anal. Calcd for $C_{15}H_{21}IN_2$: C, 50.57; H, 5.94; N, 7.86. Found: C, 50.57; H, 5.98; N, 7.83.

Triphenyl[[1-(phenylmethyl)-1*H*-pyrrol-2-yl]methyl]phosphonium Iodide (27). The ammonium salt (9.0 g, 25.2 mmol) was allowed to react with triphenylphosphine (8.0 g, 30.5 mmol, 1.2 equiv) in refluxing acetonitrile (50 mL) for 5 h. After cooling and diluting with benzene, the product, a pink powder, was separated; 13.6 g (96%). Crystallization from ethyl acetate–chloroform afforded an analytically pure sample as white microcrystals: mp 182–184 °C dec; ^{1}H NMR ($CDCl_3$) δ 4.76 (s, 2 H, NCH_2Ph) 4.96 (d, 2 H, J = 12.7 Hz, CH_2P), 5.66 (m, 1 H, pyrrole *H*), 5.98–6.01 (m, 1 H, pyrrole *H*), 6.57–6.58 (m, 1 H, pyrrole *H*), 6.95–7.00 (m, 2 H, Ar-*H*), 7.19–7.28 (m, 3 H, Ar-*H*), 7.52–7.84 (m, 15 H, PPh_3); IR (KBr, cm^{-1}) 2860, 1480, 1430, 1403, 710. Anal. Calcd for $C_{30}H_{27}INP$: C, 64.44; H, 4.86; N, 2.50. Found: C, 63.80; H, 4.97; N, 2.63.

2-[2-(2-Thienyl)ethenyl]-1-(phenylmethyl)-1*H*-pyrrole (23). To a solution of phosphonium iodide **27** (5.59 g, 10.0 mmol), 2-thiophenecarboxaldehyde (1.23 g, 11 mmol), and dimethylforamide (75 mL) was added potassium *tert*-butoxide (1.23 g, 11 mmol). The reaction was stirred for 30 min, poured into water, and extracted with ether–hexanes (1:1; 3 × 50 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The crude product was chromatographed (hexanes:methylene chloride = 3:1) to give the heterocyclic stilbenoids as a mixture of cis–trans isomers, 2.25 g (85%). These compounds darken quickly on exposure to light and air: ^{1}H NMR ($CDCl_3$) trans δ 5.13 (s, 2 H, CH_2Ph), 6.21 (m, 1 H, Ar-*H*), 6.51 (m, 1 H, Ar-*H*), 6.70 (m, 2 H, Ar-*H*), 6.91 (m, 3 H, Ar-*H*), 7.04 (m, 3 H, Ar-*H*), 7.28 (m, 3 H, Ar-*H*); IR (KBr, cm^{-1}) 3115, 3080, 3040, 1630, 1505, 1478, 1461, 1450, 1310, 1088, 949, 710; MS (EI) m/e (relative intensity) 266 (M + 1, 16.2), 265 (M^+, 100.0), 264 (10.9), 175 (16.2), 172 (19.0), 174 (75.5), 173 (96.8), 171 (29.1), 168 (10.5), 147 (21.7), 142 (12.8), 141 (69.9), 130 (24.4), 91 (100.0), 65 (52.8). HRMS (CI) m/e (M^+) 265.0928 (calcd for $C_{17}H_{15}NS$ 265.0936).

6-(Phenylmethyl)-6*H*-thieno[3,2-*e*]indole (25). A solution of *p*-nitrobenzoic acid (0.80 g, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol), 5% palladium on carbon (Engelhard; 0.50 g), acetonitrile (500 mL), and the stilbene **23** (1.33 g, 5.0 mmol) was heated to a gentle reflux, purged with nitrogen for 30 min, and then irradiated, maintaining a slow, constant stream of nitrogen. The reaction proceeded with gradual disappearance of starting material [^{1}H NMR ($CDCl_3$) δ 4.98, 5.13 (CH_2Ph, cis and trans, respectively)] and concomitant appearance of product [^{1}H NMR ($CDCl_3$) δ 5.40 (CH_2Ph)]. After complete disappearance of starting material (ca. 48 h), the cooled solution was filtered to remove the palladium on carbon and the solvent was removed at reduced pressure. The crude mixture was then adsorbed onto silica gel (30 mL, methylene chloride) and chromatographed (hexanes:methylene chloride 3:1) to yield white needles [1.12 g (85%)], which crystallized from absolute ethanol: mp 113.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2 H, CH_2Ph), 6.84 (d, 1 H, J = 2.7 Hz, Ar-*H*), 7.08 (d, 2 H, J = 9 Hz, Ar-*H*), 7.19 (d, 1 H, J = 3.0 Hz, Ar-*H*), 7.23–7.30 (m, 4 H, Ar-*H*), 7.48–7.66 (m, 3 H, Ar-*H*); IR (KBr, cm^{-1}) 1505, 1460, 1422, 1360, 1330, 1276, 1151, 853, 738, 712, 708; MS (EI) m/e (relative intensity) 264 (M + 1, 17.1), 263 (M^+, 83.2), 262 (11.6), 172 (25.3), 91.0 (100), 65 (13.9). Anal. Calcd for $C_{17}H_{13}NS$: C, 77.53; H, 4.98; N, 5.32. Found: C, 77.52; H, 5.04; N, 5.16.

6-(Phenylmethyl)-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid, Ethyl Ester (28a). To a mixture of indole **25** (1.32 g, 5.0 mmol), tetrahydrofuran (50 mL), *N*,*N*,*N*',*N*'-tetramethylethylenediamine (1 mL), and 2,2'-bipyridyl indicator (1 mg) in a 100-mL, two-neck flask at −78 °C was added butyllithium (5.5 mmol) by syringe. The solution was stirred at −78 °C for 0.5 h. Ethyl chloroformate (0.53 mL, 5.5 mmol) was then added very quickly by syringe, followed by a saturated sodium bicarbonate solution (5 mL). The solution was warmed to room temperature,

and the tetrahydrofuran was removed at reduced pressure. The crude product was extracted with ether (3 × 50 mL), and the organic layer was washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (hexanes:methylene chloride = 1:1) to yield **28a** [1.61 g (96%)] as yellow needles (mp 117.5 °C), after crystallization from absolute ethanol: ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.42 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.42 (s, 2 H, CH_2Ph), 6.87 (m, 1 H, J = 3.0 Hz, Ar-H), 7.09 (m, 1 H, J = 9.0 Hz, Ar-H), 7.23–7.30 (m, 5 H, Ar-H), 7.40 (d, 1 H, J = 8.8 Hz, Ar-H), 7.56 (d, 1 H, J = 8.8 Hz, Ar-H), 8.37 (s, 1 H, thiophene H); IR (KBr, cm^{-1}) 1695 (C=O), 1516, 1494, 1354, 1284, 1187, 1134, 1075, 754, 736, 702; MS (EI) m/e (relative intensity) 336 (M + 1, 15.3), 335 (M^+, 72.2), 92 (8.2), 91 (100.0). Anal. Calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.18. Found: C, 71.73; H, 5.25; N, 4.10.

6-(Phenylmethyl)-7,8-dihydro-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid, Ethyl Ester (29a). To indole **28a** (0.65 g, 1.9 mmol) in methylene chloride (25 mL) at 0 °C was added borane (1 M in tetrahydrofuran; Aldrich; 4.0 mL, 4 mmol) and then trifluoroacetic acid (4.0 mls) dropwise, followed with water (0.5 mL). The volatiles were removed under reduced pressure. The solution was poured into water and extracted with ether (3 × 50 mL). The organic layer was carefully neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. The crude product was chromatographed (hexanes:methylene chloride = 1:1) to yield a yellow solid [0.61 g (89%)], which crystallized from absolute ethanol: mp 80.5–81 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.20 (t, 2 H, J = 8.4 Hz, NCH_2CH_2), 3.44 (t, 2 H, J = 8.2 Hz, NCH_2CH_2), 4.30 (s, 2 H, CH_2Ph), 4.39 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.82 (d, 1 H, J = 8.6 Hz, Ar-H), 7.26–7.40 (m, 5 H, Ar-H), 7.55 (d, 1 H, J = 8.5 Hz, Ar-H), 7.86 (s, 1 H, thiophene H); IR (KBr, cm^{-1}) 2840, 1705 (C=O), 1600, 1522, 1450, 1412, 1348, 1270, 1250, 1185, 1070, 1060, 860, 800, 758, 735, 700; MS (EI) m/e (relative intensity) 338 (M + 1, 29.4), 337 (M^+, 100.0), 260 (12.9), 200 (10.6), 191 (24.4), 174 (34.6), 173 (50.0), 147 (10.3), 91 (35.3); HRMS (CI) m/e (M^+) 337.1146 (calcd for $C_{20}H_{19}NO_2S$ 337.1138).

7,8-Dihydro-6*H*-thieno[3,2-*e*]indole-2,6-dicarboxylic Acid, 6-(2,2,2-Trichloroethyl) 2-Ethyl Ester (32a). To indoline **29a** (2.30 g, 6.8 mmol) in acetonitrile (25 mL) was added trichloroethyl chloroformate (0.100 mL, 6.8 mmol). The mixture was stirred for 30 min and concentrated. The crude product was chromatographed (hexanes:methylene chloride = 1:1) to yield white needles [2.68 g (93%)], which crystallized from absolute ethanol: mp 162.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.42 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.30 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 4.41 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.88 (s, 2 H, $CO_2CH_2CCl_3$), 7.71 (d, 1 H, J = 8.7 Hz, Ar-H), 7.92 (s, 1 H, thiophene H), 8.12 (d, 1 H, J = 8.8 Hz, Ar-H); IR (KBr, cm^{-1}) 1710 (C=O), 1693 (C=O), 1522, 1470, 1322, 1285, 1190, 1130, 1095, 1065; MS (EI) m/e (relative intensity) 425 (M + 4, 32.0), 423 (M + 2, 100.0), 422 (M + 1, 19.0), 421 (M^+, 90.9), 291 (33.2), 191 (40.6), 174 (52.6), 173 (87.7), 133 (43.7), 131 (38.9), 97 (43.7), 95 (48.3), 81 (38.5), 69 (85.1). Anal. Calcd for $C_{16}H_{14}Cl_3NO_4S$: C, 45.46; H, 3.34; N, 3.31. Found: C, 45.70; H, 3.22; N, 3.15.

7,8-Dihydro-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid, 2-Ethyl Ester (33a). To a solution of **32a** (1.40 g, 3.3 mmol) in acetic acid (30 mL) was added powdered zinc (0.5 g) in portions over a period of 2 h. The reaction was filtered, and the precipitate was washed thoroughly with methylene chloride. The filtrate was concentrated and extracted with ether. The organic layer was neutralized with saturated sodium bicarbonate solution and dried (Na_2SO_4). The crude product was concentrated and chromatographed (methylene chloride:ether = 10:1) to yield **33a** as a yellow oil [0.72 g (88%)], which gradually crystallized: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.27 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 3.70 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.40 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.91 (d, 1 H, J = 8.5 Hz, Ar-H), 7.52 (d, 1 H, J = 8.5 Hz, Ar-H) 7.87 (s, 1 H, thiophene H); IR (KBr, cm^{-1}) 3330 (NH), 1700 (C=O), 1610, 1530, 1420, 1370, 1315, 1268, 1190, 1180, 1080, 1025, 865, 810, 760, 740, 720, 650; MS (EI) m/e (relative intensity) 248 (M + 1, 17.7), 247 (M^+, 100.0), 245 (20.1), 220 (19.4), 219 (73.0), 218 (26.1), 217 (19.0), 205 (37.7), 202 (11.4), 200 (26.7), 175 (12.6), 174 (60.1), 173 (52.8), 172 (19.0), 147 (16.3), 145 (13.4), 130 (15.7), 129 (12.3), 128 (19.2), 102 (10.6), 100 (20.6), 86 (11.6), 69 (13.2); HRMS (CI) m/e (M^+) 247.0642 (calcd for $C_{13}H_{13}NO_2S$ 247.0668).

6-(Aminocarbonyl)-7,8-dihydro-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid, 2-Ethyl Ester (34a). To a mixture of indoline **33a** (0.59 g, 2.3 mmol) in acetic acid (30 mL) was added a solution of potassium cyanate (0.42 g, 5.0 mmol) in water (20 mL). After the mixture was stirred for 30 min, the crude product was extracted with ether (2 × 25 mL). The ethereal layer was neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (methylene chloride:ether = 10:1), to yield **34a** as an off-white solid [0.63 g (91%)], which crystallized from absolute methanol: dec pt >230 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.34 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.37 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 4.01 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 4.35 (q, 2 H, J = 7.0 Hz, $CO_2CH_2CH_3$), 6.36 (s, 2 H, $CONH_2$), 7.75 (d, 1 H, J = 8.8 Hz, Ar-H), 7.99 (s, 1 H, thiophene H), 8.19 (d, 1 H, J = 8.8 Hz, Ar-H); IR (KBr, cm^{-1}) 3420, 1680, 1612, 1518, 1470, 1410, 1305, 1255, 1195, 1080, 810, 760; MS (EI) m/e (relative intensity) 291 (M + 1, 22.6), 290 (M^+, 100.0), 247 (90.7), 219 (86.8), 218 (30.0), 174 (59.5), 173 (56.9), 69 (25.8); HRMS (CI) m/e (M^+) 290.0743 (calcd for $C_{14}H_{14}N_2O_3S$ 290.0726).

6-Acetyl-7,8-dihydro-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid, 2-Ethyl Ester (35a). To a solution of indoline **33a** (0.59 g, 2.3 mmol) in methylene chloride (10 mL) was added acetic anhydride (5 mL). After the mixture was stirred for 0.5 h, water (25 mL) was added, and the crude product was extracted with ether (2 × 25 mL). The organic layer was neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (methylene chloride:ether = 10:1), to yield **35a** [0.63 g (95%)] as an off-white solid, which crystallized from absolute ethanol, dec pt >225 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.0 Hz, $CO_2CH_2CH_3$), 2.27 (s, 3 H, $COCH_3$), 3.45 (t, 2 H, J = 8.6 Hz NCH_2CH_2), 4.22 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.41 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 7.69 (d, 1 H, J = 8.6 Hz, Ar-H), 7.93 (s, 1 H, thiophene H), 8.48 (d, 1 H, J = 8.9 Hz, Ar-H); IR (KBr, cm^{-1}) 1698, 1660, 1640, 1520, 1470, 1402, 1305, 1288, 1191, 1080, 1058, 755; MS (EI) m/e (relative intensity) 290 (M + 1, 13.1), 289 (M^+, 66.2), 248 (14.8), 247 (100.0), 220 (10.2), 219 (70.7), 218 (13.0), 200 (10.4), 191 (11.4), 174 (32.4), 173 (30.4), 147 (16.0), 145 (10.5), 130 (10.0), 102 (11.1), 83 (11.3), 81 (13.6), 69 (23.4); HRMS (CI) m/e (M^+) 289.0775 (calcd for $C_{15}H_{15}NO_3S$ 289.0774).

6-(Aminocarbonyl)-7,8-dihydro-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid (6). A suspension of **34a** (0.29 g, 1.0 mmol) in methanol (15 mL) was basified with 0.1 N NaOH to pH 10 and was stirred until starting material was consumed as indicated by TLC. The solution was acidified with 0.1 N HCl to pH 1, chilled, and filtered. The product was dried over P_2O_5 to yield acid **6** [0.21 g (80%)] as an off-white solid: dec pt >225 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.39 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 4.01 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 6.35 (s, 2 H, $CONH_2$), 7.74 (d, 1 H, J = 8.7 Hz, Ar-H), 7.93 (s, 1 H, thiophene H), 8.17 (d, 1 H, J = 8.8 Hz, Ar-H); IR (KBr, cm^{-1}) 3440 (NH), 3200, 1660 (C=O), 1510, 1488, 1430, 1200, 1175, 1145, 1098, 802, 760, 670; MS (EI) m/e (relative intensity) 262 (M^+, 10.7), 219 (100.0), 218 (22.3), 200 (21.0), 174 (58.8), 173 (33.1); HRMS m/e (M^+) 262.0412 (calcd for $C_{12}H_{10}N_2O_3S$ 262.0419).

6-Acetyl-7,8-dihydro-6*H*-thieno[3,2-*e*]indole-2-carboxylic Acid (8). A solution of amide **35a** (0.29 g, 1.0 mmol) in methanol (15 mL) was basified with 0.1 N NaOH to pH 10 and was stirred until starting material was consumed as indicated by TLC. The solution was acidified with 0.1 N HCl to pH 1 and chilled, and the solid was filtered and dried over P_2O_5 to yield acid **7** [0.21 g (80%)] as an off-white solid, which crystallized from methanol: mp >275 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.18 (s, 3 H, $COCH_3$), 3.40 (t, 2 H, J = 8.4 Hz, NCH_2CH_2), 4.20 (t, 2 H, J = 8.4 Hz, NCh_2CH_2), 7.80 (d, 2 H, J = 8.8 Hz, Ar-H), 7.97 (s, 1 H, thiophene H), 8.32 (d, 2 H, J = 8.8 Hz, Ar-H); IR (KBr, cm^{-1}), 1685 (C=O), 1592, 1518, 1479, 1410, 1281, 1241, 1190, 750, 660; MS (EI) m/e (relative intensity) 262 (M + 1, 6.9), 261 (M^+, 58.2), 220 (14.8), 219 (100.0), 218 (23.1), 200 (12.3), 175 (10.8), 174 (31.1), 173 (15 .2), 147 (13.9). Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.76; H, 4.24; N, 5.36. Found: C, 59.81; H, 4.26; N, 5.34.

2-[2-(2-Furanyl)ethenyl]-1-(phenylmethyl)-1*H*-pyrrole (24). To a mixture of the phosphonium iodide **27** (5.59 g, 10.0 mmol) and furfural (1.06 g, 11 mmol) in dimethylformamide (75

mL) was added potassium *tert*-butoxide (1.23 g, 11 mmol). The reaction was stirred for 30 min and poured into water. The crude product was extracted with ether–hexanes (1:1; 3 × 50 mL), dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (hexanes:methylene chloride = 3:1) to give the heterocyclic stilbenoids as a mixture of cis–trans isomers, 2.25 g (85%). These compounds darken quickly on exposure to light and air: ^1H NMR ($CDCl_3$ cis/trans mixture δ 5.10 (s, 2 H, CH_2Ph, cis), 5.17 (s, 2 H, CH_2Ph, trans), 6.10 (ad, 2 H, Ar-*H*), 6.18–6.26 (m, 4 H, Ar-*H*), 6.36–6.38 (m, 2 H, Ar-*H*), 6.45–6.53 (m, 2 H, Ar-*H*) 6.72 (m, 2 H, Ar-*H*), 6.72 (m, 2 H, Ar-*H*), 6.73 (dd, 2 H, J = 16 Hz, trans olefin *H*), 7.01–7.10 (m, 4 H, Ar-*H*), 7.23–7.38 (m, 8 H, Ar-*H*); IR (KBr, cm^{-1}) 1628, 1492, 1470, 1452, 1440, 1415, 1353, 1300, 1240, 1128, 1072, 1012, 945, 925, 885, 800, 720, 610; MS (EI) m/e (relative intensity) 250 (M + 1, 9.0), 249 (M^+, 66.3), 158 (25.5), 157 (18.6), 131 (10.7), 130 (100), 103 (19.0), 91 (59.5), 65 (27.2); HRMS m/e (M^+) 249.1175 (calcd for $C_{17}H_{15}NO$ 249.11545).

6-(Phenylmethyl)-6*H*-furo[3,2-*e*]indole (26). A solution of *p*-nitrobenzoic acid (0.80 g, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol), 5% palladium on carbon (0.50 g), acetonitrile (500 mL), and the heterostilbenes **24** (1.25 g, 5.0 mmol) was heated to a gentle reflux, purged with nitrogen for 30 min, and then irradiated, maintaining a slow, constant stream of nitrogen. The reaction proceded with gradual disappearance of starting material [^1H NMR ($CDCl_3$) δ 5.10, 5.17 (CH_2Ph, cis and trans, respectively)] and concomitant appearance of product [^1H NMR ($CDCl_3$) δ 5.37 (CH_2Ph)]. After complete disappearance of starting material (ca. 4 days), the cooled solution was filtered to remove the palladium on carbon and the solvent was removed at reduced pressure. The crude mixture was then adsorbed onto silica gel (30 mL, methylene chloride) and chromatographed (hexanes:methylene chloride = 3:1) to yield **26** [0.99 g (80%)] as white needles (mp 76–77 °C) after crystallization from absolute ethanol: ^1H NMR ($CDCl_3$) δ 5.37 (s, 2 H, CH_2Ph), 6.72 (m, 1 H, Ar-*H*), 7.01 (m, 1 H, Ar-*H*), 7.07 (m, 2 H, Ar-*H*), 7.14–7.35 (m, 6 H, Ar-*H*), 7.66 (s, 1 H, Ar-*H*); IR (KBr, cm^{-1}) 1500, 1460, 1386, 1368, 1248, 1154, 752, 738, 722; MS (EI) m/e (relative intensity) 248 (M + 1, 10.8), 247 (M^+, 62.8), 156 (11.9), 91 (100), 65 (19.0). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.50; H, 5.17; N, 5.57.

6-(Phenylmethyl)-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid, Ethyl Ester (28b). To a solution of **26** (1.24 g, 5.0 mmol), tetrahydrofuran (50 mL), *N,N,N′,N′*-tetramethylethylenediamine (1 mL), and 2,2′-bipyridyl indicator (1 mg) in a 100-mL, two-neck flask at −78 °C was added butyllithium (5.5 mmol) by syringe. The solution was stirred at −78 °C for 0.5 h. Ethyl chloroformate (0.53 mL, 5.5 mmol) was added very quickly by syringe, followed by saturated sodium bicarbonate solution (5 mL). The solution was warmed to room temperature, and the tetrahydrofuran was removed at reduced pressure. The crude product was extracted with ether (3 × 50 mL), washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (hexanes.methylene chloride = 1:1) to yield **28b** [1.50 g (94%)] as yellow needles (mp 128–128.5 °C) after crystallization from absolute ethanol: ^1H NMR ($CDCl_3$) δ 1.44 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.46 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.40 (s, 2 H, CH_2Ph), 6.77 (m, 1 H, Ar-*H*), 7.09 (m, 2 H, Ar-*H*), 7.26–7.37, (m, 6 H, Ar-*H*), 7.80 (s, 1 H, furan *H*); IR (KBr, cm^{-1}) 1710 (C=O), 1553, 1500, 1376, 1306, 1202, 1199, 1166, 764, 732, 713; MS (EI) m/e (relative intensity) 320 (M + 1, 16.2), 319 (M^+, 78.8), 91 (100). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.04; H, 5.31; N, 4.20.

6-(Phenylmethyl)-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid, Ethyl Ester (29b). To a solution of indole **28b** (0.64 g, 1.9 mmol) in methylene chloride (25 mL) at 0 °C was added borane (1 M in tetrahydrofuran; 4.0 mL, 4 mmol) and then trifluoroacetic acid (4.0 mL) dropwise, followed by water (0.5 mL). The volatiles were removed under reduced pressure. The solution was poured into water and extracted with ether (3 × 50 mL). The ethereal layer was neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (hexanes:methylene chloride = 1:1) to yield **29b** [0.57 g (89%)] as a waxy yellow solid: mp 97–99 °C; ^1H NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.10 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 3.39 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 4.25 (s, 2 H, CH_2Ph), 4.43 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.72 (d, 1 H, J = 8.7 Hz, Ar-*H*), 7.25–7.41 (m, 7 H, Ar-*H*); IR (KBr, cm^{-1}) 1700 (C=O), 1600, 1560, 1500, 1480, 1442, 1435, 1375, 1350, 1330, 1300, 1260, 1240, 1190, 1130, 1110, 1030, 960, 830, 810, 770, 740, 700, 635; MS (EI) m/e (relative intensity) 322 (M + 1, 18.4), 321 (M^+, 70.7), 320 (10.4), 319 (33.7), 248 (10.8), 244 (12.8), 220 (10.6), 205 (37.1), 187 (15.6), 175 (16.6), 172 (37.7), 158 (12.0), 157 (34.5), 149 (23.4), 131 (12.2), 130 (26.5), 129 (17.6), 128 (11.6), 92 (11.2), 91 (100.0), 65 (12.4), 57 (13.2), 40 (63.3); HRMS (CI) m/e (M^+) 321.1355 (calcd for $C_{20}H_{19}NO_3$ 321.1366).

7,8-Dihydro-6*H*-furo[3,2-*e*]indole-2,6-dicarboxylic Acid, 6-(2,2,2-Trichloroethyl) 2-Ethyl Ester (32b). To a solution of indoline **29b** (1.60 g, 5.0 mmol) in acetonitrile (25 mL) was added trichloroethyl chloroformate (0.080 mL, 5.5 mmol). The mixture was stirred for 30 min, concentrated, and chromatographed (hexanes:methylene chloride = 1:1) to yield **32b** [1.85 g (91%)], which crystallized from absolute ethanol: mp 125.0–125.5 °C; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.35 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.30 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.45 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.87 (s, 2 H, $CO_2CH_2CCl_3$), 7.43 (s, 1 H, furan *H*), 7.45 (d, 1 H, J = 8.9 Hz, Ar-*H*), 8.09 (d, 1 H, J = 8.9 Hz, Ar-*H*); IR (KBr, cm^{-1}) 1730 (C=O), 1720 (C=O), 1565, 1490, 1430, 1410, 1342, 1332, 1189, 1150, 765; MS (EI) m/e (relative intensity) 409 (M + 4, 29.6), 408 (15.8), 407 (M + 2, 100), 406 (M + 1, 21.1), 405 (M^+, 92.7), 319 (39.3), 275 (26.8), 175, 127.5), 157 (37.2), 133 (38.0), 131 (45.4), 130 (40.7), 129 (25.2), 91 (49.4), 77 (21.1). Anal. Calcd for $C_{16}H_{14}Cl_3NO_5$; C, 47.26; H, 3.47; N, 3.44. Found: C, 47.39; H, 3.37; N, 3.37.

7,8-Dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid, 2-Ethyl Ester (33b). A solution of carbamate **32b** (2.03 g, 5.0 mmol), acetic acid (30 mL), and powdered zinc (0.5 g) was stirred for 2 h. The solution was filtered, and the precipitate was washed thoroughly with methylene chloride. The filtrate was concentrated and extracted with ether, and the ethereal extract was neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. The crude product was chromatographed (hexanes:methylene chloride = 1:1) to yield **33b** [0.96 g (83%)], which crystallized from absolute ethanol: mp 138–140 °C dec; ^1H NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.20 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 3.68 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.43 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.84 (d, 1 H, J = 8.6 Hz, Ar-*H*), 7.27 (d, 1 H, J = 8.6 Hz, Ar-*H*), 7.38 (s, 1 H, furan *H*); IR (KBr, cm^{-1}) 3340 (NH), 1700 (C=O), 1555, 1492, 1432, 1370, 1322, 1290, 1245, 1190, 1180, 1135, 1125, 1110, 1015, 950, 850, 810, 770, 720, 700, 610; MS (EI) m/e (relative intensity) 232 (M + 1, 15.7), 231 (M^+, 100, 203 (62.8), 202 (39.8), 158 (20.6), 130 (39.8), 129 (14.7), 128 (14.1), 102 (11.2), 92 (12.5), 77 (12.2); HRMS (CI) m/e 231.0904 (calcd for $C_{13}H_{13}NO_3$ 231.0896).

6-(Aminocarbonyl)-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid, Ethyl Ester (34b). To a solution of indoline **33b** (0.50 g, 2.2 mmol) in acetic acid (30 mL) was added a solution of potassium cyanate (0.42 g, 5.0 mmol) dissolved in water (20 mL). After the mixture was for 2 h, the crude product was extracted with ether (2 × 25 mL) and the ethereal layer neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated. The concentrate was chromatographed (methylene chloride:ether = 10:1) to yield **34b** [0.54 g (91%)] as an off-white solid: dec pt >230 °C; ^1H NMr (Me_2SO-d_6) δ 1.34 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.29 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 4.00 (t, 2 H, J = 8.8 Hz, NCH_2CH_2), 4.35 (q, 2 H, J = 7.0 Hz, $CO_2CH_2CH_3$), 6.30 (s, 2 H, $CONH_2$), 7.42 (d, 1 H, J = 9.1 Hz, Ar-*H*), 7.66 (s, 1 H, furan *H*), 8.14 (d, 1 H, J = 9.1 Hz, Ar-*H*); IR (KBr, cm^{-1}) 3440 (NH), 1710 (C=O), 1680, 1612, 1560, 1490, 1415, 1375, 1320, 1245, 1199, 1170, 810, 765; MS (EI) m/e (relative intensity) 274 (M^+, 24.6), 231 (62.9), 203 (46.4), 202 (30.0), 149 (30.7), 97 (45.7), 91 (47.4), 85 (49.4), 71 (64.9), 69 (84.0), 57 (100.0); HRMS (CI) m/e (M^+) 274.0941 (calcd for $C_{14}H_{14}N_2O_4$ 274.0954).

6-Acetyl-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid, Ethyl Ester (35b). To a solution of indoline **33b** (0.50 g, 2.2 mmol) in methylene chloride (10 mL) was added acetic anhydride (5 mL). After the mixture was for 2 h, the crude product was extracted with ether (2 × 25 mL), neutralized with saturated sodium bicarbonate solution, dried (Na_2SO_4), and chromatographed (methylene chloride:ether = 10:1), to yield **35b** [0.55 g (93%)] as an off-white solid, which crystallized from absolute ethanol, dec pt >230 °C; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.26 (s, 3 H, $COCH_3$), 3.37 (t, 2 H, J = 8.6 Hz,

NCH_2CH_2), 4.20 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.46 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 7.42 (d, 1 H, J = 8.6 Hz, Ar-H), 7.43 (s, 1 H, furan H), 8.46 (d, 1 H, J = 8.6 Hz, Ar-H); IR (KBr, cm^{-1}), 1720 (C=O), 1660 (C=O), 1600, 1572, 1485, 1470, 1452, 1430, 1405, 1370, 1340, 1295, 1240, 1185, 1140, 1130, 1120, 1110, 1055, 1020, 990, 815, 765, 645; MS (EI) m/e (relative intensity) 273 (M^+, 65.6), 232 (14.4), 231 (100), 203 (48.9), 202 (20.1), 158 (13.0), 157 (13.3), 130 (23.2), 129 (11.3), 128 (11.7), 102 (11.0), 77 (13.9); HRMS (CI) m/e (M^+) 273.0993 (calcd for $C_{15}H_{15}NO_4$ 273.1001).

6-(Aminocarbonyl)-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid (7). A suspension of **35b** (0.27 g, 1.0 mmol) in methanol (15 mL) was basified with 0.1 N NaOH to pH 10 and was stirred until starting material was consumed as indicated by TLC. The solution was acidified with 0.1 N HCl to pH 1 and chilled, and the solid was filtered and dried over P_2O_5 to yield acid **7** [0.20 g (80%)] as an off-white solid: dec pt >230 °C; ^1H NMR (Me_2SO-d_6) δ 3.30 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.01 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 6.27 (s, 2 H, $CONH_2$), 7.40 (d, 1 H, J = 9.1 Hz, Ar-H), 7.57 (s, 1 H, furan H), 8.13 (d, 1 H, J = 9.0 Hz, Ar-H); IR (KBr, cm^{-1}) 3460 (NH), 3340, 3220, 1690 (C=O), 1565, 1500, 1430, 1355, 1320, 1300, 1240, 1195, 1140, 1050, 950, 920, 810, 790, 775, 685, 640; MS (EI) m/e 246 (M^+, 3.2), 231 (8.0), 204 (12.0), 203 (100.0), 202 (36.5), 158 (11.0), 157 (12.1), 130 (35.0), 129 (12.6), 128 (10.6), 44 (15.3), 43 (22.4); HRMS m/e (M^+) 246.0630 (calcd for $C_{14}H_{12}N_2O_4$ 246.0641).

6-Acetyl-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid (9). A suspension of urea **35b** (0.10 g, 0.4 mmol) in methanol (15 mL) was basified with 0.1 N NaOH to pH 10 and was stirred until starting material was consumed as indicated by TLC. The solution was acidified with 0.1 N HCl to pH 1 and chilled and the solid filtered and dried to yield **9** [78 mg (80%)] as an off-white solid, which crystallized from methanol: dec pt >275 °C; ^1H NMR (Me_2SO-d_6) δ 2.18 (s, 3 H, $COCH_3$), 3.34 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 4.20 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 7.48 (d, 1 H, J = 8.9 Hz, Ar-H), 7.63 (s, 1 H, furan H), 8.30 (d, 1 H, J = 8.9 Hz, Ar-H); IR (KBr, cm^{-1}) 2500 (br), 1730 (C=O), 1720 (C=O), 1620, 1580, 1500, 1420, 1365, 1285, 1250, 1190, 1140, 1030, 990, 970, 945, 895, 870, 840, 800, 775, 760, 700, 600; MS (EI) m/e 246 (M + 1, 5.0), 245 (M^+, 36.1), 204 (12.1), 203 (100.0), 202 (36.5), 159 (10.6), 158 (15.5), 130 (17.7), 43 (11.3); HRMS m/e (M^+) 245.0689 (calcd for $C_{13}H_{11}NO_4$ 245.0688).

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Enantioselective Ring Construction: Synthesis of (+)-Estrone Methyl Ether

Douglass F. Taber,*[1] Krishna Raman, and Micheal D. Gaul

Department of Chemistry, University of Delaware, Newark, Delaware 19716

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A general method for the construction of functionalized cyclopentane derivatives **10** of high optical purity, via diastereoselective intramolecular C–H insertion, is described. A methylation–retro Dieckmann dianion alkylation procedure on **10b** (R = vinyl) gives **12**. Decarbomethoxylation of **12** followed by thermolysis yields (+)-estrone methyl ether **1** having 91% ee.

The estrogenic steroids have been the target of extensive synthetic investigation,[2] both because they are economically significant and because they are among the structurally simplest biologically active representatives of the steroid family. We report herein the details of a general method for the construction of functionalized cyclopentanes of high optical purity[3] and the application of this method to the enantioselective construction of (+)-estrone methyl ether **1**.[4]

In considering a route to estrone that might be modified to allow enantioselection, we were led to the *o*-quinone methide mediated intramolecular Diels–Alder approach pioneered by Oppolzer[5] and Kametani.[6,7] While ketone

(1) Fellow of the Alfred P. Sloan Foundation, 1983–1987.

(2) (a) For a summary of previous routes to the estrogens, see: Taub, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed. Wiley: New York, 1973; p 641. (b) For a more recent approach, see: Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, *25*, 2121.

(3) A portion of this work was reported in a preliminary communication: Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.

(4) For a review of enantioselective routes to the steroids, see: (a) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637. For more recent approaches, see: (b) Stevens, R. V.; Gaeta, F.C.A.; Lwarence, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 7713. (c) Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460. (d) Takahashi, T.; Okumoto, H.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 1975. (e) Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, *26*, 1819. (f) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *107*, 1239.

(5) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833.

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