Synthesis of 3,9b-Dihydro-5*H*-pyrrolo[2,1-*a*]isoindoles and 3,5,6,10b-Tetrahydropyrrolo[2,1-*a*]isoquinolines with 1,3-Dipolar Cycloaddition Reactions.

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The title classes of compounds have been prepared using a sequence of two ring-forming reactions. Initial 1,3-dipolar cycloaddition with an azomethine ylide gave *N*-acylated 3-pyrrolines which were further elaborated to the target compounds by a tandem deprotection/cyclization reaction.

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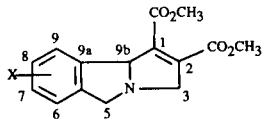
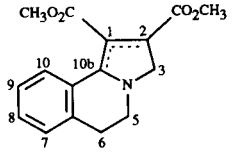
During the course of an ongoing investigation of 3-pyrrolines as pyrrole prodrugs in cancer chemotherapy [1], we required **1a**, **1b** and **2a** as intermediates (Figure 1). To the best of our knowledge, no synthetic methodology for the preparation of these (or closely related) heterocycles exist in the literature. Therefore, a synthetic investigation of these compounds using azomethine ylide cycloaddition and a tandem deprotection/cyclization reaction was undertaken. This report describes a synthetic approach to 3,9b-dihydro-5*H*-pyrrolo[2,1-*a*]isoindoles, **1**, and 3,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolines, **2**.



1a. X=H
b. X=7,8-Cl_2

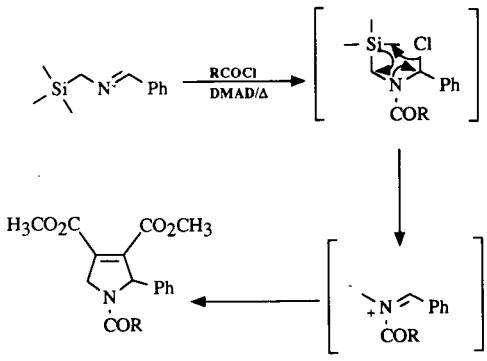


2a. 1,2-dehydro
b. 1,10b-dehydro

Figure 1

N-(Silylmethyl)imines are important sources for azomethine ylides which undergo 1,3-dipolar cycloaddition reactions in the presence of activated dipolarophiles [2,3]. Specifically, *N*-trimethylsilylmethylphenylmethanimine, dimethyl acetylenedicarboxylate (DMAD), and a variety of acyl chlorides undergo cycloaddition to give *N*-protected 3-pyrrolines in high yield [4,5] (Scheme 1). The formation of the 1,3-dipole is believed to proceed through a thermally-induced concerted (or stepwise) desilylation which originates from chloride elimination of a chloromethylamide intermediate. This reaction, followed by established methods for mild *N*-deprotection [6] and *N*-alkylation, offers an attractive route to *N*-alkyl-3-pyrrolines. From this, intramolecular *N*-alkylations provide for a new entry into a number of polycyclic 3-pyrrolines.

Scheme 1



Results and Discussion.

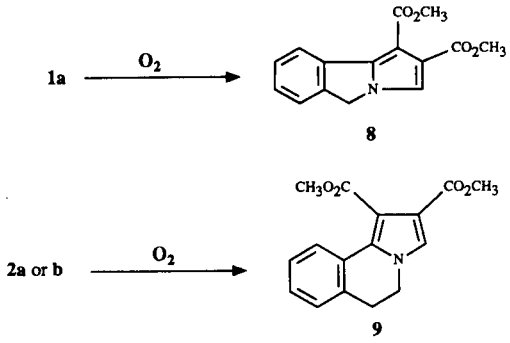
The syntheses of dihydropyrrolo[2,1-*a*]isoindoles, **1a** and **1b**, and the tetrahydropyrrolo[2,1-*a*]isoquinoline, **2a**, are outlined in Scheme 2. The appropriate 2-(ω-hydroxyalkyl)benzenemethanols were obtained by lithium aluminum hydride (LAH) reduction of phthalide to give **3a**, 4,5-dichlorophthalic acid to give **3b**, and homophthalic acid to give **3c**. Monosilylation using 1.1 equivalents of *t*-butyldimethylsilyl chloride (TBDMSCl), triethylamine (TEA), and catalytic 4-dimethylaminopyridine (DMAP), followed by pyridinium chlorochromate (PCC) oxidation furnished the desired aldehydes **4a-c**. The yield of monosilylation was lower for **3c** than for **3a,b** due to low selectivity between the two hydroxyl moieties of 2-(2-hydroxyethyl)benzenemethanol. The imines, **5a-c**, were prepared using a slightly modified method from the reported method described by Tsuge [7] using trimethylsilyl azide and triphenylphosphine. It was necessary to heat the reaction mixture at reflux for 60 hours to obtain the maximum yield. The product imines were always contaminated with up to 20% of the starting aldehydes [8]. The product yields were not improved when the molar equivalent ratios of triphenylphosphine and trimethylsilylmethyl azide to substrate were increased. Longer reaction times resulted in a gradual decomposition of the product already formed. The reported experimental conditions [7] (benzaldehyde, triphenylphosphine, trimethylsilylmethyl azide, benzene) required only one hour at reflux. Therefore, it appears that the steric barrier imposed by the *ortho* substituent of **4a-c** caused significant retardation of the reaction rate.

1,3-Dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) and benzyl chloroformate (CBZCl) appeared to be completely insensitive to steric bulk on the aromatic group and proceeded smoothly at room temperature to afford the racemic 3-pyrrolines, **6a-c**. The yields for the cycloaddition reactions were high, but the 3-pyrroline products, **6a-c**, were contaminated with a trace amount of what was apparently a polymer of the dipolarophile. The polymeric impurity was more easily removed after the next step so the contaminated product was used as such in the subsequent reaction. The 2'-chloroalkyl derivatives, **7a-c**, were prepared by acid hydrolysis of the *t*-butyldimethylsilyl-protected alcohol, followed by treatment with thionyl chloride. Cyclization, the final step of the sequence, was accomplished through trimethylsilyl iodide (TMSI) deprotection of the carbobenzyloxy (CBZ) group, then aqueous workup.

The dichlorophenyl intermediate, **7b**, was insoluble in acetonitrile and required dichloromethane as a cosolvent in the deprotection step. The change in the solvent polarity had a significant rate-reducing effect necessitating a threefold longer reaction time than for the deprotection of **7a** and **7c**. This observation is consistant with the hypothesized mechanism [9] where trimethylsilyl iodide complexes with acetonitrile ($[CH_3\text{-}C{\equiv}N^{+}\text{-}Si(CH_3)_3]I^{-}$) and facilitates deprotection.

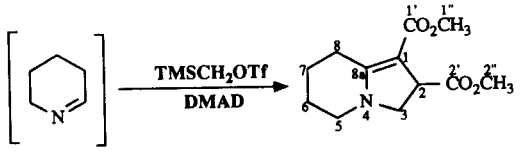
All of the tricyclic hydropyrroles were air sensitive, and if left exposed to air, would oxidize to the corresponding pyrroles within several hours (Scheme 3). The 3-pyrrolines, **1a** and **2**, were allowed to air oxidize and small quantities of **8** and **9** were isolated through ether extraction of a 5% aqueous hydrochloric acid solution of the partially oxidized mixtures. The pyrroles, **8** and **9**, are known [10,11] and the ^{1}H nmr spectra of the air oxidized compounds were identical to the corresponding reported spectra.

Scheme 3



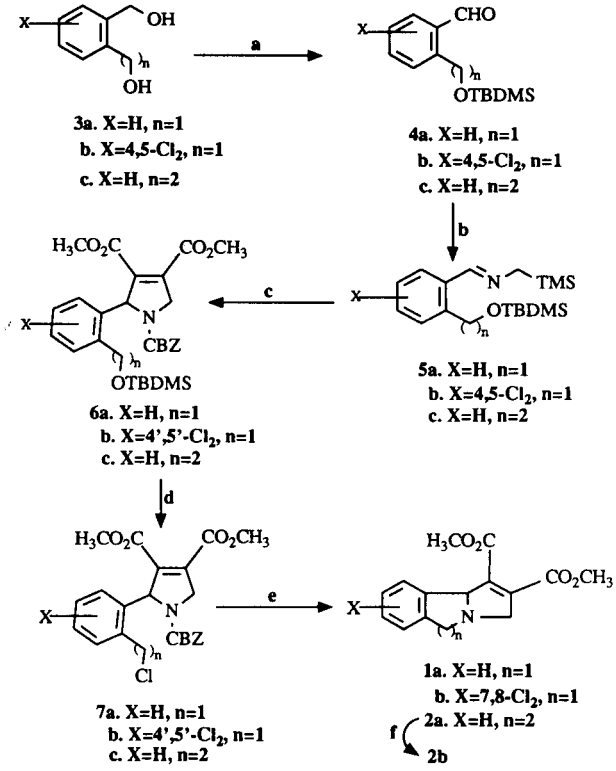
The tetrahydropyrrolo[2,1-*a*]isoquinoline, **2a**, was also thermally unstable, and existed only transiently as a 3-pyrroline before isomerizing into the 2-pyrroline, **2b**. This phenomenon has also been observed by Sekiya [12], who reported that the 1,3-dipolar cycloaddition product from 2,3,4,5-tetrahydropyridine, trimethylsilylmethyl trifluoromethanesulfonate, and dimethyl acetylenedicarboxylate gave exclusively the 1,8a-dehydroindolizidine isomer, **10**, rather than the expected 1,2-dehydroindolizidine (Scheme 4). The reported ^{13}C nmr spectra of **10** was useful in characterizing the vinylogous amide moiety in **2b**. The relevant ^{13}C nmr data for **2b** may be compared with **10** (in parenthesis): 95.3 (Cl, 94.9), 176 (Cl', 175.4), 52.4 (Cl'', 52.5), 55.3 (C2, 56.5), 167 (C2', 166.4), 50.8 (C2'', 50.1), 47 (C3, 47.1), 43.1 (C5, 44.9).

Scheme 4



The successful extension of *N*-(silylmethyl)imine syntheses presented here has provided for more elaborate 3-pyrroline cycloaddition adducts and, through cyclization, has ultimately resulted in tricyclic 3-pyrrolines. The cycloaddition was tolerant of steric crowding, which augers well for further synthetic endeavors with highly substituted azomethine ylides.

Scheme 2



Reagents: (a) (i) TBDMSCl (1.1 equiv), TEA, cat. DMAP; (ii) PCC, CH_2Cl_2. (b) $(CH_3)_3SiCH_2N_3$, PPh_3, Δ. (c) DMAD, CBZCl, THF, r.t. (d) (i) 5%aq HCl; (ii) $SOCl_2$, DMF. (e) (i) TMSI, CH_3CN; (ii) 5% aq HCl, then NH_4OH. (f) 25°

EXPERIMENTAL

Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover Unimelt apparatus. The ir spectra were determined with a Mattson Polaris FT-ir interferometer. The ^{1}H nmr spectra were determined with a Varian EM390 spectrometer. The ^{13}C nmr spectra were determined with a Varian Gemini 300 spectrometer. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

Dimethyl 3,9b-Dihydro-5*H*-pyrrolo[2,1-*a*]isoindole-1,2-dicarboxylate (**1a**).

Trimethylsilyl iodide (8 ml, 0.0564 mole) was added in one portion to a stirred solution of **7a** (12.5 g, 0.0282 mole) and acetonitrile (150 ml) at -10° (acetone/ice bath) under a positive pressure of argon. The resulting organge-red solution was allowed to warm to room temperature, then stirred for *ca.* 1 hour. The reaction mixture was cooled (ice bath) and 5% aqueous hydrochloric acid (100 ml) was added portionwise. Most of the actonitrile was evaporated, and the aqueous residue was diluted with water (100 ml) and washed with ether (3 × 100 ml). The acidic aqueous fraction was basified to *p*H 9 with aqueous ammonia, then extracted with dichloromethane (3 × 200 ml), dried (sodium sulfate), and concentrated *in vacuo* to give 6.3 g (82%) of pale yellow gummy solid; ir (neat): 3029, 2952, 2856, 1731, 1714, 1658, 1434, 1286 cm^{-1}; ^{1}H nmr (deuteriochloroform, TMS) δ 7.25 (m, 4H), 5.65 (m, 1H), 4.2-3.8 (broad m, 4H), 3.85 (s, 3H), 3.75 (s, 3H).

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.69; H, 5.63; N, 5.03.

Dimethyl 3,9b-Dihydro-7,8-dichloro-5*H*-pyrrolo[2,1-*a*]isoindole-1,2-dicarboxylate (**1b**).

Trimethylsilyl iodide (4.5 ml, 0.0312 mole) was added in one portion to a stirred solution of **7b** (8 g, 0.156 mole), acetonitrile (15 ml) and dichloromethane (75 ml) at -10° (acetone/ice bath) under a positive pressure of argon. The resulting red solution was allowed to warm to room temperature, then stirred for 3 hours. The reaction mixture was cooled (ice bath), 5% aqueous hydrochloric acid (60 ml) was added portionwise. Most of the organic solvent was evaporated and 5% hydrochloric acid (200 ml) was added to the aqueous residue. This mixture was then washed with ether (3 × 75 ml). The acidic aqueous fraction was basified to *p*H 9 with aqueous ammonia, then extracted with dichloromethane (3 × 200 ml), dried (sodium sulfate), and concentrated *in vacuo* to give a white solid which was crystallized from dichloromethane-hexanes to give **1b** as a white granular solid (3.8 g, 72%), mp 119-121°; ir (chloroform): 3030, 2954, 2862, 1721, 1657, 1437, 1277 cm^{-1}; ^{1}H nmr (deuteriochloroform, TMS) δ 7.45 (s, 1H), 7.25 (s, 1H), 5.55 (m, 1H), 4.5-3.7 (broad m, 4H), 3.85, (s, 3H), 3.75 (s, 3H).

Anal. Calcd. for $C_{15}H_{13}Cl_2NO_4$: C, 52.65; H, 3.83; N, 4.09. Found: C, 52.71; H, 3.86; N, 4.02.

Dimethyl 2,3,5,6-Tetrahydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**2b**).

Trimethylsilyl iodide (0.4 ml, 0.0028 mole) was added in one portion to a stirred solution of **7c** (0.64 g, 0.0014 mole) and acetonitrile (15 ml) at -10° (acetone/ice bath) under a positive pressure of argon. The resulting orange-red solution was allowed to warm to room temperature, then stirred for 15 minutes. The reaction mixture was cooled (ice bath) and 5% aqueous hydrochloric acid (5 ml) was added. The acetonitrile was removed *in vacuo*, the acidic aqueous residue was diluted with water (50 ml), washed with ether (3 × 25 ml), then basified to *p*H 9 with aqueous ammonia. The basic mixture, which immediately developed a yellow hue, was extracted with dichloromethane, the organic solution was dried (sodium sulfate) and concentrated *in vacuo* to give a bright yellow oil which was chromatographed (silica gel eluted with 1:1, ethyl acetate-hexanes) to give **2b** as an intensely fluorescent yellow gum (0.24 g, 60%); ir (neat): 3070, 2948, 2839, 1737, 1680, 1581, 1433, 1327, 1269, 1203 cm^{-1}; ^{1}H nmr (deuteriochloroform, TMS) δ 8.85 (m, 1H), 7.3 (m, 3H), 4.0 (m, 2H), 3.8 (m, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.2 (m, 2H), 2.9 (m, 2H); ^{1}H nmr (deuteriochloroform, deuteriotrifluoroacetic acid, TMS): δ 7.8 (m, 2H), 7.45 (m, 2H), 4.65 (m, 2H), 4.1 (m, 4H), 3.8 (s, 6H), 3.4 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 176.06, 166.85, 157.32 (C10b), 137.09, 132.0, 131.48, 127.93, 126.92, 95.28 (Cl), 55.32 (C2), 52.43, 50.85, 47.11 (C3), 43.99 (C5), 30.16 (C6).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.75; H, 5.98; N, 4.79.

Benzene-1,2-dimethanol (**3a**).

A solution of phthalide (30 g, 0.224 mole) and tetrahydrofuran (150 ml) was added dropwise to a stirred ice-cold suspension of lithium aluminum hydride (13 g, 0.336 mole) and ether (250 ml) under a positive pressure of argon. The suspension was stirred for 16 hours at room temperature. The reaction was cooled (ice bath) and quenched with the sequential dropwise addition of water (13 ml), 15% sodium hydroxide solution (13 ml), and water (39 ml), then stirred at room temperature for 3 hours. The oxidized aluminum salts were removed by filtration and washed with ethyl acetate. The filtrates were concentrated *in vacuo* to give an oil which was shaken vigorously with benzene (200 ml) until a white precipitate formed. The crystalline product was filtered and dried to give **3a** as a white crystalline solid (26 g, 85%), mp 62-63° (lit [13] mp 63-65°); ir (chloroform): 3368, 3010, 2963, 2882, 1454, 1426, 1234, 1185, 1008 cm^{-1}; ^{1}H nmr (deuteriochloroform, TMS): δ 7.2 (s, 4H), 4.5 (s, 4H), 3.5 (s, 2H).

4,5-Dichlorobenzene-1,2-dimethanol (**3b**).

A solution of 4,5-dichlorophthalic acid (20 g, 0.0851 mole) and tetrahydrofuran (150 ml) was added dropwise to a stirred ice-cold suspension of lithium aluminum hydride (6.5 g 0.17 mole) and ether (175 ml) under a positive pressure of argon. The suspension was stirred for 16 hours at room temperature. The reaction mixture was cooled (ice bath) and quenched with the sequential dropwise addition of water (7 ml), 15% sodium hydroxide solution (7 ml), and water (20 ml), then stirred at room temperature for 3 hours. The aluminum salts were removed by filtration and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give **3b** as a white solid (14.6 g, 83%), mp 139-141° (lit [14] 137-139°); ir (potassium bromide): 3294, 2908, 2851, 1444, 1212 cm^{-1}; ^{1}H nmr (deuteriochloroform, TMS) δ 7.5 (s, 2H), 5.2 (t, J = 6 Hz, 2H), 4.4 (d, J = 6 Hz, 4 H).

2-(2-Hydroxyethyl)benzenemethanol (**3c**).

The diol **3c** was obtained (by the method described for **3a**) from homophthalic acid as a thick opaque oil (92%); ir (neat): 3306, 3066, 3020, 2943, 2880, 1451, 1213 cm^{-1}; ^{1}H nmr (deuteriochloroform, TMS): δ 7.25 (sharp m, 4H), 4.5 (s, 2H), 4.25

(s, 2H), 3.65 (t, J = 6 Hz, 2H), 2.8 (t, J = 6 Hz, 2H).

2-(*t*-Butyldimethylsilyloxymethyl)benzaldehyde (**4a**).

t-Butyldimethylsilyl chloride (24 g, 0.16 mole) was added in one portion to a stirred solution of **3a** (20 g, 0.145 mole), triethylamine (60 ml, 0.435 mole), 4-dimethylaminopyridine (0.1 g), and dichloromethane (250 ml) at room temperature under a positive pressure of argon. A white cloudy precipitate formed after 1 hour of stirring. The mixture was stirred for 16 hours, the solvent was evaporated, and the off-white solid residue was dissolved in ether (300 ml) and swirled vigorously. The ammonium salts were removed by filtration and the ether filtrate was concentated *in vacuo* to give an oily residue. An analytical sample was prepared by chromatography (silica gel eluted with 9:1, ethyl acetate-hexanes) to give the monosilyl derivative of **3a** as a clear oil; ir (neat): 3384, 2955, 1857, 1462, 1256 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 7.35 (sharp m, 4H), 4.8 (s, 2H), 4.65 (d, J = 6 Hz, 2H), 3.15 (t, J = 6 Hz, 1H), 0.9 (s, 9H), 0.15 (s, 6H).

Anal. Calcd. for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.73; H, 9.61.

The crude monosilyl ether was dissolved in dichloromethane (400 ml), and pyridinium chlorochromate (62.5 g, 0.29 mole) was added portionwise. The resulting black tarry mixture was stirred for 2 hours, then suction-filtered through a pad of flash silica gel and washed repeatedly with dichloromethane (1 liter total volume). The combined filtrates were concentrated to an oil under reduced pressure and chromatographed (silica gel eluted with 9:1, ethyl acetate-hexanes) to give **4a** as a clear oil (32.6 g, 90%); ir (neat): 2955, 2856, 1695, 1602, 1463, 1256 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 10.2 (s, 1H), 7.9-7.3 (broad m, 4H), 5.2 (s, 2H), 0.95 (s, 9H), 0.15 (s, 6H).

Anal. Calcd. for $C_{14}H_{22}O_2Si$: C, 67.15; H, 8.86. Found: C, 67.25; H, 8.90.

2-(*t*-Butyldimethylsilyloxymethyl)-4,5-dichlorobenzaldehyde (**4b**).

The method used for **4a** first gave the monosilyl derivative of **3b** as a clear oil; ir (neat): 3350, 2954, 2883, 2857, 1462, 1257 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 7.5 (s, 1H), 7.45 (s, 1H), 4.75 (s, 2H), 4.6 (d, J = 6 Hz, 2H), 2.8 (t, J = 6 Hz, 1H), 0.9 (s, 9H), 0.15 (s, 6H).

Anal. Calcd. for $C_{14}H_{22}Cl_2O_2Si$: C, 52.33; H, 6.90. Found: C, 52.36; H, 6.93.

The yield for the aldehyde, **4b**, was 85% (clear oil); ir (neat): 2954, 2930, 2885, 2856, 1702, 1549, 1258, 1205 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 10.1 (s, 1H), 7.85 (s, 2H), 5.05 (s, 2H), 0.9 (s, 9H), 0.15 (s, 6H).

Anal. Calcd. for $C_{14}H_{20}Cl_2O_2Si$: C, 52.66; H, 6.31. Found: C, 52.50; H, 6.34.

2-[2-(*t*-Butyldimethylsilyloxy)ethyl]benzaldehyde (**4c**).

2-[2-(*t*-Butyldimethylsilyloxy)ethyl]benzenemethanol was obtained (by the method described for **4a**) as a clear oil (36%). It was separated from a mixture of the other monosilyl ether and the disilyl ether by chromatography (silica gel eluted with 9:1, ethyl acetate-hexanes); ir (neat): 3424, 2954, 2929, 2857, 1471, 1255 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 7.3 (sharp m, 4H), 4.7 (d, J = 6 Hz, 2H), 3.95 (t, J = 6 Hz, 2H), 3.45 (t, J = 6 Hz, 1H), 3.0 (t, J = 6 Hz, 2H), 0.85 (s, 9H), 0.05 (s, 6H).

Anal. Calcd. for $C_{15}H_{26}O_2Si$: C, 67.61; H, 9.84. Found: C, 67.59; H, 9.85.

Compound **4c** was obtained (by the method described for **4a**) as a clear oil (81%); ir (neat): 3069, 2955, 2930, 2857, 2734, 1700, 1600, 1459, 1255 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 10.3 (s, 1H), 7.8 (m, 1H), 7.4 (m, 3H), 3.8 (t, J = 7 Hz, 2H), 3.2 (t, J = 7 Hz, 2H), 0.8 (s, 9H), -0.1 (s, 6H).

Anal. Calcd. for $C_{15}H_{24}O_2Si$: C, 68.13; H, 9.15. Found: C, 68.22; H, 9.18.

Trimethylsilylmethyl Azide.

A mixture of trimethylsilylmethyl chloride (56 ml, 0.4 mole), sodium azide (29 g, 0.44 mole), and tetramethylene sulfone (200 ml) was stirred at 70-80° for 16 hours. The product azide was distilled from the reaction mixture at 60-64°, 80 mm Hg (lit [15] 58-61°, 80 mm Hg) as a clear oil (42.1 g, 81%); ir (neat): 2959, 2898, 2186, 2094, 1410, 1289, 1261 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 2.65 (s, 2H), 0.00 (s, 9H).

N-Trimethylsilylmethyl-[2-(*t*-butyldimethylsilyloxymethyl)phenyl]-methanimine (**5a**).

Trimethylsilylmethyl azide (15.5 g, 0.12 mole) was added portionwise to a stirred solution of triphenylphosphine (21 g, 0.08 mole) and benzene (300 ml, distilled from calcium hydride) at 25° under a positive pressure of argon. The reaction mixture was stirred at reflux for 1 hour (or until no triphenylphosphine was detectable by thin layer chromatography). The reaction was allowed to cool to room temperature, then a solution of **4a** (10 g, 0.04 mole) in benzene (50 ml) was added portionwise. The reaction was returned to reflux for *ca.* 60 hours, then cooled to room temperature and concentrated *in vacuo* to give a white solid. The product mixture was vigorously swirled with hexane (500 ml), then filtered, and the solid washed further with hexane (500 ml). The filtrate was reduced to an oil *in vacuo* and passed through a short flash column (230-400 mesh, 7 × 10 cm, eluted with 9:1, ethyl acetate-hexane) to give **5a** as a clear oil, 12.3 g (contaminated with approximately 20% **4a**), that was used without further purification in the next reaction.

Dimethyl 2,5-Dihydro-1-benzyloxycarbonyl-2-[2-(*t*-butyldimethylsilyloxymethyl)phenyl]pyrrole-3,4-dicarboxylate (**6a**).

A solution of **5a** (12.3 g, 0.0366 mole) in tetrahydrofuran (200 ml, distilled from sodium metal) was added dropwise (3 drops per 2 seconds) to a stirred solution of dimethyl acetylenedicarboxylate (7 ml, 0.0548 mole), benzyl chloroformate (8 ml, 0.0548 mole), and tetrahydrofuran (300 ml) at 25° under a positive pressure of argon, then stirred an additional 12 hours. The resulting pale yellow solution was concentrated to an oil *in vacuo* and chromatographed (silica gel eluted with 4:1, ethyl acetate-hexane) to give **6a** as a clear viscous oil (14 g, 71%); ir (neat): 2954, 2929, 2856, 1721, 1662, 1411, 1282 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 7.7-6.7 (broad m, 9H), 6.1 (m, 1H), 5.2-4.5 (broad m, 6H), 3.8 (s, 3H), 3.6 (s, 3H), 0.9 (s, 9H), 0.15 (s, 6H).

Anal. Calcd. for $C_{29}H_{37}NO_7Si$: C, 64.54; H, 6.91; N, 2.60. Found: C, 64.48; H, 6.94; N, 2.59.

Dimethyl 2,5-Dihydro-1-benzyloxycarbonyl-2-[2-(*t*-butyldimethylsilyloxymethyl)-4,5-dichlorophenyl]pyrrole-3,4-dicarboxylate (**6b**).

The crude *N*-(silylmethyl)imine, **5b**, was prepared from **4b** as described for **5a**. The method used for **6a** gave the 3-pyrroline, **6b**, as a white solid (96%), mp 91-92°; ir (chloroform): 3035, 2955, 2884, 2857, 1725, 1662, 1438, 1413, 1283, 1208, 1096 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 7.7 (m, 1H), 7.35 (m,

5H), 6.95 (m, 1H), 5.95 (m, 1H), 5.2-4.7 (broad m, 6H), 3.95 (s, 3H), 3.75 (s, 3H), 1.05 (s, 9H), 0.15, 0.25 (two s, 6H total).

Dimethyl 2,5-Dihydro-1-benzyloxycarbonyl-2-[2-[2-(*t*-butyldimethylsilyloxyethyl)phenyl]]pyrrole-3,4-dicarboxylate (**6c**).

The crude *N*-(silylmethyl)imine, **5c**, was prepared from **4c** as described for **5a**. The method used for **6a** gave the 3-pyrroline, **6c**, from **5c** as a clear oil (77%); ir (neat): 2954, 2856, 1721, 1662, 1431, 1207 cm^{-1}; ^1H nmr (deuteriochloroform, TMS external): δ 7.4-6.7 (broad m, 9H), 6.15 (m, 1H), 5.0 (t, J = 9 Hz, 2H), 4.7 (d, J = 5 Hz, 2H), 3.85 (m, 2H), 3.8 (s, 3H), 3.65 (s, 3H), 2.9 (m, 2H), 0.9 (s, 9H), 0.05 (s, 6H).

Dimethyl 2,5-Dihydro-1-benzyloxycarbonyl-2-(2-chloromethylphenyl)pyrrole-3,4-dicarboxylate (**7a**).

A solution of **6a** (25 g, 0.046 mole), tetrahydrofuran (50 ml), ethanol (50 ml), and 5% hydrochloric acid solution (100 ml) was stirred at room temperature for 2 hours. The organic solvents were evaporated, the cloudy aqueous residue was diluted with water (100 ml) and extracted with dichloromethane (3 × 200 ml). The organic solution was dried (sodium sulfate) and concentrated *in vacuo*. The residual oil was dissolved in dimethylformamide (150 ml) and cooled to 5° (ice bath) and thionyl chloride (7 ml, 0.093 mole) was added in one portion to the cold, stirred solution. The mixture was allowed to warm to room temperature and stirred an additional 0.5 hour. The reaction mixture was then poured into a large (1*l*) beaker two-thirds full of crushed ice and allowed to melt and stand for approximately 16 hours. The aqueous mixture was carefully decanted into a separatory funnel leaving a viscous residue in the beaker. The aqueous mixture was extracted with ether (4 × 150 ml) and the combined ether extracts were mixed with the residue in the beaker and dried (sodium sulfate), then reduced to an oil *in vacuo*, and chromatographed (silica gel eluted with 7:3, ethyl acetate-hexane) to give **7a** as a clear oil (12.5 g, 61%); ir (neat): 3031, 2954, 1746, 1721, 1666, 1440, 1275 cm^{-1}; ^1H nmr (deuteriochloroform, TMS): δ 7.5-6.8 (broad m, 9H), 6.2 (m, 1H), 4.95 (m, 2H), 4.8 (m, 3H), 4.2 (m, 1H), 3.8 (s, 3H), 3.6 (s, 3H).

Anal. Calcd. for $C_{23}H_{22}ClNO_6$: C, 62.23; H, 5.00; N, 3.16. Found: C, 61.98; H, 5.04; N, 3.13.

Dimethyl 2,5-Dihydro-1-benzyloxycarbonyl-2-(2-chloromethyl-4,5-dichlorophenyl)pyrrole-3,4-dicarboxylate (**7b**).

The method used for **7a** gave the 3-pyrroline, **7b**, from **6b** as a white prismatic crystalline solid (95%, from ethyl acetate-hexane), mp 133-135°; ir (chloroform): 3032, 3012, 2955, 1725, 1664, 1438, 1283 cm^{-1}; ^1H nmr (deuteriochloroform, TMS): δ 7.6-6.8 (broad m, 7H), 6.1 (m, 1H), 5.2-4.0 (broad m, 7H), 3.8 (s, 3H), 3.6 (s, 3H).

Anal. Calcd. for $C_{23}H_{20}Cl_3NO_6$: C, 53.87; H, 3.93; N, 2.73. Found: C, 54.06; H, 3.97; N, 2.68.

Dimethyl 2,5-Dihydro-1-benzyloxycarbonyl-2-[2-(2-chloroethyl)-phenyl]pyrrole-3,4-dicarboxylate (**7c**).

The method used for **7a** gave the 3-pyrroline, **7c**, from **6c** as a clear oil (67%); ir (neat): 3030, 2952, 1741, 1718, 1707, 1663, 1438, 1283, 1205 cm^{-1}; ^1H nmr (deuteriochloroform, TMS): δ 7.4-6.8 (broad m, 9H), 6.1 (m, 1H), 5.0 (m, 2H), 4.7 (d, J = 5 Hz, 2H), 3.85 (m, 1H), 3.8 (s, 3H), 3.6 (s, 3H), 3.4 (m, 2H), 3.0 (m, 1H).

Anal. Calcd. for $C_{24}H_{24}ClNO_6$: C, 62.95; H, 5.28; N, 3.06. Found: C, 62.82; H, 5.35; N, 3.02.

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