A Dipolar Cycloaddition Approach to Pyrrolo[1,2-*a*]indoles Using *N*-[(Trimethylsilyl)methyl]-Substituted Indoles

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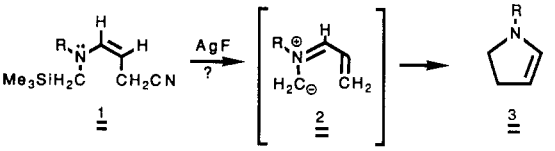
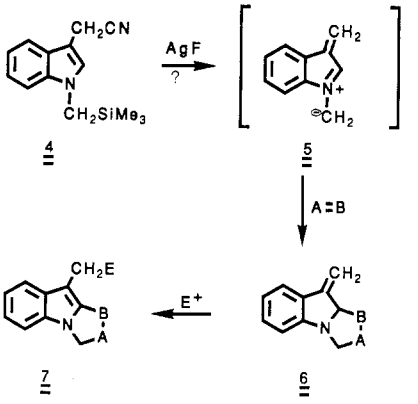
The 1,3-dipolar cycloaddition of a number of *N*-[(trimethylsilyl)methyl]-substituted indoles with several dipolarophiles has been investigated. The reaction requires the use of an equivalent amount of silver fluoride and provides a direct and efficient synthesis of the pyrrolo[1,2-*a*]indole ring system. The structures of the cycloadducts were established by high-field NMR spectroscopy as well as by several X-ray crystal structures. The cycloaddition reactions show all the characteristics of a concerted reaction, including complete stereospecificity and regioselectivity. The results are consistent with a mechanism that involves the intermediacy of an azomethine ylide. Formation of the dipole is rationalized by assuming that silver ion behaves as a very specific Lewis acid that attacks the indole ring to give a silver bonded carbonium ion. This is followed by a rapid desilylation reaction to give the azomethine ylide. After the cycloaddition step, the resulting silver-bonded intermediate undergoes consecutive loss of silver and a hydrogen to give the observed product. Attempts to extend the cycloaddition methodology to *N*-[(trimethylsilyl)methyl]-substituted enamines and pyrroles are also described.

Development of methodology for the stereocontrolled synthesis of pyrrolidine containing natural products continues to receive significant attention.[1] Of the numerous strategies for pyrrolidine construction, 1,3-dipolar cycloaddition of an azomethine ylide across a C–C π bond represents a particularly attractive approach.[2-4] Studies conducted in these[5] and other laboratories[6-11] have shown that the desilylation of α-trimethylsilyl onium salts represents a convenient method for azomethine ylide generation. More recently, we have described the use of α-(cyanomethyl) amino silanes as convenient azomethine

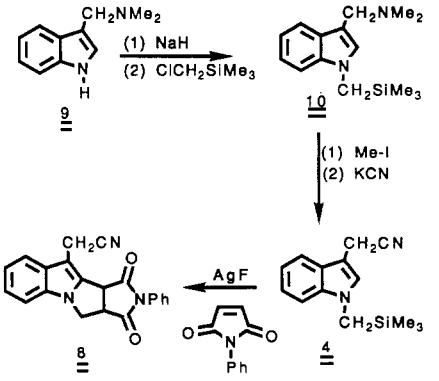
Scheme I



Scheme II



Scheme III



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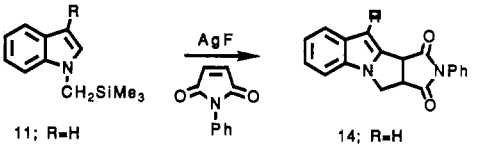
ylide precursors.[12] Exposure of these compounds to silver fluoride promotes a metal-assisted decyanation to an immonium salt[13,14] and a concomitant desilylation[15] to give the unsubstituted 1,3-dipole. We reasoned that exposing a vinylogous silyl cyano amine such as **1** to silver fluoride might generate the 2-pyrroline ring via the intermediacy of the 1,5-dipole **2** (Scheme I). The formation of five-membered rings by 6π-electrocyclization of 1,5-dipoles is an important principle in heterocyclic chemistry.[16-18] Little is known, however, about vinyl-substituted azomethine ylides[19] since these species are not as synthetically accessible as their carbonyl-substituted counterparts, which are known to readily cyclize to oxazolines.[20] We were particularly interested in trapping the vinyl-substituted dipole with an added dipolarophile prior to electrocyclization. In the light of our earlier findings,[12] we envisioned a convenient approach to the pyrroloindole nucleus to lie along the pathway illustrated in Scheme II. The development of new methods for the general synthesis of varied members of the indole alkaloid family continues to attract considerable interest.[21-25] In particular, the emergence of mitomycin C as a clinically useful anticancer chemotherapeutic agent has stimulated a considerable effort at the synthesis of related natural products.[26-32] Although only one approach has as yet culminated in a total synthesis of the natural mitomycins,[33] the antitumor activity of the simpler mitosenes and the antibacterial properties of related indoloquinones[34,35] provide incentive for the development of new synthetic methods to these heterocyclic compounds. A number of synthetic approaches to various mitosenes have been reported lately.[30,31,36] In this paper we describe our results using azomethine ylides derived from silyl-substituted indoles as a method for synthesizing the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole nucleus.[37]

Results and Discussion

The propensity of silicon to transfer to a silylophile when bound to an electronegative carbon strongly inferred that the treatment of indole **4** with silver fluoride would generate azomethine ylide **5**. The desired silylated indole **4** was prepared in the manner outlined in Scheme III. Surprisingly, the reaction of **4** with silver fluoride in the presence of *N*-phenylmaleimide afforded cycloadduct **8** in 85% yield, which still retained the nitrile functionality. The structure of cycloadduct **8**, was assigned on the basis of its characteristic spectral data [NMR ($CDCl_3$, 360 MHz) δ 3.92 (d, 1 H, J = 18.0 Hz), 4.10 (d, 1 H, J = 18.0 Hz), 4.34 (ddd, 1 H, J = 8.9, 8.3, and 2.1 Hz), 4.47 (dd, 1 H, J = 10.7 and 2.1 Hz), 4.69 (dd, 1 H, J = 10.7 and 8.9 Hz), 4.75 (d, 1 H, J = 8.3 Hz), 7.2–7.5 (m, 8 H), and 7.66 (d, 1 H, J = 7.1 Hz)]. The structure of **8** was unequivocally established by an X-ray single-crystal structure analysis.

This surprising result suggests that the nitrile functionality plays little or no role in dipole formation and that it might be possible to effect cycloaddition with related indoles that are devoid of a 3-(cyanomethyl) group. In order to test this possibility, indoles **11–13** were prepared.



11; R=H
12; R=CHO
13; R=Me

14; R=H
15; R=CHO
16; R=Me

Treatment of these compounds with silver fluoride in the presence of a suitable dipolarophile led to the formation of the corresponding cycloadducts in each case. The overall yield of the dihydropyrroloindole system (**14–16**) ranged from 53 to 83%. For the record, finely ground silver fluoride was the only agent employed that induced cycloaddition to any significant extent. A silver nitrate–cesium fluoride mixture resulted in only trace quantities of the cycloadducts. Other reagents such as HgF_2,$PdCl_2$,$FeCl_3$, and $(C_2H_5)_2AlCl$ were totally ineffective.

Since we were interested in the synthetic utility of this reaction, we undertook a systematic study of the cycloaddition with a number of related dipolarophiles. Several aspects of the cycloadditions are deserving of individual discussion. Heating a solution of **13** with DMAD and silver fluoride at 80 °C produced pyrrole **18** in 75% yield. The conversion of **13** to **18** probably proceeds via the intermediacy of cycloadduct **17**, which undergoes a subsequent 1,5-hydrogen shift under the reaction conditions to give **18**. The driving force for this rearrangement is undoubtedly the aromatization of the bis(carbomethoxy)-substituted pyrrole ring.

In order to ascertain the stereospecificity of the reaction, we studied the cycloaddition of **13** with cis and trans disubstituted dipolarophiles. All octet-stabilized 1,3-dipoles examined so far in the literature have been shown to un-

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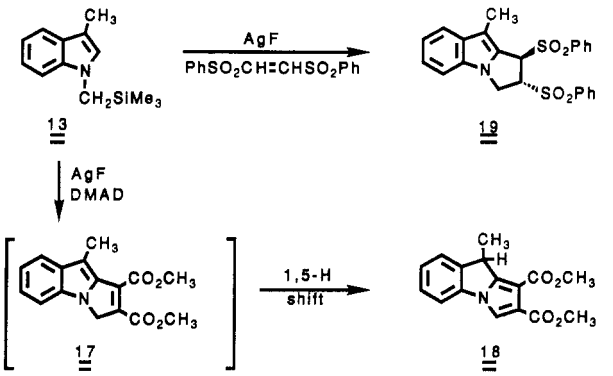
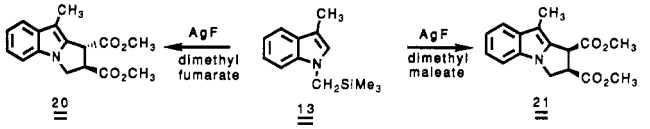
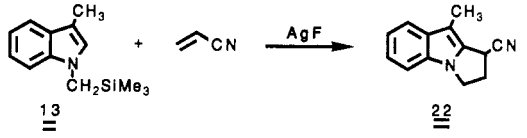


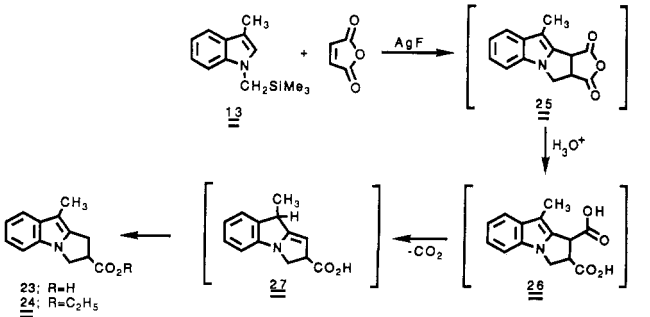
dergo stereospecific cis cycloaddition.[38] Interestingly, treatment of **13** with either (*Z*)- or (*E*)-1,2-bis(phenylsulfonyl)ethene in the presence of silver fluoride afforded cycloadduct **19** as the exclusive product. We found that the *Z*-substituted dipolarophile rearranged to the thermodynamically more stable *E* isomer before the cycloaddition had occurred. The reaction did proceed with complete stereospecificity with dimethyl fumarate and maleate, however, giving rise to cycloadducts **20** and **21**.



We also examined the cycloaddition behavior of an unsymmetrically substituted dipolarophile so as to probe the regioselectivity of the reaction. When acrylonitrile was used as the dipolarophile, cycloadduct **22** was the exclusive product. Structure **22** was rigorously established by X-ray structure analysis.



When the cycloaddition was carried out with maleic anhydride, the major product isolated corresponded to a carboxylic acid whose structure was assigned as **23**: NMR ($CDCl_3$, 360 MHz) δ 2.24 (s, 3 H), 3.27 (d, 2 H, J = 7.9 Hz), 3.84 (dd, 1 H, J = 7.9 and 7.5 Hz), 4.29 (d, 2 H, J = 7.5 Hz), 7.05–7.2 (m, 3 H), 7.48 (d, 1 H, J = 8.0 Hz), and 9.71 (br s, 1 H). Esterification of **23** with ethanol produced the corresponding ethyl ester **24**. Structure **23** can be rationalized as being formed by hydrolysis and decarboxylation of the initially produced cycloadduct **25**. It should be noted that this process conveniently allows for the formation of the opposite regioisomer from that predicted for cycloaddition with acrylates.



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The above cycloadditions show all the characteristics of a concerted reaction, including complete stereospecificity and regioselectivity and, therefore, are consistent with the intermediacy of an azomethine ylide.[38] All attempts to obtain a cycloadduct from the reaction of **13** with nonactivated olefins (i.e. cyclohexene, 1-octene, norbornene, etc.) failed. Our inability to isolate a 1,3-cycloadduct with these systems is consistent with the principles of frontier MO theory.[39] Azomethine ylides generally prefer to react with electron-deficient alkenes and alkynes, since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap.[40] The preferential formation of cycloadduct **22** is the result of the union of the larger azomethine ylide HO coefficient on the methylene carbon with that of the larger dipolarophile LU coefficient on the unsubstituted carbon (vide infra). It should be noted, however, that Roussi and co-workers[41] have recently reported that trimethylamine *N*-oxide undergoes reaction with LDA to give an azomethine ylide, which cycloadds with simple alkenes. It is not clear to us why the azomethine ylide (**29**) derived from **13** does not undergo 3 + 2 cycloaddition with alkyl-substituted olefins. Perhaps the silver ion used to liberate the dipole coordinates with the π-bond of the alkene, thereby inhibiting the cycloaddition. Further work is needed in order to establish this point.

What role is silver fluoride playing in the above cycloadditions? There are three discrete chemical processes involved here: (a) desilylation, (b) cycloaddition, and (c) oxidation. Presumably, desilylation occurs before cycloaddition as is observed with related systems.[5-12] It is unlikely that C-2 of indole **13** will undergo oxidation while in the sp^2 hybridization state since this would involve an unstabilized vinyl radical. Therefore, oxidation must follow cycloaddition. With this ordering and the reactivity patterns established for silver fluoride, it seems reasonable to suggest the following mechanism. Formation of the azomethine ylide intermediate **29** can be interpreted by assuming that silver ion behaves as a very specific Lewis acid that attacks the indole ring to give a silver-bonded carbonium ion. Fluoride ion accomplishes desilylation, affording the silver-substituted azomethine ylide, which then undergoes cycloaddition with the added dipolarophile. After the cycloaddition step, the resulting silver-bonded intermediate undergoes consecutive loss of silver and a hydrogen to give the observed product.[42] It should be noted that these reactions require a full equivalent of silver ion, which ultimately results in the production of metallic silver.

The structural features of the proposed mechanism in no way require the reacting centers to be part of an indole nucleus. Indeed, it may well be possible to effect a similar cycloaddition from an appropriately substituted silyl enamine. In order to probe this possibility, enamine **32** was prepared and subjected to silver fluoride desilylation. However, all attempts to effect the cycloaddition of **32** with a variety of dipolarophiles went unrewarded. In no instance was evidence uncovered for the formation of a cycloadduct. Only polymeric products were obtained from this particular system.

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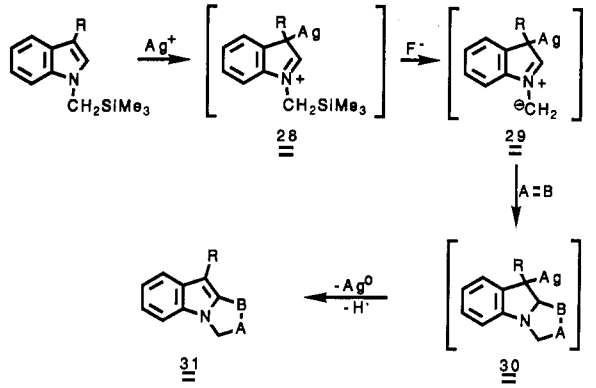
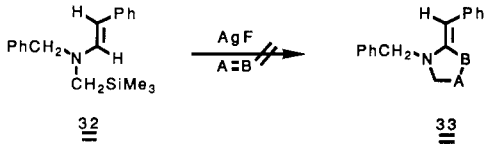
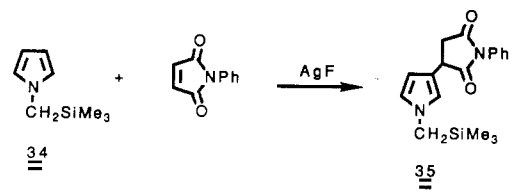
(42) The reduction of Ag(I) to the metallic state is somewhat reminiscent of results reported by Koser, G. F.; Fairclosth, J. J. *J. Org. Chem.* **1976**, *41*, 583.



Next, we turned our attention to the utilization of the pyrrole nucleus for a related cycloaddition. To this end, pyrrole **34** was prepared and exposed to silver fluoride in the presence of *N*-phenylmaleimide. In this case a 1:1

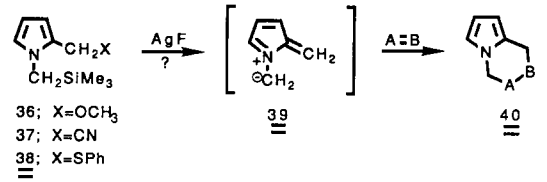


adduct was isolated in 60% yield and whose structure was assigned as **35** on the basis of its spectral properties [NMR ($CDCl_3$, 360 MHz) δ 0.05 (s, 9 H), 3.05 (dd, 1 H, J = 18.0 and 4.6 Hz), 3.32 (dd, 1 H, J = 18.0 and 9.7 Hz), 3.65 (d, 2 H, J = 1.4 Hz), 4.25 (ddd, 1 H, J = 9.7, 4.6, and 1.4 Hz), 6.0–6.7 (m, 3 H), and 7.2–7.5 (m, 5 H)]. Surprisingly, no desilylation or cycloaddition occurred. Pyrroles containing bulky substituents on the nitrogen atom are known to undergo electrophilic substitution at the 3-position of the ring.[43,44] Thus, the formation of **35** can be accounted for



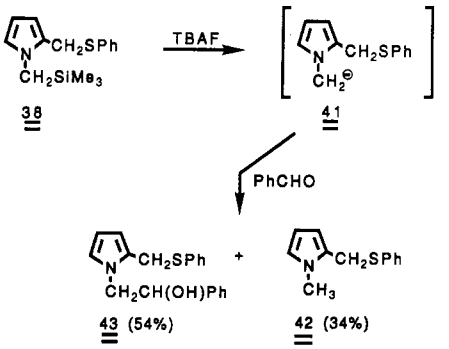
in terms of a Lewis acid catalyzed electrophilic substitution reaction. No signs of a bimolecular cycloadduct were encountered when dimethyl acetylenedicarboxylate or acrylonitrile were used as trapping agents. Only polymeric material was observed.

Since the C-2 atom of the pyrrole nucleus is inherently more nucleophilic then the C-3 position, we felt that our original objective of eliminating the elements of Me_3SiX so as to generate a 1,3-dipole might be more favorable if the CH_2X substituent were appended to the C-2 position. The resulting dipole (i.e. **39**) can be viewed as a pyrrole



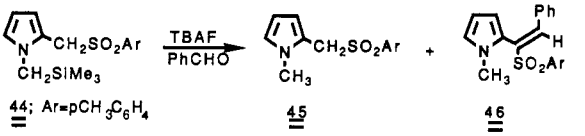
analogue of *o*-xylylene.[45] Heterocyclic analogues of *o*-xylylene are of considerable interest for their potential in organic synthesis. Apart from the indole 2,3-xylylenes, used so elegantly by Magnus and his co-workers in alkaloid synthesis,[46] such systems remain largely unexplored.[47–50] With this goal in mind, pyrroles **36–38** were prepared and treated with silver fluoride in the presence of suitable dipolarophiles. In each case starting material decomposition was noted; however, no characterizable products could be obtained.

Since the mechanistic picture of this process could be seriously complicated by the intervention of a silver-catalyzed polymerization, an alternature source of fluoride ion was employed. Recent work in our laboratory has shown that α-(phenylthio)-substituted silylamines can act as azomethine ylide equivalents when treated with tetrabutylammonium fluoride (TBAF).[51] We found that the treatment of **38** with TBAF in the presence of benzaldehyde gave a mixture of two products, which were identified as pyrroles **42** (34%) and **43** (54%). These two



products are derived from a fluoride-induced desilylation to produce carbanion **41**, which is either quenched by a proton source (presumably H_2O from TBAF) or attacks a molecule of benzaldehyde. Unfortunately, numerous attempts to generate and trap the desired dipole (i.e. **39**) failed, and further work with this system was abandoned.

Simple and stable reagents possessing a nucleophilic and an electrophilic site, which can be deployed selectively and sequentially, are of great potential use in synthesis. Since we were successful in accomplishing the first step for dipole formation (i.e. desilylation), our attention became focused on the leaving ability of the nucleofuge. Sulfone **44** was targeted for study as sulfinates tend to be better leaving groups than sulfides. When **44** was treated with TBAF in the presence of benzaldehyde, two products were obtained. The major product (66%) was the *N*-methylpyrrole **45** while the minor product corresponded to the condensation product **46**. As was the case with the thiophenyl-substituted pyrrole **38**, the first step corresponds to a fluoride-induced desilylation reaction to give a *N*-



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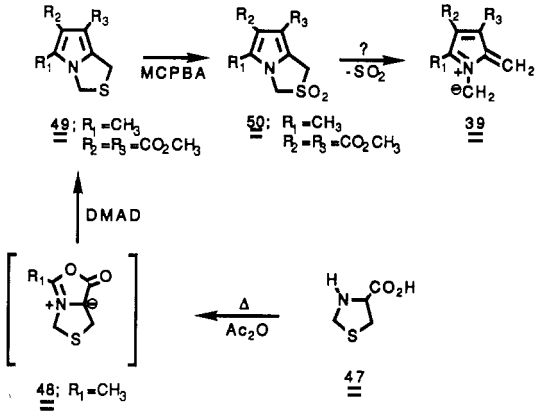
methide anion. In this case, as a consequence of the difference in acidity of the *N*-methyl protons and the methylene protons adjacent to the sulfonyl group, a rapid proton transfer occurred to give the more stable α-sulfonyl carbanion. This anion can either be quenched by adventitious water to give **45** or else it undergoes condensation with benzaldehyde to produce **46**. The problem with this particular approach for the generation of dipole **39** clearly relates to the difference in acidities of the two sites present in the substrate. Loss of the substituent group (i.e. X = OCH_3, CN, SPh, SO_2Ph) on the 2-position of the *N*-[(trimethylsilyl)methyl]pyrrole is slow enough as to discourage further efforts along these lines.

One last approach that we explored for the generation of dipole **39** involves the attempted extrusion of SO_2 from the pyrrolothiazole ring system. In recent years the extrusion of sulfur dioxide from cyclic sulfones has been extensively utilized in organic synthesis.[52] Accordingly,



we focused our attention on the synthesis and chemistry of pyrrolothiazole **50**. Entry into this ring system was expediently accomplished via a 1,3-dipolar cycloaddition of munchnone thioether **48** with DMAD. The oxidation of the resulting cycloadduct **49** with MCPBA was achieved uneventfully. Unfortunately, all of our attempts to extrude SO_2, both thermally (300 °C) and photochemically, were unsuccessful. In no instance was evidence uncovered for the formation of **39**.

In summary, the 1,3-dipolar cycloaddition of *N*-[(trimethylsilyl)methyl]indoles offers a direct and efficient synthesis of the pyrrolo[1,2-*a*]indole ring system and opens the way to various [1,2-*a*]-annelated indole quinones. It should be possible to prepare analogues and derivatives of these compounds by altering the C_3 substituent and/or by using suitably substituted dipolarophiles. Although our attempts to generate and cycloadd an extended dipole in the pyrrole series have thus far been thwarted, some useful alkylation and condensation methods have surfaced.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390 and a Nicolet NMC-360 MHz spectrometer. ^{13}C NMR spectra were recorded on an IBM NB 200 SY FT spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Prepartion of 1-[(Trimethylsilyl)methyl]indole-3-acetonitrile (4). A solution containing 6 g of gramine in 120 mL of anhydrous tetrahydrofuran at 0 °C was treated wth 27 mL of a 1.4 M solution of *n*-butyllithium in hexane. The mixture was stirred at room temperature for 2 h, treated with 6.9 mL of hexamethylphosphoramide, and cooled to 0 °C. After the reaction mixture was stirred for an additional 10 min, (chloromethyl)-trimethylsilane was added, and the reaction mixture was allowed to stir overnight. A similar alkylation occurred when 1.1 equiv of sodium hydride was used. The reaction mixture was then poured into water and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 6.82 g (76%) of a pale yellow oil (bp 106–108 °C (0.05 mm)), which was identified as 3-[(dimethylamino)methyl]-1-[(trimethylsilyl)methyl]indole (**10**): IR (neat) 3050, 2950, 2900, 2860, 2810, 2760, 1615, 1550, 1460, 1330, 1250, 1180, 1165, 1090, 1020, 1010, 850, 760, and 740 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.01 (s, 9 H), 2.09 (s, 6 H), 3.38 (s, 2 H), 3.42 (s, 2 H), 6.63 (s, 1 H), 6.7–7.0 (m, 3 H), 7.35–7.6 (m, 2 H); UV (95% ethanol) 293 (ϵ 5600) and 225 nm (ϵ 35 600); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −2.0, 37.2, 54.3, 45.1, 109.5, 111.0, 118.5, 119.1, 121.0, 127.8, 127.9, and 136.8; *m/e* 260 (M^+), 217, 216 (base), 102, 91, and 74. Anal. Calcd for $C_{15}H_{24}N_2Si$: C, 69.17; H, 9.29; N, 10.76. Found: C, 68.98; H, 9.34; N, 10.71.

A solution containing 3.8 g of the above material in 50 mL of tetrahydrofuran was treated with 2.8 g of methyl iodide. The mixture was stirred for 2 h at room temperature and was concentrated under reduced pressure to give the iodomethyl salt. This material was dissolved in 100 mL of water and treated with 4.0 g of potassium cyanide. The aqueous solution was heated at reflux for 3 h. At the end of this time the solution was extracted with ether. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give a brown oil. Silica gel chromatography of this material using a 10% ethyl acetate–hexane mixture as the eluent gave 2.8 g (80%) of 1-[(trimethylsilyl)methyl]indole-3-acetonitrile (**4**) as a pale yellow oil: IR (neat) 2955, 2900, 2250, 1460, 1420, 1340, 1235, 1165, 850, and 745 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.06 (s, 9 H), 3.57 (s, 2 H), 3.66 (s, 2 H), 6.93 (br s, 1 H), 7.03–7.23 (m, 3 H), and 7.36–7.56 (m, 1 H); UV (acetonitrile) 296 (ϵ 5620) and 228 nm (ϵ 33 330); ^{13}C NMR ($CDCl_3$, 20 MHz) δ −2.3, 14.1, 37.4, 102.3, 109.8, 117.8, 118.1, 119.0, 121.7, 125.8, 126.5, and 136.8; *m/e* 242 (M^+), 241, 169, 144, 143 (base), 115, and 73. Anal. Calcd for $C_{14}H_{18}N_2Si$: C, 69.37; H, 7.48; N, 11.56. Found: C, 69.13; H, 7.57; N, 11.48.

Reaction of 1-[(Trimethylsilyl)methyl]indole-3-acetonitrile (4) with *N*-Phenylmaleimide in the Presence of Silver Fluoride. A solution containing 960 mg of indole 4 and 690 mg of *N*-phenylmaleimide in 20 mL of anhydrous acetonitrile was treated with 527 mg of finely ground silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to leave behind a brown solid. Silica gel chromatography of this material using the Chromatotron unit and eluting with a 30% acetone–hexane mixture gave 1.15 g (85%) of a crystalline solid, which was identified as 5b,6,7,8,8a,9-hexahydro-6,8-dioxo-7-phenyl-5*H*-pyrrolo-[3′,4′:3,4]pyrrolo[1,2-*a*]indoline-5-acetonitrile (**8**) on the basis of its spectral data and by an X-ray crystal structure determination: mp 137–138 °C; IR (KBr) 3075, 2970, 2945, 2920, 2260, 1785, 1715, 1600, 1500, 1485, 1460, 1390 (s), 1380, 1295, 1200, 1170, 1160, and 745 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.92 (d, 1 H, J = 17.9 Hz), 4.10 (d, 1 H, J = 17.9 Hz), 4.34 (ddd, 1 H, J = 8.9, 8.3, and 2.1 Hz), 4.47 (dd, 1 H, J = 10.7 and 2.1 Hz), 4.69 (dd, 1 H, J = 10.7 and 8.9 Hz), 4.75 (d, 1 H, J = 8.3 Hz), 7.2–7.5 (m, 8 H), and 7.66 (d, 1 H, J = 7.1 Hz); UV (95% ethanol) 292 (ϵ 5140), 282 (ϵ 7190), 272 (ϵ 7830), and 221 nm (ϵ 19 810); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 12.5 (t), 44.2 (d), 45.8 (t), 48.1 (d), 96.9 (s), 110.8, 118.6, 118.7, 119.8, 121.7, 126.9, 128.5, 128.8, 130.9, 132.1, 132.2, 136.6, 173.7, and 176.9; *m/e* 341 (M^+), 340, 315, 167, and 149. Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.72; H, 4.48; N, 12.29.

Crystals suitable for an X-ray determination were grown from a methylene chloride–hexane solution. A crystal of approximately 0.2 × 0.2 × 0.3 mm was mounted on a quartz fiber with epoxy cement such that the longest crystal dimension was parallel to the fiber axis. Unit cell parameters were determined on a Syntex $P2_1$ automated diffractometer using nonmonochromatic Mo Kα radiation. Twenty-five reflections were machine centered and used in the least-squares refinement of the lattice parameters and orientation matrix. The unit cell parameters obtained were a =

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7.98 (2) Å, b = 13.89 (6) Å, c = 15.11 (8) Å, β = 90.84 (35)°, V = 1664.6 (8) Å^3, d_{calcd} = 1.36 g cm^{-3}, $F(000)$ = 711.86, Z = 4, and space group $P2_{1/n}$.

Intensity data were collected by using the ω scan technique with a variable scan rate of 3–29.3° min^{-1}. A scan width of 2.0° was sufficient to collect all of the peak intensity. Control reflections monitored after each set of 97 scans showed no significant change during the course of data collection. Lorentz and polarization corrections were made in the usual way. No absorption correction was applied. Of the total of 2494 reflections collected with 3.0° < 2θ < 45.0°, 1426 were found to be unique. The structure was solved by direct methods with the SHELXTL program. Following anisotropic refinement of the backbone atoms, all hydrogens were located in a weighted electron density difference Fourier synthesis. Refinement of hydrogens with isotropic thermal parameters reduced the structure factor to R = 0.077 and R_W = 0.070, where $R_W = \sum_\omega{}^{1/2}(F_o - F_c)/\sum_\omega{}^{1/2}F_o$.

Preparation of 1-[(Trimethylsilyl)methyl]indole (11). A solution containing 5.7 g of indole in 100 mL of tetrahydrofuran at 0 °C was treated with 37 mL of a 1.4 M solution of *n*-butyllithium in hexane. The solution was allowed to warm to room temperature over a 2-h period. At the end of this time the mixture was cooled to 0 °C and was treated with 8.6 mL of hexamethylphosphoramide. After the mixture was stirred for 5 min, 8.2 mL of (chloromethyl)trimethylsilane was added, and the mixture was stirred for an additional 10 h at room temperature, poured into water, and extracted with ether. The ethereal layer was washed five times with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown oil. Silica gel chromatography of this material using a 10% ethyl acetate–hexane mixture as the eluent gave 3.2 g (32%) of 1-[(trimethylsilyl)methyl]indole (**11**) as a crystalline solid: mp 31–32 °C; IR (neat) 3060, 2970, 2910, 1520, 1490, 1470, 1425, 1405, 1373, 1320, 1255, 1170, 1030, 860, 770, 745, 720, and 710 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.10 (s, 9 H), 3.63 (s, 2 H), 6.38 (d, 1 H, J = 3.0 Hz), 6.87 (d, 1 H, J = 3.0 Hz), 6.9–7.2 (m, 3 H), and 7.45–7.65 (m, 1 H); UV (95% ethanol) 224 (ϵ 34 400), 277 (ϵ 4800), 288 (ϵ 5000), and 292 nm (ϵ 3300); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 2.1, 37.3, 100.3, 109.4, 118.6, 120.6, 120.9, and 128.0; m/e 203 (M$^+$), 202, 130, 77, and 73. Anal. Calcd for $C_{12}H_{17}NSi$: C, 70.88; H, 8.43; N, 6.89. Found: C, 70.95; H, 8.46; N, 6.89.

Preparation of 1-[(Trimethylsilyl)methyl]indole-3-carboxaldehyde (12). A solution containing 17.2 g of indole-3-carboxaldehyde, 35 g of sodium iodide, 26 mL of (chloromethyl)trimethylsilane, and 33 g of anhydrous potassium carbonate in 420 mL of acetone was heated at reflux for 4 days. At the end of this time the suspension was filtered, and the filtrate was concentrated under reduced pressure to leave behind a crude yellow solid. Silica gel chromatography of this material using a 4:3:3 mixture of hexane, ethyl acetate, and chloroform as the eluent gave 18.4 g (67%) of 1-[(trimethylsilyl)methyl]indole-3-carboxaldehyde (**12**) as a yellow crystalline solid: mp 91–92 °C; IR (KBr) 3115, 3060, 2960, 2900, 2820, 1650, 1615, 1580, 1530, 1490, 1467, 1400, 1385, 1250, 1170, 1150, 865, 845, 790, and 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.11 (s, 9 H), 3.74 (s, 2 H), 7.23–7.43 (m, 3 H), 7.60 (s, 1 H), 8.22–8.47 (m, 1 H), and 10.03 (s, 1 H); UV (95% ethanol) 309 (ϵ 16 200) and 255 nm (ϵ 14 400); ^{13}C NMR ($CDCl_3$, 20 MHz) δ −2.4, 38.3, 110.1, 117.4, 121.6, 122.4, 123.4, 124.9, 137.8, 138.0, and 183.8; m/e 231 (M$^+$), 203, 202, 130, and 73. Anal. Calcd for $C_{13}H_{17}NOSi$: C, 67.48; H, 7.41; N, 6.05. Found: C, 67.34; H, 7.43; N, 6.01.

Preparation of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13). A solution containing 8.0 g of skatole in 250 mL of anhydrous tetrahydrofuran at −78 °C was treated with 48 mL of a 1.4 M solution of *n*-butyllithium in hexane. The reaction mixture was stirred for 1 h at −78 °C and was allowed to warm to room temperature over a period of 1 h. At the end of this time the solution was cooled to −78 °C and was treated with 10.6 mL of hexamethylphosphoramide. After the mixture was stirred for 5 min, 9.1 mL of (iodomethyl)trimethylsilane was added. The reaction mixture was allowed to stir overnight and was then extracted with ether. The ethereal layer was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Silica gel chromatography of the crude oil using a 10% ethyl acetate–hexane mixture as the eluent gave 13.0 g (98%) of 3-methyl-1-[(trimethylsilyl)methyl]indole (**13**) as a colorless oil: IR (neat) 2950, 2920, 2890, 1460, 1420, 1360, 1330, 1250, 1165, 855, 760, and 740 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.00 (s, 9 H), 2.23 (s, 2 H), 3.46 (s, 2 H), 6.52 (s, 1 H), 6.63–7.0 (m, 3 H), and 7.1–7.4 (m, 1 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ −2.1, 9.4, 36.9, 109.2, 109.4, 117.8, 118.6, 120.8, 125.9, 128.0, and 136.8; UV (acetonitrile) 234 (ϵ 30 430) and 302 nm (ϵ 4430); m/e 217 (M$^+$), 216, 144, and 73. Anal. Calcd for $C_{13}H_{19}NSi$: C, 71.83; H, 8.81; N, 6.44. Found: C, 71.81; H, 8.84; N, 6.41.

Reaction of 1-[(Trimethylsilyl)methyl]indole (11) with *N*-Phenylmaleimide in the Presence of Silver Fluoride. A solution containing 500 mg of 1-[(trimethylsilyl)methyl]indole (**11**) and 460 mg of *N*-phenylmaleimide in 15 mL of anhydrous acetonitrile was treated with 400 mg of finely ground silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to leave behind a brown solid. Silica gel chromatography of this material using a 30% acetone–hexane mixture as the eluent gave 180 mg (60%) of 8a,9-dihydro-7-phenyl-5*H*-pyrrolo[3′,4′:3,4]pyrrolo[1,2-*a*]-indoline-6,8(5b*H*,7*H*)-dione (**14**) on the basis of its spectral properties: mp 226–227 °C; IR (KBr) 1780, 1720, 1600, 1505, 1495, 1460, 1385, 1360, 1350, 1310, 1210, 1190, 1170, 1160, and 750 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 4.22 (ddd, 1 H, J = 8.7, 8.1, and 2.0 Hz), 4.36 (dd, 1 H, J = 10.6 and 8.7 Hz), 4.57 (dd, 1 H, J = 8.1 and 1.0 Hz), 4.64 (dd, 1 H, J = 10.6 and 2.0 Hz), 6.56 (s, 1 H), 7.1–7.5 (m, 8 H), and 7.60 (d, 1 H, J = 7.9 Hz); UV (acetonitrile) 220 (ϵ 47 600), 276 (s) (ϵ 8600), 282 (ϵ 9000), and 291 nm (ϵ 7500); m/e 302 (M$^+$), 167, 149, 71 and 57. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.45; H, 4.71; N, 9.21.

Reaction of 1-[(Trimethylsilyl)methyl]indole-3-carboxaldehyde (12) with *N*-Phenylmaleimide in the Presence of Silver Fluoride. A solution containing 228 mg of indole **12** and 201 mg of *N*-phenylmaleimide in 8 mL of acetonitrile was treated with 202 mg of finely ground silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure. Silica gel flash chromatography of the crude reaction mixture using a 4:3:3 mixture of hexane, ethyl acetate, and chloroform as the eluent gave 97 mg (50%) of a white crystalline solid, which was identified as 5-formyl-8a,9-dihydro-7-phenyl-5*H*-pyrrolo[3′,4′:3,4]pyrrolo[1,2-*a*]indole-6,8-(5b*H*,7*H*)-dione (**15**) on the basis of its spectral properties: mp 195–196 °C; IR (KBr) 2940, 2810, 1780, 1715, 1660, 1650, 1380, and 1200 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 4.37 (ddd, 1 H, J = 9.2, 8.4, and 2.2 Hz), 4.47 (dd, 1 H, J = 11.2 and 9.2 Hz), 4.68 (dd, 1 H, J = 11.2 and 2.2 Hz), 4.84 (d, 1 H, J = 8.4 Hz), 7.0–7.5 (m, 7 H), 8.2–8.4 (m, 2 H), and 10.26 (s, 1 H); m/e 330 (M$^+$), 327, 167, 149, 145, and 144. Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 75.92; H, 5.10; N, 8.86. Found: C, 75.87; H, 5.02; N, 8.73.

Reaction of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13) with *N*-Phenylmaleimide in the Presence of Silver Fluoride. A solution containing 530 mg of indole **13** and 445 mg of *N*-phenylmaleimide in 12 mL of acetonitrile was treated with 410 mg of finely ground silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to give a brown solid. Silica gel flash chromatography of this material using a 20% ethyl acetate–hexane mixture as the eluent gave 280 mg (83%) of a white crystalline solid, which was identified as 8a,9-dihydro-5-methyl-7-phenyl-5*H*-pyrrolo[3′,4′:3,4]pyrrolo[1,2-*a*]indole-6,8(5b*H*,7*H*)-dione (**16**) on the basis of its spectral properties: mp 181–182 °C; IR (KBr) 3060, 2940, 1785, 1715, 1495, 1460, 1390, 1360, 1345, 1310, 1245, 1195, 1170, 1160, 775, and 745 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.43 (d, 3 H, J = 1.0 Hz), 4.24 (ddd, 1 H, J = 8.6, 8.1, and 1.8 Hz), 4.33 (dd, 1 H, J = 10.3 and 8.6 Hz), 4.59 (dd, 1 H, J = 8.1 and 1.0 Hz), 4.64 (dd, 1 H, J = 10.3 and 1.8 Hz), 7.1–7.28 (m, 5 H), 7.34–7.48 (m, 3 H), and 7.55 (d, 1 H, J = 7.9 Hz); UV (acetonitrile) 292 (ϵ 6500), 286 (ϵ 7100), 280 (ϵ 6600), and 227 nm (ϵ 42 800); m/e 316 (M$^+$), 167, 154, 150, and 149. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.99; H, 5.13; N, 8.85.

Reaction of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13) with Dimethyl Acetylenedicarboxylate in the Presence of Silver Fluoride. A solution containing 431 mg of indole **13** and 0.3 mL of dimethylacetylenedicarboxylate in 10 mL of acetonitrile was treated with 528 mg of finely ground silver fluoride, and the

mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure. Silica gel flash chromatography of this material using a 30% ethyl acetate–hexane mixture as the eluent gave 400 mg (75%) of a light yellow solid, which was identified as dimethyl 9-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (**18**) on the basis of its spectral properties: mp 153–154 °C; IR (KBr) 1720, 1690, 1560, 1510, 1380, 1300, 1290, 1220, 1205, 1165, 1150, and 1080 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.60 (d, 3 H, J = 7.3 Hz), 3.87 (s, 3 H), 3.90 (s, 3 H), 4.28 (q, 1 H, J = 7.3 Hz), 7.22–7.48 (m, 4 H), and 7.64 (s, 1 H); UV (acetonitrile) 248 nm (ϵ 24 160); m/e 285 (M^+), 217, 216, 144, and 73. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.20; H, 5.37; N, 4.85.

Reaction of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13) with *trans*-1,2-Bis(phenylsulfonyl)ethylene in the Presence of Silver Fluoride. A solution containing 424 mg of indole **13** and 670 mg of *trans*-1,2-bis(phenylsulfonyl)ethylene in 11 mL of acetonitrile was treated with 580 mg of finely ground silver fluoride, and the mixture was stirred for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to give a brown solid. Silica gel flash chromatography of this material with use of a 30% acetone–hexane mixture as the elent gave 320 mg (37%) of a white crystalline solid whose structure was identified as *trans*-2,3-dihydro-9-methyl-1,2-bis(phenylsulfonyl)-1*H*-pyrrolo[1,2-*a*]indole (**19**) on the basis of its spectral properties: mp 195–196 °C; IR (KBr) 1490, 1455, 1390, 1320 (s), 1310, 1260, 1160, 1150, 1130, 1085, 755, and 740 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.68 (s, 3 H), 4.31 (dd, 1 H, J = 12.0 and 6.9 Hz), 4.48 (dd, 1 H, J = 12.0 and 1.2 Hz), 4.73 (dd, 1 H,m J = 6.9 and 1.2 Hz), 5.02 (s, 1 H), and 7.0–7.95 (m, 14 H); UV (acetonitrile) 290 (ϵ 8900), 272 (ϵ 8100), 266 (ϵ 7200), and 225 nm (ϵ 44 500). Anal. Calcd for $C_{24}H_{21}NS_2O_4$: C, 63.84; H, 4.69; N, 3.10; S, 14.20. Found: C, 63.67; H, 4.74; N, 3.05; S, 14.13.

Similar results were obtained from the reaction of **13** with the cis isomer.

Reaction of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13) with Dimethyl Fumarate in the Presence of Silver Fluoride. A solution containing 510 mg of indole **13** and 374 mg of dimethyl fumarate in 11 mL of anhydrous acetonitrile was treated with 610 mg of finely ground silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to give 230 mg of a (50%) brown solid. The first fraction obtained from silica gel chromatography with a 15% ethyl acetate–hexane mixture as the eluent contained 140 mg of a white crystalline solid, which was identified as *trans*-dimethyl 2,3-dihydro-9-methyl-1*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (**20**) on the basis of its spectral properties: mp 123–124 °C; IR (KBr) 1725, 1435, 1380, 1370, 1340 (s), 1330, 1235, 1200, 1170, and 745 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.29 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 4.30 (ddd, 1 H, J = 8.5, 4.9, and 4.5 Hz), 4.35 (dd, 1 H, J = 9.8 and 4.9 Hz), 4.43 (dd, 1 H, J = 9.8 and 8.5 Hz), and 4.55 (d, 1 H, J = 4.5 Hz); UV (acetonitrile) 230 (ϵ 36 400) and 288 nm (ϵ 7030); m/e 287 (M^+), 217, 216, 168, 144, and 73. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.82; H, 6.00; N, 4.82.

A similar reaction of indole **13** with dimethyl maleate afforded *cis*-dimethyl 2,3-dihydro-9-methyl-1*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (**21**) as the major cycloadduct: NMR ($CDCl_3$, 360 MHz) δ 2.29 (s, 3 H), 3.66 (s, 3 H), 3.78 (s, 3 H), 3.95 (ddd, 1 H, J = 9.7, 9.0, and 7.9 Hz), 4.38 (dd, 1 H, J = 9.7 and 9.0 Hz), 4.44 (d, 1 H, J = 7.9 Hz), 4.49 (dd, 1 H, J = 9.7 and 9.7 Hz), 7.05–7.25 (m, 3 H), and 7.51 (d, 1 H, J = 7.9 Hz). This material rapidly isomerized to the trans cycloadduct **20** upon standing at room temperature.

Reaction of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13) with Acrylonitrile in the Presence of Silver Fluoride. A solution containing 525 mg of indole **13** and 0.18 mL of acrylonitrile in 10 mL of acetonitrile was treated with 640 mg of silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to give a brown solid. Silica gel chromatography of this material using a 15% ethyl acetate–hexane mixture as the eluent gave 120 mg (38%) of a light yellow solid whose structure was identified as 2,3-dihydro-1-cyano-9-methyl-1*H*-pyrrolo[1,2-*a*]indole (**22**) on the basis of its spectral data and by an X-ray crystal structure determination: mp 98–99 °C; IR (KBr) 2930, 2900, 2250, 1480, 1460, 1455 (s), 1385, 1335, 1310, 1245, 765, and 755 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.32 (s, 3 H), 2.85 (dddd, 1 H, J = 13.5, 8.2, 6.5, and 6.3 Hz), 3.03 (dddd, 1 H, J = 13.5, 8.5, 7.7, and 5.2 Hz), 4.04 (ddd, 1 H, J = 10.1, 7.7, and 5.2 Hz), 4.19 (ddd, 1 H, J = 10.1, 8.2, and 5.2 Hz), 4.37 (dd, 1 H, J = 8.5 and 6.5 Hz), 7.02–7.3 (m, 3 H), and 7.51 (d, 1 H, J = 8.0 Hz); UV (acetonitrile) 230 (ϵ 38 230) and 286 nm (ϵ 6260); m/e 196 (M^+), 195, 181, 169, 168, and 143. Anal. Calcd for $C_{13}H_{12}N$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.58; H, 6.19; N, 14.23.

Suitable crystals were grown from methylene chloride–hexane. A crystal of approximately 0.3 × 0.4 × 0.3 mm was mounted on a quartz fiber with epoxy cement such that the longest crystal dimension was parallel to the fiber axis. Unit cell parameters were determined on a Syntex $P2_1$ automated diffractometer using monochromatic Mo Kα radiation. Seventeen reflections were machine centered and used in the least-squares refinement of the lattice parameters and orientation matrix. The unit cell parameters obtained were a = 7.707 (4) Å, b = 8.638 (7) Å, c = 16.366 (13) Å, β = 99.28 (5)°, V = 1075.3 (12) $Å^3$, d_{calcd} = 1.21 g cm^{-3}, $F(000)$ = 415.91, Z = 4, and space group $P2_{1/n}$.

Intensity data were collected by using the ω scan technique with a variable scan rate of 5.5–29.30 min^{-1}. A scan width of 2.0° was sufficient to collect all of the peak intensity. Control reflections, monitored after each set of 97 scans, showed no significant change during the course of data collection. Lorentz and polarization corrections were made in the usual way. Of the total of 1653 reflections collected with 3.0° < 2θ < 45°, 1145 were found to be unique and 1017 had $I > 3(I)$. The structure was solved by direct methods with the SHELXTL program. Following anisotropic refinement of the backbone atoms, all hydrogens were located in a weighted electron density difference Fourier synthesis. Refinement of hydrogens with isotropic thermal parameters reduced the structure factor to R = 0.063 and R_W = 0.063 where $R_W = \sum_\omega^{1/2}(F_o - F_c)/\sum_\omega^{1/2}F$.

Reaction of 3-Methyl-1-[(trimethylsilyl)methyl]indole (13) with Maleic Anhydride in the Presence of Silver Fluoride. A solution containing 1.0 g of indole **13** and 570 mg of maleic anhydride in 25 mL of anhydrous acetonitrile was treated with 1.2 g of silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure. The crude residue was redissolved in 50 mL of methylene chloride and extracted with 50 mL of a 10% sodium hydroxide solution. The aqueous solution was acidified with a 10% hydrochloric acid solution and extracted with chloroform. The chloroform layer was dried over magnesium sulfate and concentrated under reduced pressure to give 420 mg (42%) of an oil whose structure was assigned as 2,3-dihydro-9-methyl-1*H*-pyrrolo-[1,2-*a*]indole-2-carboxylic acid (**23**): NMR ($CDCl_3$, 360 MHz) δ 2.24 (s, 3 H), 3.27 (d, 2 H, J = 7.9 Hz), 3.84 (dd, 1 H, J = 7.9 and 7.5 Hz), 4.29 (d, 2 H, J = 7.5 Hz), 7.05–7.2 (m, 3 H), 7.48 (d, 1 H, J = 8.0 Hz), and 9.7 (br s, 1 H). External irradiation of the signal at 3.84 gave rise to two singlets at 3.27 and 4.29. This material was esterified due to the difficulty in purification of the free acid.

The above acid was dissolved in 100 mL of absolute ethanol and was treated with 5 drops of concentrated hydrochloric acid and heated at reflux over 4-Å molecular sieves for 15 h. Filtration of the crude residue and removal of the solvent under reduced pressure left 220 mg of a brown oil. Silica gel chromatography of this material afforded 96 mg of a light yellow solid, which was identified as ethyl 2,3-dihydro-9-methyl-1*H*-pyrrolo[1,2-*a*]-indole-2-carboxylate (**24**) on the basis of its spectral properties: mp 53–54 °C; IR (neat) 2980, 2910, 1730, 1480, 1373, 1345, 1230 (s), 1215, 1190, and 745 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.30 (t, 3 H, J = 7.1 Hz), 2.24 (s, 3 H), 3.23 (d, 2 H, J = 7.8 Hz), 3.79 (tt, 1 H, J = 8.0 and 7.8 Hz), 4.27 (d, 2 H, J = 8.0 Hz), 4.22 (q, 2 H, J = 7.1 Hz), 7.0–7.25 (m, 3 H), and 7.56 (d, 1 H, J = 7.5 Hz); UV (acetonitrile) 232 (ϵ 39 900) and 288 nm (ϵ 6950); m/e 243 (M^+), 214, 170, 169, 168, and 154. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.88; H, 7.07; N, 5.69.

Reaction of *N*-[(Trimethylsilyl)methyl]pyrrole (34) with *N*-Phenylmaleimide in the Presence of Silver Fluoride. A

solution containing 500 mg of pyrrole **34** and 848 mg of *N*-phenylmaleimide in 11 mL of anhydrous acetonitrile was treated with 634 mg of finely ground silver fluoride, and the mixture was heated for 4 days at 80 °C. At the end of this time the solution was filtered through Celite, and the solvent was removed under reduced pressure to give a brown oil. This material was subjected to silica gel chromatography with a mixture of 20% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 490 mg (60%) of clear oil whose structure was identified as 3-(2,5-dioxo-*N*-phenylpyrrolidin-3-yl)-1-[(trimethylsilyl)-methyl]pyrrole (**35**) on the basis of its spectral data: IR ($CHCl_3$) 3020, 2980, 1720, 1600, 1500, 1380, 1350, 1280, 860, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.05 (s, 9 H), 3.05 (dd, J = 18.0 and 4.6 Hz, 1 H), 3.32 (dd, J = 18.0 and 9.7 Hz, 1 H), 3.65 (d, J = 1.4 Hz, 2 H), 4.25 (ddd, J = 9.7, 4.6, and 1.4 Hz, 1 H), 6.00–6.10 (m, 1 H), 6.15–6.20 (m, 1 H), 6.60–6.70 (m, 1 H), and 7.25–7.50 (m, 5 H); MS, m/e 326 (M^+) 297, 223, 151 and 106. Anal. Calcd for $C_{18}H_{22}N_2SiO_2$: C, 66.22; H, 6.79; N, 8.58. Found: C, 66.16; H, 6.59; N, 8.46.

Preparation of *N*-[(Trimethylsilyl)methyl]-2-(methoxymethyl)pyrrole (36). A solution containing 1.00 g of pyrrole-2-carboxaldehyde, 690 mg of powdered potassium hydroxide, and 79 mg of 18-Crown-6 in 20 mL of anhydrous benzene was heated at reflux for 2 h. At the end of this time, a solution containing 3.21 g of (iodomethyl)trimethylsilane in 10 mL of benzene was added, and the reaction mixture was heated at reflux for 6 h. The solution was filtered, and the filtrate was concentrated under reduced pressure to give a dark colored liquid, which was subjected to silica gel chromatography with a mixture of 5% ethyl acetate–hexane as the eluent. The major fraction isolated contained 790 mg (42%) of *N*-[(trimethylsilyl)methyl]pyrrole-2-carboxaldehyde as a clear oil: IR (neat) 3100, 2950, 2900, 2800, 1670, 1520, 1480, 1370, 1315, 1250, 1135, 1070, 1030, 855, 770, and 745 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.11 (s, 9 H), 4.05 (s, 2 H), 6.00–6.15 (m, 2 H), 6.50–6.70 (m, 1 H), and 9.50 (s, 1 H). Anal. Calcd for $C_9H_{15}NSiO$: C, 59.55; H, 8.28; N, 7.73. Found: C, 59.55; H, 8.36; N, 7.65.

To a stirred suspension containing 600 mg of lithium aluminum hydride in 10 mL of anhydrous tetrahydrofuran was added in drops a solution containing 1.42 g of the above aldehyde in 10 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 5 h. At the end of this time, the solution was poured into water and extracted with ether. The organic extracts were washed with water and a saturated salt solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 1.19 g (83%) of *N*-[(trimethylsilyl)methyl]pyrrole-2-carbinol as a clear oil: IR (neat) 3360 (broad), 2960, 2900, 1550, 1490, 1420, 1300, 1250, 1070, 1000, 850, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.11 (s, 9 H), 1.70 (br s, 1 H), 3.45 (s, 3 H), 4.40 (s, 2 H), 5.80–5.95 (m, 2 H), and 6.30–6.50 (m, 1 H).

To a stirred suspension containing 230 mg of a 50% sodium hydride in mineral oil and 1.13 g of iodomethane in 10 mL of dry tetrahydrofuran was added a solution containing 200 mg of the above material in 10 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 3 h. At the end of this time, the solution was poured into water and extracted with ether. The combined ether extracts were washed with water and a saturated salt solution and dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to give 200 mg (95%) of *N*-[(trimethylsilyl)methyl]-2-(methoxymethyl)pyrrole (**36**) as a clear oil: IR (neat), 3100, 2960, 2900, 2820, 1485, 1360, 1300, 1250, 1085, 1065, 855, and 710 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.11 (s, 9 H), 3.1 (s, 3 H), 3.45 (s, 2 H), 4.25 (s, 2 H), 5.70–5.95 (m, 1 H), and 6.30–6.45 (m, 1 H). Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.91; H, 9.64; N, 7.10. Found: C, 60.85; H, 9.60; N, 7.02. Treatment of this compound with silver fluoride in the presence of a variety of dipolarophiles led to dark oils, which could not be purified.

Preparation of *N*-[(Trimethylsilyl)methyl]-2-(cyanomethyl)pyrrole (37). To a solution containing 1.53 g of *N*-[(trimethylsilyl)methyl]pyrrole in 30 mL of tetrahydrofuran at room temperature was added a mixture containing 0.98 g of dimethylamine hydrochloride and 0.98 g of a 37% aqueous formalin solution. After the mixture was stirred for 2 h, a white precipitate appeared. Sufficient water was added to dissolve the solid, and the mixture was stirred at room temperature for another 48 h. The solution was poured into a saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the oily residue that remained was distilled at 58 °C (0.5 mm) to give 1.54 g (73%) of *N*-[(trimethylsilyl)methyl]-2-[(dimethylamino)methyl]pyrrole as a colorless oil: IR (neat) 3080, 2940, 2800, 1485, 1450, 1355, 1260, 1180, 1070, 1025, 850, 760, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.06 (s, 9 H), 2.15 (s, 6 H), 3.28 (s, 2 H), 3.58 (s, 2 H), 5.86–6.04 (m, 2 H), and 6.50–6.55 (m, 1 H); UV (95% ethanol) 221 nm (ϵ 10 100); m/e 210 (M^+), 166 (base), 73, and 57. Anal. Calcd for $C_{11}H_{22}N_2Si$: C, 62.79; H, 10.54; N, 13.32. Found: C, 62.94; H, 10.51; N, 13.07.

On several occasions variable amounts of *N*-[(trimethylsilyl)-methyl]-3-[(dimethylamino)methyl]pyrrole was observed. The 3-substituted isomer could be readily separated from the 2-isomer by silica gel chromatography by using a 15% ethyl acetate–hexane mixture as the eluent. The 3-substituted isomer showed the following spectral characteristics: IR (neat) 3115, 2960, 2760, 1560, 1500, 1460, 1325, 1250, 1160, 1025, 850, 695, and 620 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.05 (s, 9 H), 2.03 (s, 6 H), 3.13 (s, 2 H), 3.36 (s, 2 H), 5.80 (t, 1 H, J = 2.25 Hz), and 6.26 (d, 2 H, J = 2.25 Hz); UV (95% ethanol) 217 nm (sh, ϵ 6100); m/e 210 (M^+), 166 (base), 83, and 73. Anal. Calcd for $C_{11}H_{22}N_2Si$: C, 62.79; H, 10.54; N, 13.32. Found: C, 62.84; H, 10.51; N, 13.08.

A solution containing 1.61 g of the 2-substituted isomer in 100 mL of ether was added to a solution containing 5 mL of methyl iodide in 200 mL of ether at 0 °C over a period of 30 min. After being stirred at 0 °C for 2 h, the mixture was allowed to warm to room temperature and was stirred overnight. The mixture was concentrated under reduced pressure and filtered to give 2.16 g (87%) of *N*-[(trimethylsilyl)methyl]-2-[(dimethylamino)-methyl]pyrrole methiodide as a white solid. This material was used directly in the next step without further purification.

To a solution containing 2.16 g of the above compound in 15 mL of dimethylformamide was added 1.66 g of potassium cyanide. The mixture was heated at 100 °C for 2 h under a nitrogen atmosphere, poured into water, and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was distilled to give 0.80 (68%) of a clear oil, which rapidly colored upon exposure to air. The NMR spectrum of this material showed that it consisted of a 1:1 mixture of 2-methyl-3-cyano-*N*-[(trimethylsilyl)methyl]pyrrole and *N*-[(trimethylsilyl)methyl]-2-(cyanomethyl)pyrrole (**37**). These two isomers could be separated by silica gel chromatography with a 5% ethyl acetate–hexane mixture as the eluent. The first component isolated from the column contained 2-methyl-3-cyano-*N*-[(trimethylsilyl)methyl]-pyrrole: IR (neat) 2960, 2210, 1475, 1320, 1250, 1170, 1025, 850, and 755 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 2.16 (s, 3 H), 3.58 (s, 2 H), 5.85 (d, 1 H, J = 3.0 Hz), and 6.63 (d, 1 H, J = 3.0 Hz); UV (95% ethanol) 263 (ϵ 13 300) and 236 nm (ϵ 8130); m/e 192 (M^+), 93, and 73 (base). Anal. Calcd for $C_{10}H_{16}N_2Si$: C, 62.44; H, 8.39; N, 14.57. Found: C, 62.34; H, 8.43; N, 14.49.

The second component isolated from the column was assigned as *N*-[(trimethylsilyl)methyl]-2-(cyanomethyl)pyrrole (**37**) on the basis of its spectral properties: IR (neat) 2960, 2250, 2210, 1470, 1420, 1300, 1065, 900, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 3.37 (s, 2 H), 3.60 (s, 2 H), 6.0–6.05 (m, 2 H), and 6.52–6.57 (m, 1 H); UV (95% ethanol) 258 (ϵ 860) and 219 nm (ϵ 7800); m/e 192 (M^+), 177, 166, 93 (base), and 73. Anal. Calcd for $C_{10}H_{16}N_2Si$: C, 62.44; H, 8.39; N, 14.57. Found: C, 62.42; H, 8.42; N, 14.56. Treatment of this compound with silver fluoride in the presence of a variety of dipolarophiles led to dark oils, which could not be purified.

Preparation of *N*-[(Trimethylsilyl)methyl]-2-[(phenylthio)methyl]pyrrole (38). A solution of sodium thiophenolate in dry dimethylformamide was prepared by treating 258 mg of sodium hydride (50%) with 0.57 mL of thiophenol in 20 mL of dimethylformamide at 0 °C under a nitrogen atmosphere. To this mixture was added 1.26 g of *N*-[(trimethylsilyl)methyl]-2-[(dimethylamino)methyl]pyrrole methiodide. The resulting mixture was allowed to warm to room temperature and was heated at 50 °C for 2.5 h. After cooling, the mixture was poured into ether, and the ether solution was washed with water and a sat-

urated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with a 1% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 0.96 g (97%) of *N*-[(trimethylsilyl)methyl]-2-[(phenylthio)methyl]pyrrole (**38**) as a colorless oil: IR (neat) 3080, 2970, 1580, 1485, 1440, 1305, 1255, 1070, 850, 740, and 705 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.13 (s, 9 H), 3.50 (s, 2 H), 4.00 (s, 2 H), 5.73–5.88 (m, 2 H), 6.36–6.43 (m, 1 H), and 7.13–7.23 (m, 5 H); UV (95% ethanol) 255 (ϵ 11 100) and 236 nm (ϵ 11 900); *m/e* 275 (M^+), 167, 109, 93, 73, and 59 (base). Anal. Calcd $C_{15}H_{21}NSSi$: C, 65.39; H, 7.68; N, 5.09; S, 11.64. Found: C, 65.41; H, 7.72; N, 5.07; S, 11.70. Treatment of this compound with silver fluoride in the presence of a variety of dipolarophiles led to dark oils, which could not be purified.

Reaction of *N*-[(Trimethylsilyl)methyl]-2-[(phenylthio)methyl]pyrrole (38) with Tetrabutylammonium Fluoride in the Presence of Benzaldehyde. A mixture containing 0.13 mL of benzaldehyde, 1.55 mL of a 1.0 M tetrabutylammonium fluoride solution, and 4-Å molecular sieves in 10 mL of tetrahydrofuran was stirred for 6 h at room temperature under a nitrogen atmosphere. A solution containing 340 mg of **38** in 1 mL of dry tetrahydrofuran was added, and the mixture was allowed to stir for another 14 h. The reaction mixture was filtered into a 1:1 mixture of ether and water. The two layers were separated, and the ether solution was washed with water and a saturated sodium chloride solution and was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography with a 1% ethyl acetate–hexane mixture as the eluent. The first component contained 87 mg (34%) of an oil, which was recrystallized from 95% ethanol to give a white solid, mp 62–63 °C, whose structure was assigned as *N*-methyl-2-[(phenylthio)methyl]pyrrole (**42**) on the basis of its spectroscopic properties: IR (KBr) 2980, 2920, 2360, 2340, 1600, 1490, 1380, 1350, 1195, 1150, and 725 cm^{-1}; NMR (CCl_4, 90 MHz) δ 3.60 (s, 3 H), 4.00 (s, 2 H), 5.70–5.83 (m, 2 H), 6.37–6.41 (m, 1 H), 7.07–7.23 (m, 5 H); UV (95% ethanol) 253 (ϵ 10 600) and 234 nm (ϵ 11 200); *m/e* 203 (M^+), 149, 105, and 94 (base). Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.44; N, 6.89; S, 15.78. Found: C, 70.70; H, 6.46; N, 6.87; S, 15.73.

Further elution of the column with a 20% ethyl acetate–hexane mixture gave 205 mg (54%) of a pale yellow oil whose structure was assigned as *N*-(2-phenyl-2-hydroxyethyl)-2-[(phenylthio)-methyl]pyrrole (**43**) on the basis of its spectroscopic properties: IR (neat) 3450, 3070, 2960, 1585, 1485, 1300, 1235, 1090, 850, 745, 700, and 620 cm^{-1}; UV (95% ethanol) 252 nm (ϵ 11 700); *m/e* 309 (M^+), 199 (base), 143, 110, 93, and 77. Anal. Calcd for $C_{19}H_{19}NOS$: C, 73.75; H, 6.19; N, 4.53; S, 10.36. Found: C, 73.41; H, 6.60; N, 4.61; S, 10.16.

Reaction of *N*-[(Trimethylsilyl)methyl]-2-[(tolylsulfonyl)methyl]pyrrole (44) with Tetrabutylammonium Fluoride in the Presence of Benzaldehyde. A mixture containing 1.0 g of *N*-[(trimethylsilyl)methyl]-2-[(dimethylamino)-methyl]pyrrole methiodide and 1.26 g of sodium *p*-tolyl sulfinate in 10 mL of dimethylformamide and 3 mL of water was heated at 55-60 °C for 2 days. After cooling to room temperature, the reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with water and a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the resulting oil was crystallized from 95% ethanol to give 0.82 g (90%) of *N*-[(trimethylsilyl)methyl]-2-[(tolylsulfonyl)methyl]pyrrole (**44**) as a white solid: mp 112–113 °C; IR ($CHCl_3$) 2970, 1608, 1480, 1400, 1320, 1305, 1150, 1090, 1070, 855, and 550 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.07 (s, 9 H), 2.40 (s, 3 H), 3.40 (s, 2 H), 4.30 (s, 2 H), 5.70 (dd, 1 H, J = 3.6 and 1.8 Hz), 5.95 (dd, 1 H, J = 3.6 and 2.7 Hz), 6.57 (dd, 1 H, J = 2.7 and 1.8 Hz), 7.25 (d, 2 H, J = 8.4 Hz), and 7.50 (d, 2 H, J = 8.4 Hz); UV (95% ethanol) 278 (ϵ 2270) and 224 nm (ϵ 19 500); *m/e* 321 (M^+) and 155 (base). Anal. Calcd for $C_{16}H_{23}NO_2SSi$: C, 59.77; H, 7.21; N, 4.36; S, 9.97. Found: C, 59.84; H, 7.24; N, 4.32; S, 9.97.

To a solution containing 600 mg of **44** and 0.19 mL of benzaldehyde in 25 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere at room temperature was added 2.8 mL of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran. After being stirred for 6 h, the reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with water and a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography with a 25% ethyl acetate–hexane mixture as the eluent. The first component isolated from the plate contained 151 mg (25%) of a white solid, mp 167–168 °C, whose structure was assigned as *N*-methyl-2-[1-(tolylsulfonyl)-2-phenylvinyl]pyrrole (**46**) on the basis of its spectroscopic properties: IR ($CHCl_3$) 2960, 2940, 1635, 1605, 1595, 1450, 1315, 1300, 1145, 1085, and 610 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.43 (s, 3 H), 3.01 (s, 3 H), 5.88 (dd, 1 H, J = 3.6 and 1.8 Hz), 6.13 (dd, 1 H, J = 3.6 and 2.7 Hz), 6.67 (dd, 1 H, J = 2.7 and 1.8 Hz), 6.92–7.40 (m, 7 H), 6.67 (dd, 1 H, J = 2.7 and 1.8 Hz), 6.92–7.40 (m, 7 H), 7.61 (d, 2 H, J = 7.5 Hz), and 8.07 (s, 1 H); UV (95% ethanol) 350 (ϵ 1600), 272 (ϵ 18 800), and 219 nm (ϵ 22 800); *m/e* 337 (M^+), 182 (base), and 149. Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.69; N, 4.16; S, 9.50. Found: C, 71.40; H, 5.89; N, 4.62; S, 9.72.

The second component isolated from the column contained 307 mg (66%) of a white solid, mp 156–157 °C, whose structure was assigned as *N*-methyl-2-[(tolylsulfonyl)methyl]pyrrole (**45**) on the basis of its spectral properties: IR ($CHCl_3$) 2960, 2940, 1600, 1595, 1400, 1340, 1300, 1150, 1085, 900, 870, and 640 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.42 (s, 3 H), 3.53 (s, 3 H), 4.32 (s, 2 H), 5.73 (dd, 1 H, J = 3.6 and 1.8 Hz), 5.97 (dd, 1 H, J = 3.6 and 2.7 Hz), 6.56 (dd, 1 H, J = 2.7 and 1.8 Hz), 7.23 (d, 2 H, J = 9.0 Hz), 7.52 (d, 2 H, J = 9.0 Hz); UV (95% ethanol) 263 (ϵ 2750) and 223 nm (ϵ 17 800); *m/e* 249 (M^+) and 94 (base). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.61; H, 6.07; N, 5.59; S, 12.91.

Preparation of Dimethyl 5-Methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 2,2-Dioxide (50). A 15.2-g sample of cysteine hydrochloride was dissolved in 40 mL of water along with 10 mL of a 37% aqueous formaldehyde solution. After being stirred overnight at room temperature, the reaction mixture was neutralized with 7.8 mL of pyridine, and after cooling in an ice bath, 9.54 g of 4-thiazolidinecarboxylic acid (**47**) was isolated as white needles (74% yield): mp 197–198 °C (lit.[53] mp 196–197 °C); IR (KBr) 3040, 2940, 2460, 1615, 1550, 1470, 1435, 1385, 1335, 1310, 1290, 1230, 1180, 1165, 1150, 1015, 985, 955, 915, 890, 865, 810, 755, and 630 cm^{-1}.

A 5.3-g sample of this acid and 8.0 mL of dimethyl acetylenedicarboxylate were dissolved in 40 mL of acetic anhydride, and the mixture was heated at reflux under nitrogen for 3 h. The solvent was removed under reduced pressure, and the crude oil was crystallized from methanol to give 6.3 g (62% yield) of dimethyl 5-methyl-1*H*,3*H*-pyrrolo[1,2-c]thiazole-6,7-dicarboxylate (**49**): mp 131–132 °C (lit.[54] mp 134–135 °C); IR (KBr) 2980, 2935, 2840, 1710, 1535, 1450, 1390, 1300, 1260, 1210, 1165, 1095, 950, 890, 805, and 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 4.93 (s, 2 H), 4.27 (s, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H), and 2.37 (s, 3 H).

A 2.0-g sample of this material was dissolved in 50 mL of dichloromethane, and the resulting solution was cooled to 0 °C. To this solution was added 4.0 g of *m*-chloroperbenzoic acid in one portion, and the reaction mixture was allowed to warm to room temperature. After being stirred for 3 h, the mixture was washed twice with a 10% sodium bisulfite solution and twice with a 10% sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 2.26 g of a white solid that was chromatographed on silica gel with dichloromethane as the eluent to give 2.12 g (99% yield) of dimethyl 5-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 2,2-dioxide (**50**) as a white crystalline solid: mp 166–167 °C; IR (KBr) 3010, 2960, 2945, 1725, 1710, 1595, 1540, 1455, 1420, 1335, 1315, 1260, 1235, 1210, 1180, 1145, 1105, 995, 830, and 790 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 4.90 (s, 2 H), 4.57 (s, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H), and 2.38 (s, 3 H); UV (methanol) 264 nm (ϵ 6700); HRMS calcd for $C_{11}H_{13}NSO_6$ 287.0463, found 287.0461.

All attempts to extrude sulfur dioxide from **50** either by heating or by irradiation failed to give characterizable material, even when

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the reaction was carried out in the presence of various trapping reagents.

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Registry No. **4**, 91003-52-0; **8**, 117985-28-1; **9**, 87-52-5; **10**, 117985-29-2; **11**, 100208-13-7; **12**, 100208-14-8; **13**, 100208-15-9; **14**, 117985-30-5; **15**, 117985-31-6; **16**, 117985-32-7; **18**, 117985-33-8; **19**, 117985-34-9; **20**, 117985-35-0; **21**, 117985-36-1; **22**, 117985-37-2; **23**, 117985-38-3; **24**, 117985-39-4; **32**, 117985-40-7; **34**, 5833-50-1; **35**, 117985-41-8; **36**, 118017-03-1; **37**, 117985-42-9; **38**, 117985-43-0; **42**, 117985-44-1; **43**, 117985-45-2; **44**, 117985-46-3; **45**, 113334-35-3; **46**, 117985-47-4; **47**, 19291-02-2; **49**, 75475-91-1; **50**, 107124-28-7; DMAD, 762-42-5; (*E*)-$PhSO_2CH{=}CHSO_2Ph$, 963-16-6; (*Z*)-$PhSO_2CH{=}CHSO_2Ph$, 963-15-5; PhCHO, 100-52-7; indole, 120-72-9; 3-indolecarboxaldehyde, 487-89-8; skatale, 83-34-1; *N*-phenylmaleimide, 941-69-5; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6; acrylonitrile, 107-13-1; maleic anhydride, 108-31-6; pyrrole-2-carboxaldehyde, 1003-29-8; *N*-[(trimethylsilyl)methyl]pyrrole-2-carboxaldehyde, 117985-48-5; *N*-[(trimethylsilyl)methyl]pyrrole-2-carbinal, 117985-49-6; *N*-[(trimethylsilyl)methyl]-2-[(dimethylamino)methyl]pyrrole, 117985-50-9; *N*-[(trimethylsilyl)methyl]-3-[(dimethylamino)methyl]-pyrrole, 117985-51-0; *N*-[(trimethylsilyl)methyl]-2-[(dimethylamino)methyl]pyrrole methiodide, 117985-52-1; 2-methyl-3-cyano-*N*-[(trimethylsilyl)methyl]pyrrole, 117985-53-2; sodium *p*-toluenesulfinate, 824-79-3; cysteine hydrochloride, 52-89-1.

Studies on the Structures of Imipenem, Dehydropeptidase I Hydrolyzed Imipenem, and Related Analogues

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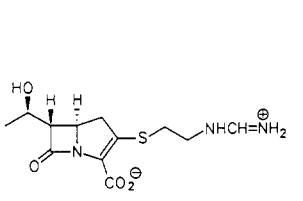
Dehydropeptidase I catalyzed hydrolysis of the carbapenem antibiotics imipenem (**1**) and the 3-methylthio analogue **14** was examined by spectroscopic methods. The principal product in both cases was a mixture of β-lactam ring-opened 1-pyrrolines epimeric at C3. A transient 2-pyrroline intermediate was observed by ^1H NMR in the methylthio carbapenem case. Nonenzymatic acid-catalyzed hydrolysis of each antibiotic under dilute conditions rapidly afforded a protonated 2-pyrroline product that isomerized to the diastereomeric 1-pyrroline mixture on neutralization. At higher carbapenem concentrations, the acid-catalyzed process also produced a diketopiperazine structure resulting from initial bimolecular attack of the carboxyl group of one carbapenem molecule on the β-lactam group of a second molecule. The analysis of the imipenem-derived products was complicated by the observation of side-chain formamidinium rotational isomers. Under mildly acidic conditions, the imipenem side-chain isomers were separable by high pressure liquid chromatography and the major form was identified as the *Z* isomer by X-ray crystallography.

Imipenem (**1**), the crystalline *N*-formimidoyl derivative[1,2] of thienamycin, is the first clinically available member of a new class of β-lactam antibiotics that possess the carbapenem ring system. Imipenem exhibits an extremely broad spectrum of activity[3] against gram-positive and gram-negative aerobic and anaerobic species, which is due in part to its high stability in the presence of β-lactamases[4] of both plasmid and chromosomal origin. Unlike the classical penicillins and cephalosporins, however, imipenem and related carbapenem antibiotics show varying degrees of susceptibility to the mammalian renal dipeptidase, dehydropeptidase I (DHP-I).[5] Localization of this enzyme in the kidney proximal tubule leads to poor urinary recovery of imipenem and requires coadministration of the DHP-I inhibitor[6] sodium cilastatin (**2**) to increase efficacy against urinary tract infections. The clinically used 1:1 combination of imipenem and sodium cilastatin is known as Primaxin.



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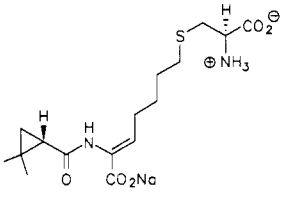

2

Our interest in the structure of DHP-I degraded imipenem arose from questions concerning the possible role of degradate in the toxicological evaluation of imipenem. Furthermore, it was of interest to determine whether enzymatically degraded antibiotic produced structures similar to those obtained by deliberate chemical hydrolysis or by

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