Biochemicals, Inc., Milwaukee, WI; 177 mg/mL in the above pH 8.0 buffer) was added to the chamber and allowed to equilibrate for 1.5 min, and then the endogenous oxygen consumption rate was determined for 1 min. After 0.5 min, 0.2 mL of the glycoside solution that was 2.0 mM in 80% polyethylene glycol 200 (PG 200, J. T. Baker Chemical Co., Phillipsburg, NJ) in water was added and allowed to equilibrate for 1 min, and then the rate of oxygen consumption was again measured for 1 min.

Antitumor Assays. Leukemia L1210 cells are grown in McCoy's 5A medium supplemented with glutamine, HCO_3^-, antibiotics, and 10% heat-inactivated horse serum at 37 °C in a humidified atmosphere of 95:5 air/CO_2. Cells are dispensed at 10^5 cells/mL, and drug is added at 10, 1, 0.1, or 0.01 μg/mL final concentration. Cell concentration is measured 72 h later using a Coulter Counter, and the ID_{50} value (the theoretical drug concentration required to inhibit cell growth by 50%) is determined.

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Registry No. 1, 104112-62-1; 2, 104070-16-8; 3, 104070-17-9; 4, 104070-18-0; 5, 104112-63-2; 6, 104070-19-1; 7, 104070-20-4; 8, 104070-21-5; 9, 104070-22-6; 15, 104070-23-7; 16, 104112-64-3; 17, 104070-24-8; 18, 104070-25-9; α-19, 104070-26-0; β-19, 104112-65-4; α-20, 104070-27-1; β-20, 104112-66-5; α-21, 104070-28-2; β-21, 104112-67-6; α-22, 104089-95-4; α-23, 104070-29-3; 3,4,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucopyranosyl bromide, 104070-30-6; 4-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-3-(trifluoroacetamido)-α-L-lyxopyranosyl chloride, 78548-38-6.

Synthesis and Antineoplastic Activity of Bis[[[(alkylamino)carbonyl]oxy]methyl]-Substituted 3-Pyrrolines as Prodrugs of Tumor Inhibitory Pyrrole Bis(carbamates)[1]

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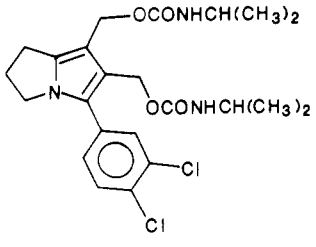
Received April 10, 1986

A series of bis[(carbamoyloxy)methyl]pyrrolines **2**–**4** were synthesized from either the appropriate α-silylated iminium salt, or an aziridine, or a 2*H*-azirine in a sequence involving 1,3-dipolar cycloaddition reactions. The antineoplastic activities of the pyrrolines were compared to the corresponding pyrroles. The C-2 *gem*-dimethyl-substituted pyrroline, **4**, which cannot be converted to the pyrrole in vivo, was inactive. The activity of the 2-phenyl-substituted pyrrolines **3** was markedly dependent on the nature of the phenyl substituent, although the corresponding phenylpyrroles all showed comparable activity. The differences in the activities of the pyrrolines **3** may be due to the rate of metabolic conversion of the pyrroline to the pyrrole. Electron-withdrawing substituents on the phenyl ring appear to retard this process.

The pyrrolizine **1** (NSC 278214) has been shown to possess significant reproducible activity against a broad range of experimental murine neoplasias and human tumor xenografts in nude athymic mice.[2] The compound was



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a potential candidate for human clinical trials, but one major problem impeded progress to human studies: the pyrrolizine **1** was very lipophilic (water insoluble) and was unstable in aqueous mixtures. This has led to very major problems in the development of an effective formulation of the agent.[3] One water-soluble prodrug of **1** was prepared, but the compound was unstable in aqueous solution and inactive in murine P388 lymphocytic leukemia test systems.[2c]

We have found that bis(carbamate) derivatives of bis(hydroxymethyl)-substituted pyrroles,[4] pyrrolizines,[5] and polycyclic benz-fused pyrroles[6] possess significant reproducible antineoplastic activity. The rationale employed

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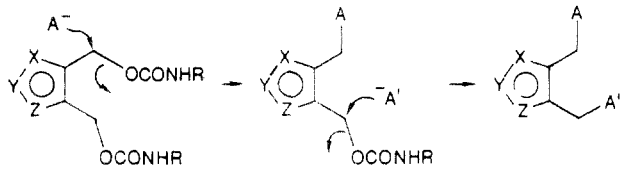
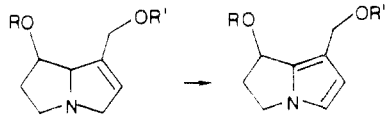
in the design of these agents was as follows: two potentially reactive electrophilic centers (*O*-alkyl ester cleavage) were incorporated on the heterocyclic ring, and the heterocycle was substituted with additional substituents to modulate the reactivity of the electrophilic centers:



The resulting compounds could act as bifunctional electrophilic agents. Other heterocyclic bis(carbamates) have been reported and, consistent with this design concept, were inactive and unreactive as bifunctional electrophiles.[7]

The problem with a number of the earlier members in this class (which we call "acylated vinylogous carbinolamines") is that the compounds, while very active, are very insoluble in water and unstable in aqueous mixtures. This report describes one aspect of our continuing effort to develop prodrugs of "acylated vinylogous carbinolamines" that possess antineoplastic activity, water solubility, and stability in aqueous mixtures.

Dihydropyrroles are known to undergo conversion to the corresponding pyrrole in vivo. An example of this is the conversion of pyrrolizidine alkaloids into the 2,3-dihydro-1*H*-pyrrolizine metabolites:[8]



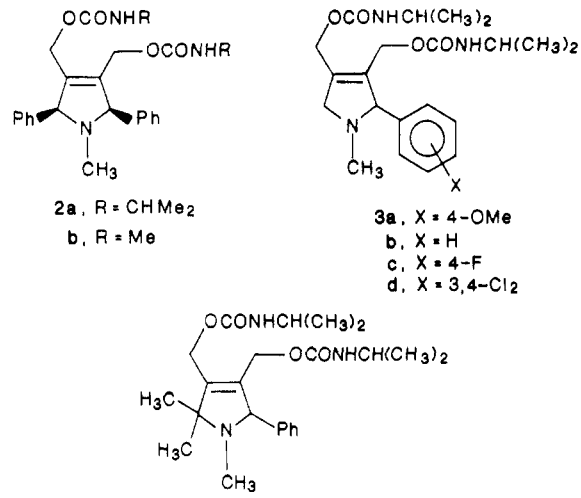
Furthermore, while the ester moieties in the pyrrole metabolites are very reactive (alkyl–oxygen fission), the ester moieties in the parent alkaloids are relatively unreactive.[9] Finally, the ring nitrogen in the 3-pyrrolines will be sufficiently basic to enable the drug to be formulated as a water-soluble salt.

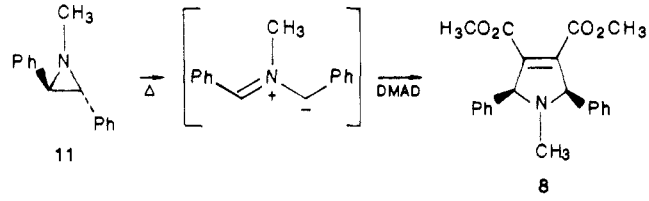
The initial targets selected for synthesis were compounds **2–4**. The phenyl-substituted 3-pyrrolines represented by **2** and **3** can be converted to the corresponding pyrroles whereas **4** cannot. Furthermore, the X substituent on **3** is expected to serve two roles: first, the X substituent is expected to influence the rate of conversion of the 3-pyrroline to the pyrrole; second, the X substituent is expected to influence the activity and toxicity of the pyrrole once it is generated in vivo.

Chemistry

The bis(carbamates) **2–4** were prepared from the corresponding diols **5–7** by treatment with the appropriate isocyanate in the presence of a catalytic amount of dibutyltin diacetate. The diols **5–7** were prepared from the corresponding diesters **8–10**.

The reduction of the diesters **8–10** gave the diols **5–7** in yields that varied from 20 to 57% depending on the diester reduced. The diols were isolated following a chromatographic separation from a mixture of over- and under-reduced products. Diisobutylaluminum hydride was found to be the reducing agent of choice. Sodium borohydride based reagents typically gave over-reduction (for example, sodium borohydride–ethanedithiol[10] gave pyrrolidinediol exclusively). Reagents based on lithium aluminum hydride, e.g. lithium dimethoxyaluminum dihydride, gave complex product mixtures. The diester **8** was prepared in 69% yield in a 1,3-dipolar cycloaddition reaction between DMAD (dimethyl acetylenedicarboxylate) and the stabilized azomethine ylide generated from the thermal (conrotatory) opening of the aziridine **11**.[11] The aziridine





was prepared from *erythro*-1,2-diphenyl-2-(methylamino)ethanol[12] by treatment with triphenylphosphine–carbon tetrachloride–triethylamine.[13] The amino alcohol was obtained in 85% yield from *trans*-stilbene oxide by treatment (reflux 15 h) with a methylamine-saturated ethanol–water (85:15) solution (the yield of the amino alcohol was lower (50–60%) when the aminolysis was carried out in pure water[12a]).

The photolysis or thermolysis of aziridines is best suited for the generation of stabilized azomethine ylides. The ylides required for the synthesis of the diesters **9** are only stabilized by a single phenyl group, and although the thermolysis and photolysis of 1-methyl-2-phenylaziridine in the presence of methyl acrylate and acrylonitrile have been reported to give adducts in low yields,[14] our attempts to thermolyze 1-methyl-2-phenylaziridine in the presence of DMAD failed to yield any 3-pyrroline.

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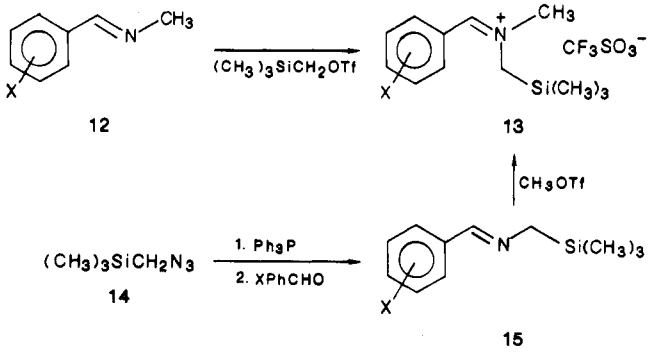
Table I. Yields[a] for the Synthesis of the Pyrrolines **9** Using the (Trimethylsilyl)methyl Trifluoromethanesulfonate Route (Route A) and the Iminophosphorane Route (Route B)

	% yield			% yield	
pyrroline	route A	route B	pyrroline	route A	route B
9a	33	35	**9c**	47	62
9b	50	45	**9d**	51	50

[a] Yields of isolated product were based on the starting imines **12** and **15** and were reproduced several times.

Unstabilized azomethine ylides can be prepared by fluoride-mediated desilylation of (trimethylsilyl)methyl iminium salts.[15] The requisite α-silylated iminium compounds **13** were prepared either by alkylation of a substituted *N*-benzylidenemethylamines **12** with (trimethylsilyl)methyl trifluoromethanesulfonate or by alkylation of substituted *N*-(benzylidene)-*N*-(trimethylsilyl)methylamines **15** with methyl trifluoromethanesulfonate. The imines **12** were prepared by condensation of the appropriate benzaldehyde with methylamine. (Trimethylsilyl)methyl trifluoromethanesulfonate was prepared from the alcohol by treatment with trifluoromethanesulfonic anhydride in dichloromethane followed by treatment with water and then distillation. Higher yields resulted when dichloromethane was used instead of carbon tetrachloride[16] as a solvent.



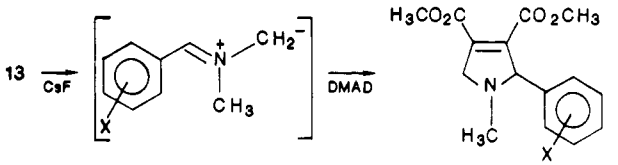
The α-silylated imines **15** were obtained by treatment of the appropriate benzaldehyde with the iminophosphorane (prepared from (trimethylsilyl)methyl azide[17] and triphenylphosphine).[18] Trimethylsilyl azide was prepared by treatment of (trimethylsilyl)methyl chloride with sodium azide in DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone];[19] the use of DMPU as a solvent proved to be an excellent alternative to the toxic, carcinogenic HMPA that had been used previously.[17] Lower boiling solvents such as DMF and Me_2SO tended to codistill with the azide.

Table II. NBP Alkylating Assay[a]

compd	k' (abs/time)	compd	k' (abs/time)
19a	2.31×10^{-1}	**20**	1.68
19b	9.35×10^{-2}	**21a**	4.49×10^{-1}
19c	5.16×10^{-2}	**21d**	1.54×10^{-3}
19d	6.05×10^{-3}		

[a] Rate constants were calculated by linear regression analysis, and the correlation coefficients were >0.99 for all cases.

The alkylation of either **12** or **15** and the subsequent desilylation–cycloaddition were carried out as a one-pot synthesis. The reactions were very sensitive to water so the hygroscopic cesium fluoride must be handled in a drybox. Overall, the iminophosphorane route was more attractive because of the lower cost of starting materials and the relative overall ease of the procedure. The yields obtained using the two methods are summarized in Table I. The yield of the *p*-methoxyphenyl compound **9a** was lowest in both routes.



9a, X = 4-OMe
b, X = H
c, X = 4-F
d, X = 3,4-Cl_2

The diester **10** is a 3-pyrroline with a tetrasubstituted carbon. The compound was prepared from the 2*H*-azirine **16**: photolysis of **16** gave the nitrile ylide[20] that was trapped with DMAD to give the isopyrrole **17**.[21] Methylation of **17** (dimethyl sulfate) followed by reduction (sodium borohydride)[22] gave **10**. The 2*H*-azirine **16** was prepared from isobutyrophenone in three steps. Treatment of isobutyrophenone with dimethylhydrazine[23a] at 120 °C (steel bomb) in the presence of molecular sieves and a catalytic[23b] amount of glacial acetic acid gave the hydrazone (the reaction was observed to be 80% complete after 24 h but longer reaction times or higher temperatures did not afford any improvement). Methylation of the hydrazone gave the methiodide (it was essential that the hydrazone be purified prior to the methylation), and

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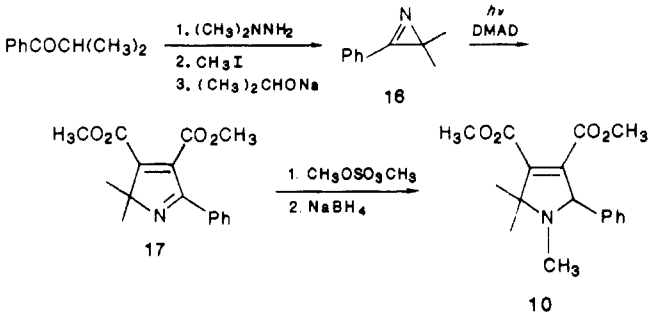
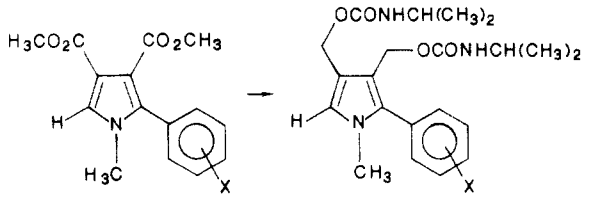
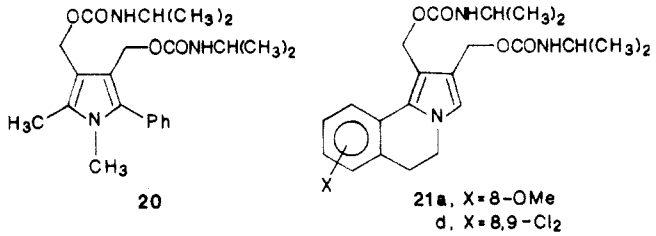
treatment of the methiodide with sodium hydride–2-propanol (anhydrous) gave **16** in over 80% yield. The method of isopropoxide generation and the reaction temperatures were absolutely critical for the success of this reaction.



The pyrrole bis(carbamate) that would expect to be produced in the oxidation of **2** has already been prepared[4c] but the pyrrole bis(carbamates) that would derive from **3** have not. The syntheses of **18** were carried out in *one pot*. Thus, bromination of the appropriate phenylacetic acid with NBS, treatment with methylamine, acylation with formic acetic anhydride, and finally treatment with acetic anhydride–DMAD gave **18**. The bis(carbamates) were prepared from **18** by reduction (lithium aluminum hydride) and carbamoylation of the resulting diol.



The reactivities of **19** were compared in a 4-(*p*-nitrobenzyl)pyridine assay (NBP) along with three additional bis(carbamates), **20**, **21a**, and **21d**. The rate constants are given in Table II.



The order of the reactivities of the pyrroles **19** was observed to be in accord with that which was predicted on the basis of the electronic effects of the phenyl substituent(s). The 4-methoxyphenyl compound **19a** was most reactive while the 3,4-dichlorophenyl compound **19d** was the least reactive of the four C-5-unsubstituted pyrroles. The same order was observed for the two tricyclic compounds, **21a** > **21d**; however, the effect was more pronounced. Compound **21a** was 292-fold more reactive than **21d** whereas **19a** was only 38-fold more reactive than **19d**. These differences are believed to be due to the differences in coplanarity of the biaryl systems. In **21** there is approximately a 15° (estimated from Dreiding models) deviation from coplanarity. The 2-phenylpyrroles have a steric interaction between the ortho hydrogens on the phenyl ring and the N-1 methyl group that will influence the conformation of this freely rotating biaryl system. The substitution of an electron-donating methyl group on C-5 of the pyrrole increased the reactivity by 18-fold (**20** vs. **18b**).

Biological Results and Discussion

The results of the initial antineoplastic evaluations of the compounds prepared in this study are given in Table III. The 3-pyrrolines **2**, **3a**, **3b**, and **3c** were active against P388 lymphocytic leukemia while **3d** and **4** were inactive. The inactivity of **4** can be attributed to the fact that this compound, with the C-5 *gem*-dimethyl substitution, cannot readily be converted to a pyrrole in vivo. The pyrrolines **2** and **3** can be converted to the corresponding pyrroles and the inactivity of **3d** leads to the suggestion that the electron-withdrawing 3,4-dichlorophenyl substituent on the 3-pyrroline retards oxidative conversion to the pyrrole. The 3,4-dichlorophenyl-substituted pyrrole **19d** and 8,9-dichloropyrrolo[2,1-*a*]isoquinoline **21d** both show activity against P388 lymphocytic leukemia so clearly this type of substitution does not inhibit activity in the pyrrole compounds.[33] The 4-fluorophenyl-substituted pyrrole **19c** was more active and more potent than the corresponding 3-pyrroline **3c**. This difference may be due to the effect of the 3-fluorophenyl substituent on the in vivo conversion of **3c** to **19c**. The 4-methoxyphenyl-substituted pyrroline **3a** showed comparable activity with the corresponding pyrrole **19a** so it would appear that the electron-donating methoxy substituent (in contrast to the electron-withdrawing substituents mentioned previously) favors the conversion of the 3-pyrroline **3a** to the pyrrole **19a**. The phenyl-substituted 3-pyrroline **3b** is more active than the corresponding pyrrole **19b**. The pyrroline **3b** is also less toxic than **19b**. The diphenyl-substituted 3-pyrroline **2** shows comparable activity to the corresponding pyrrole although the pyrroline does appear to be slightly less potent. This difference in potency may be a reflection on the facility with which the 3-pyrroline **2** is converted to the pyrrole in vivo.

A comparison of the tricyclic compounds **21** with the corresponding biaryl systems **19** show the tricyclic compounds to be more active. Also, in the case of **21a** the tricyclic compound was more potent than the 2-phenylpyrrole **19a**. This difference in activity and potency has been interpreted to be due to the coplanarity (or near coplanarity) of the phenyl and pyrrole rings in **21**. The influence of the coplanarity of the two rings was also observed in the NBP alkylation studies.

The results of these preliminary studies in the P388 lymphocytic leukemia system have led to the selection of the 3-pyrroline **3b** for study in the National Cancer Institute Division of Cancer Treatment tumor panel.

Experimental Section

Melting points (uncorrected) were taken in open capillaries on a Mel-Temp apparatus (Laboratory Devices). Infrared spectra were obtained on a Nicolet 1180 FT-IR infrared interferometer. NMR spectra were determined on Varian T60A and FT-80 and JEOL 270 spectrometers. Ultraviolet spectra were obtained with use of a Cary 118 UV–vis spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. Commercially available reagents and solvents were used as received from the manufacturer without additional purfication unless otherwise stated.

(Trimethylsilyl)methanol. A solution of (trimethylsilyl)-methyl acetate (100 g, 680 mmol) and anhydrous ether (300 mL) was added to a suspension of lithium aluminum hydride (25.8 g, 680 mmol) in ether (1.5 L) under argon at a rate that maintained

(33) Anderson, W. K.; Raju, N., unpublished results.

Table III. P388 Lymphocytic Leukemia Data[a,b]

compd	dose, mg/kg	% T/C	BWD, g	KE	compd	dose, mg/kg	% T/C	BWD, g	KE
2a	100	189	−3.0	3.06		60		−4.0	
	50	145	−2.3	0.53		30	100	−2.3	−0.15
	25	139	−1.2	0.16		15	148	−0.1	−0.04
	12.5	120	0.0	−0.90		7.5	127	0.1	−0.04
2b	100		−4.3	toxic	**3c**	240	137	−2.7	
	50	154	−1.7	1.06		120	131	−2.7	
	25	136	−1.4	0.00		60	112	−0.2	
	12.5	116	−0.1	−1.16	**19c**	240[e]			
P[c]	120	94	−4.4			120[h]			
	60	209	−2.2	6.43		60		−2.7	
	40	168	−1.6	2.85		30	188	−2.2	0.21
	20	137	−0.1	0.08		15	145	−0.4	0.04
3a	240[e]				**3d**	240	119	−2.5	
	120[f]	110	−1.9			120	117	−1.6	
	60	158	−1.2			60	110	−1.3	
19a	120[e]				**19d**	480	169	−3.6	3.40
	60	164	−0.8	0.10		240	160	−2.7	2.43
	30	117	0.4	−0.08		120	133	−1.6	−0.39
	15	123	0.0	−0.06		60	117	−0.8	−1.15
21a	30[g]		−3.1		**21d**	480	185	−3.2	5.05
	15	125	−3.0	−0.04		240	137	−2.3	0.10
	7.5	175	−2.6	0.16		120	130	−2.2	−0.68
3b	100	225	−2.2	5.18		60	86	−0.4	−1.54
	50	145	−2.0	0.53	**4**[d]	400	107	−2.3	
	25	136	−0.9	0.00		200	108	−0.1	
	12.5	121	0.0	0.84		100	113	−0.3	
19b	240[e]					50	108	0.5	
	120[g]		−4.6						

[a] Determined under the auspices of the National Cancer Institute, NIH. For general screening procedures and data interpretation see: Geran, R. L.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3.2*, 1 Also see NIH Publication No. 84-2635, *In Vivo Cancer Models*, 1976–1982. [b] Ascitic fluid (0.1 mL) containing 1×10^6 cells was implanted intraperitoneally into CD_2F_1 mice. The test compound was administered intraperitoneally as a suspension in saline and Tween 80, unless otherwise specified, 24 h after tumor inoculation, and a total of five doses was given on a daily schedule (test solutions were prepared fresh daily). Acute toxicity was evaluated on day 5, and unless otherwise noted, all test animals survived beyond that day. The experiments were evaluated on day 30 of the test schedule. The parameter measured was median survival time, and this was expressed relative to control untreated tumor-bearing animals as % T/C. A T/C of 120% is considered active, and a reproducible T/C ≥175% is considered significant activity. Body weight difference (BWD) is the relation of the test animal to control animal weight change from day 1 to day 5 of the experiment. KE refers to the log cell kill; it is the tumor cell population at the end of treatment relative to its size at the beginning of treatment. [c] **P** refers to the diphenylpyrrole bis(carbamate) that corresponds to **2**; the compound was tested in a Klucel (hydroxypropylcellulose vehicle). [d] The compound was tested in saline and Tween and alcohol as the vehicle. [e] 0/6 toxicity day survivors. [f] 5/6 toxicity day survivors. [g] 4/6 toxicity day survivors. [h] 2/6 toxicity day survivors.

a gentle reflux. The mixture was stirred for 15 h at 25 °C and then cooled to 0 °C. Water was carefully added to quench the reaction, and the salts were filtered and washed with ether. The combined filtrates were dried (sodium sulfate), and the solvent was removed in vacuo at 10 °C. The resulting clear oil was distilled (bp 115–118 °C; lit.[16] bp 121.6 °C) to give (trimethylsilyl)methanol as a colorless oil: 55 g (78%); ^{1}H NMR ($CDCl_3$/Me_4Si extract) δ 0.00 (s, 9 H), 3.26 (s, 2 H); IR (neat) 3345, 2947, 1414, 1252, 1005, 815 cm^{-1}.

(Trimethylsilyl)methyl Trifluoromethanesulfonate. A solution of (trimethylsilyl)methanol (13.87 g, 133 mmol) and dichloromethane (100 mL, dried over sodium hydride) was added dropwise to a solution of trifluoromethanesulfonic anhydride (42.02 g, 148 mmol) and dichloromethane (100 mL) at 0 °C under argon. After the addition was complete, the mixture was stirred at 25 °C for 2 h, water (100 mL) added dropwise, and the reaction stirred for 2 h. The dichloromethane layer was separated, washed with water (2 × 100 mL), dried (sodium sulfate), and concentrated in vacuo at 0 °C. The salmon-colored oil was distilled [bp 45–47 °C (10 torr); lit.[16] bp 49–51 (9 torr)] to give (trimethylsilyl)methyl trifluoromethanesulfonate as a colorless oil: 26.84 g (85%); ^{1}H NMR (CCl_4/Me_4Si extract) δ 0.20 (s, 9 H), 4.30 (s, 2 H); IR (neat) 2965, 1409, 1254, 1207, 1147, 948, 858, 705 cm^{-1}.

1-Methyl-*cis*-2,5-diphenyl-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]-3-pyrroline (2a). A solution of **5** (2.05 g, 6.9 mmol), isopropyl isocyanate (1.76 g, 21 mmol), dibutyltin diacetate (50 mg), and dichloromethane (100 mL) was stirred at reflux under argon for 15 h. The solvent was removed in vacuo, leaving a yellow gum that was crystallized from ether/hexanes to give **2a** as fine white needles: 2.2 g (68%); mp 114–118 °C dec; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.13 (d, 12 H), 2.27 (s, 3 H), 3.67 (quint, 2 H), 4.47 (complex m, 8 H), 7.43 (m, 10 H); ^{13}C NMR ($CDCl_3$/Me_4Si) δ 23.07, 37.19, 43.16, 58.90, 77.07, 127.77, 128.46, 128.69, 130.76, 141.69, 155.38; IR (KBr) 3344, 2978, 1689, 1534, 1456, 1252, 1083, 762 cm^{-1}. Anal. ($C_{27}H_{35}N_3O_4$) C, H, N.

1-Methyl-*cis*-2,5-diphenyl-3,4-bis[[(*N*-methylcarbamoyl)oxy]methyl]-3-pyrroline (2b). A mixture of **5** (4.0 g, 13.7 mmol), methyl isocyanate (15 mL), and diazabicyclooctane (10 mg) was stirred at reflux for 3 h. The excess methyl isocyanate was removed in vacuo; ether (15 mL) was added, and the mixture was concentrated under reduced pressure to give a pale yellow gum that was crystallized (dichloromethane/ether) to give bis(carbamate) **2b**: 3.7 g (66%); mp 97 °C dec; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 2.23 (s, 3 H), 2.63 (s, 3 H), 2.70 (s, 3 H), 4.43 (s, 2 H), 4.53 (q, 4 H, J_{AB} = 12 Hz), 7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$/Me_4Si) δ 27.41, 37.06, 58.78, 76.56, 127.57, 128.25, 128.39, 130.38, 141.26, 156.61; IR (KBr) 3361, 3068, 1684, 1537, 1411, 1251, 1132, 952, 779 cm^{-1}. Anal. ($C_{23}H_{27}N_3O_4$) C, H, N.

1-Methyl-2-(4-methoxyphenyl)-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]-3-pyrroline (3a). A solution of **6a** (1.85 g, 7.4 mmol), isopropyl isocyanate (2.51 g, 30 mmol), dibutyltin diacetate (50 mg), and dichloromethane (150 mL, dried over sodium hydride) was stirred for 15 h at reflux under argon. The solvent was removed under reduced pressure, yielding a white solid that was chromatographed (silica gel eluted with ethyl acetate) to give **3a**. Crystallization from dichloromethane–hexanes gave **3a** as a white powder: 1.3 g (42%); mp 138–140 °C; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.06 (d, 6 H, J = 6 Hz), 1.13 (d, 6 H, J = 6 Hz), 2.33 (s, 3 H), 3.76 (s, 3 H), 4.40 (complex m, 11 H), 6.83 (d, 2 H, J = 8 Hz), 7.23 (d, 2 H, J = 8 Hz); IR (neat) 3344, 2978, 1696, 1534, 1513, 1252, 1090 cm^{-1}. Anal. ($C_{22}H_{33}N_3O_5$) C, H, N.

1-Methyl-2-phenyl-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]-3-pyrroline (3b). A solution of **6b** (3.70 g, 16 mmol), isopropyl isocyanate (4.31 g, 50 mmol), dibutyltin diacetate (50

mg), and dichloromethane (150 mL, distilled from sodium hydride) was stirred for 15 h at reflux under argon. The product was isolated and purified as described for **3a** except ethyl acetate–dichloromethane (4:1) was used in the chromatography. Bis(carbamate) **3b**: 3.5 g (56%); mp 114–117 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.16 (m, 12 H), 2.36 (s, 3 H), 4.09 (complex m, 11 H), 7.30 (s, 5 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 23.07, 39.67, 43.16, 43.28, 58.51, 59.42, 62.70, 78.16, 128.39, 138.51, 129.16, 129.73, 129.90, 155.31, 155.64; IR (KBr) 3344, 2971, 1696, 1534, 1456, 1252, 949, 858 cm^{-1}. Anal. ($C_{21}H_{31}N_3O_4$) C, H, N.

1-Methyl-2-(4-fluorophenyl)-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]-3-pyrroline (3c). A solution of **6c** (1.05 g, 4.5 mmol) prepared from **9c** in 22% yield by the method described for **6a**], isopropyl isocyanate (1.50 g, 17 mmol), dibutyltin diacetate (50 mg), and dichloromethane (50 mL) was stirred for 15 h at reflux under argon. The product was isolated and purified by the methods described for **3a** to give **3c** as a white powder: 0.80 g (45%); mp 77–80 °C dec; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.16, (m, 12 H), 2.33 (s, 3 H), 3.46–5.09 (complex m, 11 H), 7.19 (m, 4 H); IR (KBr) 3344, 2971, 1689, 1534, 1252, 1083, 975 cm^{-1}. Anal. ($C_{21}H_{30}N_3O_4F$) C, H, N.

1-Methyl-2-(3,4-dichlorophenyl)-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]-3-pyrroline (3d). A solution of **6d** (1.40 g, 4.8 mmol), isopropyl isocyanate (2.05 g, 24 mmol), dibutyltin diacetate (50 mg), and dichloromethane (100 mL, dried over sodium hydride) was stirred for 15 h at reflux under argon. The product was isolated and purified as described for **3a** to give **3d** as a white powder: 1.4 g (64%); mp 113–116 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.10 (d, 6 H, J = 6 Hz), 1.16 (d, 6 H, J = 6 Hz), 2.36 (s, 3 H), 3.23–4.83 (complex m, 11 H), 7.36 (m, 3 H); IR (KBr) 3337, 2978, 1689, 1534, 1463, 1252, 1083 cm^{-1}. Anal. ($C_{21}H_{29}N_3O_4Cl_2$) C, H, N.

1,2,2-Trimethyl-5-phenyl-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]-3-pyrroline (4). A solution of **7** (2.85 g, 12 mmol), isopropyl isocyanate (3.06 g, 36 mmol), dibutyltin diacetate (50 mg), and dichloromethane (100 mL, distilled from sodium hydride) was stirred at reflux for 15 h under argon. The solvent was removed under reduced pressure to yield a tan oil that was chromatographed (basic alumina eluted with 3:1 dichloromethane–ethyl acetate) to give **4** as a tan foam: 3.5 g (70%); mp 60 °C dec; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.10 (m, 18 H), 2.13, (s, 3 H), 3.73 (quint, 2 H, J = 6 Hz), 4.33 (complex m, 7 H), 7.30 (s, 5 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 19.65, 22.97, 23.44, 24.57, 25.94, 43.04, 58.29, 58.74, 67.28, 74.95, 127.42, 128.17, 128.51, 136.07, 141.50, 155.35, 155.59; IR (KBr) 3330, 2971, 1703, 1527, 1456, 1245, 1062, 949, 780 cm^{-1}. Anal. ($C_{23}H_{35}N_3O_4$) C, H, N.

1-Methyl-*cis*-2,5-diphenyl-3,4-bis(hydroxymethyl)-3-pyrroline (5). A solution of diisobutylaluminum hydride (115 mL of 25% DIBAL in toluene, 173 mmol) was slowly added to a solution of **8** (10.0 g, 28 mmol) and toluene (100 mL distilled from sodium hydride) over a period of 1 h at 0 °C under argon. The mixture was stirred for 2.5 h at 25 °C and cooled to 0 °C. Methanol was added dropwise until the aluminum salts had precipitated. The salts were filtered, washed (500 mL, 3:1 chloroform–methanol) and then extracted with a Soxhlet extractor (500 mL, 3:1 chloroform–methanol) for 15 h. The combined organic solution was concentrated under reduced pressure to give a yellow gum that was chromatographed (silica gel, dichloromethane to remove nonpolar impurities and then ethyl acetate to elute product) to give **5** as a pale yellow oil: 4.3 g (53%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.20 (s, 3 H), 3.78 (q, 4 H, J_{AB} = 12 Hz), 3.91 (s, 2 H), 4.33 (s, 2 H), 7.33 (m, 10 H); IR (neat) 3314, 3068, 1601, 1490, 1274, 1001, 910, 798 cm^{-1}.

1-Methyl-2-(4-methoxyphenyl)-3,4-bis(hydroxymethyl)-3-pyrroline (6a). A solution of diisobutylaluminum hydride (200 mL of 1.0 M in toluene, 200 mmol) was added dropwise to a solution of **9a** (6.86 g, 20 mmol) and toluene (150 mL, distilled from sodium hydride) under argon at 0 °C. The mixture was stirred for 3 h at 25 °C and cooled to 0 °C, and methanol was added slowly to precipitate the salts. The salts were filtered and washed with hot chloroform–methanol (3:1, 500 mL). The salts were acidified at 0 °C to pH 1 with 15% hydrochloric acid at 0 °C, stirred for 5 min, and basified with ammonium hydroxide to pH 10. The aqueous layer was extracted with ethyl acetate (2 × 250 mL), and the combined filtrate and washes was concentrated under reduced pressure to give a gum. Chromatography (silica gel eluted with 4.1 ethyl acetate–methanol) gave **6a** as an orange gum: 1.29 g (26%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.29 (s, 3 H), 3.76 (s, 3 H), 6.83 (d, 2 H, J = 8 Hz), 7.16 (d, 2 H, J = 8 Hz).

1-Methyl-2-phenyl-3,4-bis(hydroxymethyl)-3-pyrroline (6b). Method A. The diol **6b** was prepared and isolated by the method described for **6a**. The diol **6b** was obtained as an orange gum, 57%.

Method B. This method differed from method A in that the precipitated salts were extracted once with hot chloroform–methanol (3:1, 500 mL) and then extracted in a Soxhlet extractor with chloroform–methanol (3:1, 500 mL) for 15 h to give **6b** 41%.

Method C. A solution of diisobutylaluminum hydride (145 mL of 1.0 M in tetrahydrofuran, 145 mmol) was added dropwise to a solution of **9b** (4.0 g, 14.5 mmol) and tetrahydrofuran (100 mL, distilled from sodium–benzophenone ketyl) under argon at 0 °C. The mixture was stirred at 25 °C for 3 h and then cooled to 0 °C, and methanol was slowly added to precipitate the salts. The workup was the same as used in method A; **6b** was obtained as an orange gum: 36%; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.33 (s, 3 H), 3.36 (s, 4 H), 3.59 (complex m, 11 H), 7.30 (s, 5 H); IR (neat) 3302, 2964, 1435, 1252, 1048, 948 cm^{-1}.

1-Methyl-2-(3,4-dichlorophenyl)-3,4-bis(hydroxymethyl)-3-pyrroline (6d). The diol **6d** was prepared by the method described for **6a** except the chromatography used ethyl acetate–methanol (9:1). The diol **6d** was obtained as an orange gum: 24%; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.29 (s, 3 H), 3.16–4.66 (complex m, 9 H), 7.33 (m, 3 H).

1,2,2-Trimethyl-5-phenyl-3,4-bis(hydroxymethyl)-3-pyrroline (7). Diisobutylaluminum hydride (200 mL as a 1.0 M solution in tetrahydrofuran, 200 mmol) was added dropwise to a solution of **10** (6.06 g, 20 mmol) and tetrahydrofuran (150 mL, distilled from sodium–benzophenone ketyl) at −23 °C under argon. The solution was stirred for 6 h, and methanol was added slowly to precipitate the salts. The salts were filtered, washed with hot chloroform–methanol (3:1, 500 mL), and then extracted on a Soxhlet extractor (500 mL, 3:1 chloroform–methanol) for 15 h. The combined organic solution was evaporated under reduced pressure to yield an orange gum that was chromatographed (silica gel eluted with 7% methanol–ethyl acetate) to give **7** as a yellow oil: 2.25 g (45%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.06 (s, 3 H), 1.16 (s, 3 H), 2.09 (s, 3 H), 3.96 (complex m, 7 H), 7.30 (s, 5 H); IR (neat) 3309, 2964, 1492, 1456, 1273, 998 cm^{-1}.

Dimethyl 1-Methyl-*cis*-2,5-diphenyl-3-pyrroline-3,4-dicarboxylate (8). Dimethyl acetylenedicarboxylate (8.14 g, 58 mmol) was added to a stirred solution of **11** (9.0 g, 43 mmol) and toluene (250 mL) dried over sodium hydride. The mixture was stirred at reflux for 15 h and the solvent removed under reduced pressure to give an orange gum that was chromatographed (silica gel, dichloromethane) to give a yellow oil that was crystallized (ether–methanol) to give **8** as white plates: 10.46 g (69%); mp 94–95 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.25 (s, 3 H), 3.53 (s, 6 H), 4.70 (s, 2 H), 7.38 (m, 10 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 36.46, 51.77, 75.54, 128.09, 128.29, 128.50, 139.91, 163.85; IR (KBr) 3064, 2952, 1717, 1331, 1298, 1103, 930 cm^{-1}. Anal. ($C_{21}H_{21}NO_4$) C, H, N.

Dimethyl 1-Methyl-2-(4-methoxyphenyl)-3-pyrroline-3,4-dicarboxylate (9a). Method A. A solution of **12a** (4.7 g, 25 mmol), (trimethylsilyl)methyltrifluoromethanesulfonate (6.46 g, 28 mmol), and dichloromethane (150 mL, dried over sodium hydride) was stirred under argon at 25 °C for 20 h. The solvent was removed under reduced pressure to give a white solid. 1,2-Dimethoxyethane (150 mL, distilled from sodium–benzophenone ketyl) and dimethyl acetylenedicarboxylate (5.33 g, 38 mmol) were added, and the solution was stirred at 10 °C under argon. Cesium fluoride (4.56 g, 30 mmol) was added with rapid stirring and the mixture stirred for 15 h at 25 °C. The solvent was removed under reduced pressure, water (50 mL) was added, and the mixture was acidified to pH 2 with 10% hydrochloric acid. The aqueous solution was washed with ether (2 × 100 mL), basified to pH 10 with ammonium hydroxide solution, and extracted with chloroform (3 × 105 mL), and the combined organic layers were dried (sodium sulfate). The solvent was removed under reduced pressure to give an orange oil. Chromatography (silica gel eluted with 3:2 hexanes–ethyl acetate) gave a pale yellow solid that was crystallized (ether–hexanes) to give **9a** as pale yellow needles: 2.5 g (33%); mp 62–65 °C.

Method B. A solution of methyl trifluoromethanesulfonate (13.53 g, 83 mmol) and dichloromethane (50 mL, distilled from sodium hydride) was added dropwise to a solution of **15a** (16.58 g, 75 mmol) and dichloromethane (200 mL) at 0 °C under argon. The solution was stirred at 25 °C for 15 h and then concentrated in vacuo to leave a yellow gum that was dissolved in 1,2-dimethoxyethane (250 mL, distilled from sodium–benzophenone ketyl). Dimethyl acetylenedicarboxylate (15.98 g, 113 mmol) was added, and the solution was stirred at 10 °C under argon. Cesium fluoride (13.67 g, 90 mmol) was added with rapid stirring, and the mixture was stirred for 15 h at 25 °C. The solvent was removed under reduced pressure, water (150 mL) was added, and the mixture was acidified to pH 2 with 10% hydrochloric acid. The aqueous solution was washed with ether (2 × 150 mL), basified to pH 10 with ammonium hydroxide solution, and extracted with dichloromethane (3 × 250 mL), and the combined organic layers were dried (sodium sulfate). The solvent was removed under reduced pressure to give an orange oil. Chromatography (silica gel eluted with 3:2 hexanes–ethyl acetate) gave a yellow waxy solid that was crystallized (ether–hexanes) to yield **9a** as pale yellow needles: 7.90 g (35%); mp 63–65 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.33 (s, 3 H), 3.50 (s, 3 H), 3.73 (s, 6 H), 4.33 (m, 2 H), 6.83 (d, 2 H, J = 8 Hz), 7.33 (d, 2 H, J = 8 Hz); IR (KBr) 2957, 1717, 1638, 1513, 1287, 1097, 1027 cm^{-1}. Anal. ($C_{16}H_{19}NO_5$) C, H, N.

Dimethyl 1-Methyl-2-phenyl-3-pyrroline-3,4-dicarboxylate (9b). The compound was prepared by the methods used for **9a**. Method A afforded **9b** in 50% yield, and method B gave **9b** in 45% yield as pale yellow needles: mp 76–78 °C; ^{1}H NMR (270 MHz; $CDCl_3/Me_4Si$) δ 2.36 (s, 3 H), 3.57 (s, 3 H), 3.63 (q, 1 H, J_{AB} = 8 Hz), 3.78 (s, 3 H), 4.22 (q, 1 H, J_{AB} = 14 Hz), 4.67 (q, 1 H, J_{AB} = 7 Hz), 7.33 (s, 5 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 39.10, 51.71, 51.86, 60.98, 77.65, 128.29, 133.64, 139.16, 143.46, 163.03, 164.35; IR (KBr) 3025, 2956, 1726, 1437, 1292, 1152, 1014, 944, 841 cm^{-1}. Anal. ($C_{15}H_{17}NO_4$) C, H, N.

Dimethyl 1-Methyl-2-(4-fluorophenyl)-3-pyrroline-3,4-dicarboxylate (9c). The compound was prepared by the methods used for **9a**. Method A gave **9c** in 47% yield, and method B gave **9c** in 62% yield as white needles: mp 84–87 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.33 (s, 3 H), 3.50 (s, 3 H), 3.66 (s, 3 H), 3.76 (s, 3 H), 4.13 (m, 1 H), 4.66 (m, 1 H), 7.13 (m, 4 H); IR (KBr) 2957, 2802, 1731, 1506, 1435, 1372, 1287, 1104, 1005 cm^{-1}. Anal. ($C_{15}H_{16}NO_4F$) C, H, N.

Dimethyl 1-Methyl-2-(3,4-dichlorophenyl)-3-pyrroline-3,4-dicarboxylate (9d). The compound was prepared by the methods used for **9a**. Method A gave **9d** in 51% yield, and method B gave 50% yield as white needles: mp 62–64 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.36 (s, 3 H), 3.63 (s, 3 H), 3.73 (m, 1 H), 3.79 (s, 3 H), 4.16 (m, 1 H), 4.59 (m, 1 H), 7.36 (m, 3 H); IR (KBr) 2950, 1717, 1435, 1322, 1287, 1167, 998, 787 cm^{-1}. Anal. ($C_{15}H_{15}NO_4Cl_2$) C, H, N.

Dimethyl 1,2,2-Trimethyl-5-phenyl-3-pyrroline-3,4-dicarboxylate (10). A solution of **17** (5.78 g, 20 mmol) and dimethyl sulfate (25.23 g, 200 mmol) was heated at 70 °C for 1 h. The excess dimethyl sulfate was removed under reduced pressure [40 °C (0.05 torr)] to give a brown gum that was dissolved in ethanol (50 mL). Sodium borohydride (3.02 g, 80 mmol) was added to this solution at 25 °C, and the mixture was stirred for 2 h. The solvent was removed in vacuo, leaving an orange gum that was dissolved in chloroform (250 mL), washed with water (2 × 100 mL), dried (sodium sulfate), and concentrated in vacuo. The orange oil was chromatographed (silica gel eluted with 9:1 dichloromethane–ethyl acetate) to give a yellow oil that was crystallized (ether–hexanes), yielding **10** as fine white needles: 4.9 g (81%); mp 74–76 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.26 (s, 3 H), 1.43 (s, 3 H), 2.16 (s, 3 H), 3.50 (s, 3 H), 3.79 (s, 3 H), 4.63 (s, 1 H), 7.33 (s, 5 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 19.57, 26.07, 30.85, 51.63, 51.95, 67.83, 74.01, 127.93, 128.21, 128.55, 138.33, 139.94, 145.11, 164.35, 164.75; IR (KBr) 2968, 1723, 1653, 1454, 1353, 1233, 1206, 1058 cm^{-1}. Anal. ($C_{17}H_{21}NO_4$) C, H, N.

1-Methyl-*trans*-2,3-diphenylaziridine (11). *m*-Chloroperbenzoic acid (95.74 g, 555 mmol) was added to a stirred solution of *trans*-stilbene (50 g, 277 mmol) and dichloromethane (1 L) at 25 °C. The solution was stirred for 3 days and washed with an aqueous solution of sodium thiosulfate until a negative potassium iodide starch test was obtained. The organic layer was then washed with saturated sodium carbonate solution (2 × 500 mL) and dried (magnesium sulfate) and the solvent removed in vacuo, yielding a green oil that was crystallized (petroleum ether) to give *trans*-stilbene oxide: 51 g (93%); mp 67–68 °C (lit.[24] mp 68–69 °C); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.87 (s, 2 H), 7.33 (s, 10 H); ^{13}C NMR δ ($CDCl_3/Me_4Si$) 62.72, 125.54, 128.25, 128.51, 137.28; IR ($CHCl_3$) 3092, 3035, 1952, 1887, 1810, 1760, 1604, 1496, 1452, 122, 1071, 873 cm^{-1}.

A saturated solution of methylamine in ethanol (500 mL) was added to a solution of *trans*-stilbene oxide (49 g, 250 mmol) and ethanol (100 mL), followed by water (15 mL). The solution was stirred at reflux for 15 h, and then the excess methylamine and ethanol were removed under reduced pressure until crystallization began. The mixture was cooled at 0 °C for 12 h, filtered, and washed with pentane to give *erythro*-1,2-diphenyl-2-(*N*-methylamino)ethanol as pale pink crystals that were recrystallized from ethanol: 45 g, 85%); mp 138–139 °C; lit.[12b] mp 138–138.2 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.32 (s, 3 H), 2.47 (s, 1 H), 3.80 (d, 1 H, J = 6 Hz), 4.87 (d, 1 H, J = 6 Hz), 7.23 (s, 10 H); ^{13}C NMR (Me_2SO-d_6) δ 33.98, 70.55, 76.08, 126.35, 126.60, 126.82, 127.26, 128.41, 140.65, 143.00; IR (KBr) 3320, 3085, 2879, 1952, 1878, 1760, 1449, 1346, 1115, 766 cm^{-1}.

A solution of triphenylphosphine (79.2 g, 301 mmol), carbon tetrachloride (406.5 g, 2.64 mol), triethylamine (264 g, 2.60 mol, dried over sodium hydride), and acetonitrile (1.95 L, dried over calcium hydride) was stirred at 25 °C. *erythro*-1,2-Diphenyl-2-(*N*-methylamino)ethanol (60 g, 264 mmol) was added and the mixture stirred at reflux for 3 h. The solvents were removed in vacuo to give a semicrystalline solid that was washed with hot petroleum ether (5 × 500 mL). The combined washings were cooled at 0 °C for 12 h and filtered, and the filtrate was concentrated in vacuo to give a brown oil that was distilled over potassium hydroxide to give **11** as a yellow oil: 29.5 g (53%); bp 120–125 °C (0.25 torr) [lit.[25] bp 118–119 °C (0.3 torr)]; ^{1}H NMR ($CDCl_3/Me_4Si$ δ 1.80 (s, 3 H), 2.67 (br s, 2 H), 7.25 (s, 10 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 39.35, 48.95, 127.37, 128.27; IR (neat) 3087, 2975, 1602, 1494, 1450, 1030, 1019, 744, 701 cm^{-1}.

***N*-(4-Methoxybenzylidene)methylamine (12a).** A solution of 4-methoxybenzaldehyde (13.60 g, 100 mmol) and methanol saturated with methylamine (125 mL) was stirred at reflux for 15 h. The solvent was removed under reduced pressure and the resulting oil distilled [bp 73–74 °C (0.05 torr) [lit.[26] bp 118–120 °C (12 torr)]] to give **12a** as a clear oil: 13.5 g (91%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.43 (d, 3 H, J = 1 Hz), 3.76 (s, 3 H), 6.80 (d, 2 H, J = 8 Hz), 7.53 (d, 2 H, J = 8 Hz), 8.03 (m, 1 H); IR (neat) 2943, 1654, 1604, 1513, 1308, 1259, 1167, 1027, 829 cm^{-1}.

***N*-Benzylidenemethylamine (12b).** A solution of benzaldehyde (53.06 g, 500 mmol) and methanol saturated with methylamine (200 mL) was stirred at reflux for 15 h. The solvent was removed under reduced pressure and the resulting oil distilled [bp 78–83 °C (20 torr) [lit.[27] bp 92–93 °C (34 torr)]] to give **12b** as a clear oil: 45.6 g (77%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.44 (d, 3 H, J = 2 Hz), 7.43 (m, 5 H), 8.19 (d, 1 H, J = 2 Hz); IR (neat) 3062, 3027, 2943, 1654, 1449, 1308, 1027, 756, 695 cm^{-1}.

***N*-(4-Fluorobenzylidene)methylamine (12c).** A solution of 4-fluorobenzaldehyde (24.80 g, 200 mmol) and methanol saturated with methylamine (125 mL) was stirred at reflux for 15 h. The solvent was removed under reduced pressure and the resulting oil distilled (bp 27–29 °C (0.025 torr)] to give **12c** as a clear oil: 21.8 g (80%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.46 (d, 3 H, J = 2 Hz), 7.00 (m, 2 H), 7.63 (m, 2 H), 8.16 (d, 1 H, J = 2 Hz); IR (neat) 2886, 1647, 1604, 1506, 1294, 1231, 1153, 998, 836 cm^{-1}.

***N*-(3,4-Dichlorobenzylidene)methylamine (12d).** A solution of 3,4-dichlorobenzaldehyde (35.0 g, 200 mmol) and methanol saturated with methylamine (125 mL) was stirred at reflux for 15 h. The solvent was removed under reduced pressure and the resulting oil distilled [bp 77–78 °C (0.025 torr) [lit.[28] bp 79–81 °C (10.4 torr)]] to give **12d** as a clear oil: 34.6 g (92%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.50 (d, 3 H, J = 2 Hz), 7.46 (m, 2 H), 7.80 (m, 1 H), 8.19 (d, 1 H, J = 2 Hz); IR (neat) 2950, 1654, 1555, 1470, 1400, 1210, 1118, 822 cm^{-1}.

(Trimethylsilyl)methyl Azide (14). A mixture of chloromethyltrimethylsilane (49.08 g, 400 mmol), sodium azide (28.64 g, 440 mmol), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 200 mL) was stirred at 80 °C for 15 h. The mixture was cooled, and **14** was distilled from the reaction mixture:

39.52 g (77%); bp 47–50 °C (60 torr) [lit.[17] bp 58–61 °C (80 torr)]; ^{1}H NMR (CCl_4/Me_4Si extract) δ 0.10 (s, 9 H), 2.70 (s, 2 H); IR (neat) 2975, 2886, 2189, 2097, 1407, 1252, 858 cm^{-1}.

***N*-(4-Methoxybenzylidene)-*N*-(trimethylsilyl)methylamine (15a).** A solution of (trimethylsilyl)methyl azide (**14**; 10.83 g, 84 mmol) and benzene (25 mL; distilled from sodium hydride) was added to a solution of triphenylphosphine (18.36, 70 mmol) and benzene (125 mL) at 5 °C. The reaction mixture was allowed to warm to 25 °C over a period of 0.5 h, and then it was stirred at reflux for 1.5 h. 4-Methoxybenzaldehyde (9.53 g, 70 mmol) was added and the mixture stirred at reflux for 1 h. The solvent was removed under reduced pressure to leave a white solid that was triturated with hexanes (100 mL), filtered, and washed with hexanes (250 mL). The combined filtrate was cooled at 0 °C for 15 h and filtered, and the filtrate was concentrated in vacuo to give **15a** as a clear oil: 14.8 g (96%); ^{1}H NMR (CCl_4/Me_4Si extract) δ 0.00 (s, 9 H), 3.26 (m, 2 H), 3.76 (s, 3 H), 6.76 (d, 2 H, J = 8 Hz), 7.50 (d, 2 H, J = 8 Hz), 7.96 (m, 1 H); IR 2957, 1632, 1604, 1513, 1421, 1308, 1245, 836 cm^{-1}.

***N*-Benzylidene-*N*-(trimethylsilyl)methylamine (15b).** The method used for **15a** gave **15b** (94%) as a clear oil: ^{1}H NMR (CCl_4/Me_4Si extract) δ 0.00 (s, 9 H), 3.26 (m, 2 H), 7.33 (m, 5 H), 8.00 (m, 1 H); IR (neat) 2972, 1637, 1610, 1505, 1245, 1228, 854, 697 cm^{-1}.

***N*-(4-Fluorobenzylidene)-*N*-(trimethylsilyl)methylamine (15c).** The method used for **15a** gave **15c** (99%) as a clear oil: ^{1}H NMR (CCl_4/Me_4Si extract) δ 0.00 (s, 9 H), 3.26 (m, 2 H), 6.93 (m, 2 H), 7.53 (m, 2 H), 7.96 (m, 1 H); IR (neat) 2957, 2844, 1639, 1604, 1506, 1245, 1231, 851, 703 cm^{-1}.

***N*-(3,4-Dichlorobenzylidene)-*N*-(trimethylsilyl)methylamine (15d).** The method used for **15a** gave **15d** (93%) as a clear oil: ^{1}H NMR ($CDCl_3$/Me_4Si extract) δ 0.06 (s, 9 H), 3.33 (m, 2 H), 7.43 (m, 2 H), 7.69 (m, 1 H), 7.96 (m, 1 H); IR (neat) 2957, 1632, 1470, 1351, 1252, 1132, 1027, 858 cm^{-1}.

3-Phenyl-2,3-dimethyl-2*H*-azirine (16).[23a] A mixture of isobutyrophenone (59.2 g, 400 mmol), 1,1-dimethylhdyrazine (120 g, 2.00 mol), 4A molecular sieves (25 g), and glacial acetic acid (5 mL) was heated in a steel bomb at 120 °C for 24 h. The sieves were filtered and washed with benzene, and the filtrate was washed with water (3 × 250 mL). The organic layer was dried (sodium sulfate) and concentrated in vacuo, giving a yellow oil that was chromatographed (silica gel, 3:1 dichloromethane–hexanes to remove unreacted starting material and then ethyl acetate to elute product) to give isobutyrophenone dimethylhydrazone as a pale yellow oil: 53.4 g (70%); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.03 (d, 6 H, J = 6 Hz), 2.33 (s, 6 H), 2.73 (quint, 1 H, J = 6 Hz), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$/Me_4Si) δ 20.68, 47.20, 48.00, 127.29, 127.57, 128.01, 128.32, 128.56, 128.99; IR (neat) 2964, 2858, 1463, 1442, 1224, 1013, 977 cm^{-1}.

A solution of isobutyrophenone dimethylhydrazine (53.4 g, 281 mmol), iodomethane (80.1 g, 570 mmol), and ethanol (25 mL) was stirred at reflux for 15 h. The excess iodomethane and ethanol were removed under reduced pressure to give a brown gum that was crystallized two times from 2-propanol–ether to yield isobutyrophenone dimethylhydrazone methiodide as white cubes: 62.5 g (68%); mp 139–140 °C (lit.[23a] 138–140 °C); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 0.96 (d, 6 H, J = 6 Hz), 2.66 (quint, 1 H, J = 6 Hz), 3.23 (s, 9 H), 7.50 (s, 5 H); IR (KBr) 3013, 2968, 1629, 1465, 1248, 1113, 961, 817 cm^{-1}.

A suspension of sodium hydride (2.0 g, 50 mmol, 60% dispersion in oil) in 2-propanol (200 mL; dried from sodium) was heated at 80 °C for 1.5 h under argon. The solution was cooled to 35 °C and a solution of isobutyrophenone dimethylhydrazone methiodide (16.6 g, 50 mmol) in 2-propanol (50 mL) was added. The mixture was stirred at 35 °C for 2 h, the solvent removed under reduced pressure, and the resulting solid triturated with hot ether (4 × 150 mL). The combined ether washes were concentrated in vacuo to give a yellow oil that was distilled [bp 85–87 °C (15 torr) [lit.[23a] bp 93–95 °C (15 torr)]] to yield **16** as a clear oil: yield 6.4 g (88%); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.39 (s, 6 H), 7.59 (s, 5 H); IR (neat) 3063, 2974, 1726, 1490, 1458, 1375, 1195, 1008 cm^{-1}; UV (ethanol) λ_{max} 245 nm.

Dimethyl 2,2-Dimethyl-5-phenyl-2*H*-pyrrole-3,4-dicarboxylate (17). A solution of **16** (21.75 g, 150 mmol), dimethyl acetylenedicarboxylate (42.66 g, 300 mmol), and benzene (5.00 L, dried over sodium hydride) was degassed for 0.5 h with argon, and then the solution was irradiated for 36 h (450-W Hg lamp equipped with a Vycor filter) at 25 °C under a slow stream of argon. The solvent was removed in vacuo and excess dimethyl acetylenedicarboxylate removed by distillation, bp 45 °C (0.025 torr). The resulting gum was chromatographed (silica gel with 9:1 dichloromethane–ethyl acetate) to give a yellow oil that was further purified by bulb-to-bulb distillation [bp 120–130 °C (0.025 torr) [lit.[21] bp 105–110 °C (0.01 torr)]] to give **17** as a yellow solid: 23.5 g (55%); mp 60–62 °C (lit.[21] mp 61–61.5 °C); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.60 (s, 6 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 7.56 (m, 5 H); ^{13}C NMR ($CDCl_3$/Me_4Si) δ 22.94, 55.23, 52.63, 79.74, 127.73, 128.66, 130.56, 133.33, 137.58, 160.20, 161.71, 165.39, 165.62; IR (KBr) 2982, 1747, 1712, 1629, 1540, 1449, 1254, 1125, 1065, 1019 cm^{-1}.

Dimethyl 1-Methyl-2-(4-methoxyphenyl)pyrrole-3,4-dicarboxylate (18a). The diester **18a** was obtained (by the method described for **18d**) as pale yellow prisms in 44% yield from (4-methoxyphenyl)acetic acid. Diester **18a**: mp 132–135 °C; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 3.43 (s, 3 H), 3.60 (s, 3 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 6.86 (d, 2 H, J = 8 Hz), 7.13 (s, 1 H), 7.23 (d, 2 H, J = 8 Hz); IR (KBr) 3140, 2999, 1710, 1506, 1294, 1231, 1196, 1069, 858 cm^{-1}. Anal. ($C_{16}H_{17}NO_5$) C, H, N.

Dimethyl 1-Methyl-2-phenylpyrrole-3,4-dicarboxylate (18b). A solution of α-(bromophenyl)acetic acid (21.5 g, 100 mmol) and aqueous methylamine (27 mL, 40% solution) was stirred for 2 days. The mixture was concentrated under reduced pressure to give an orange syrup that was dissolved in hot 90% ethanol (100 mL) and acidified to pH 5 with glacial acetic acid. Acetone was added until the mixture was turbid. The mixture was cooled to 0 °C for 24 h, filtered, and washed with cold ethanol to give 2-phenylsarcosine as a white powder: 6.6 g (40%); mp 267–269 °C (lit.[29] mp 270 °C); ^{1}H NMR (D_2O/Me_4Si extract) δ 2.62 (s, 3 H), 7.50 (s, 5 H); IR (KBr) 3048, 1570, 1498, 1458, 1370, 1350, 1250, 1125, 845 cm^{-1}.

Acetic anhydride (10.82 g, 100 mmol) was added dropwise to a solution of 2-phenylsarcosine (5.15 g, 31 mmol) and formic acid (20 mL) at 0 °C. After the addition, the mixture was stirred at 25 °C for 3.5 h and then cooled to 0 °C. Water (10 mL) was added over 15 min, and the solvents were removed in vacuo to give a white powder. Acetic anhydride (35 mL) and dimethyl acetylenedicarboxylate (5.06 g, 36 mmol) were added, and the mixture was stirred at 65 °C for 15 h. The mixture was concentrated under reduced pressure, leaving a semicrystalline solid that was crystallized from acetone–isopropyl ether to give dimethyl 1-methyl-2-phenylpyrrole-3,4-dicarboxylate as fine white needles: 6.74 g (80%); mp 116–118 °C (lit.[30] mp 117–118 °C); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 3.50 (s, 3 H), 3.66 (s, 3 H), 3.83 (s, 3 H), 7.23 (s, 1 H), 7.36 (s, 5 H); IR (KBr) 3138, 3032, 1706, 1529, 1494, 1452, 1296, 1205, 1063, 845 cm^{-1}. Anal. ($C_{15}H_{15}NO_4$) C, H, N.

Dimethyl 1-Methyl-2-(4-fluorophenyl)pyrrole-3,4-dicarboxylate (18c). The diester **18c** was obtained (using the method described for **18d**) as white needles (30% from 4-fluorophenylacetic acid): mp 122–125 °C; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 3.46 (s, 3 H), 3.66 (s, 3 H), 3.79 (s, 3 H), 7.26 (m, 5 H); IR (KBr) 3133, 3027, 2950, 1696, 1541, 1442, 1245, 1203, 1062, 942 cm^{-1}. Anal. ($C_{15}H_{14}NO_4F$) C, H, N.

Dimethyl 1-Methyl-2-(3,4-dichlorophenyl)pyrrole-3,4-dicarboxylate (18d). A solution of (3,4-dichlorophenyl)acetonitrile (18.6 g, 100 mmol), water (115 mL), and sulfuric acid (94 mL, concentrated) was stirred at reflux for 20 h, poured onto ice (100 g), and extracted with chloroform (2 × 250 mL). The combined chloroform extracts were dried (sodium sulfate) and concentrated under reduced pressure to give (3,4-dichlorophenyl)acetic acid as a white powder that was crystallized from hot water: 20.4 g (100%); mp 81–83 °C (lit.[31] mp 82–82.5 °C); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 3.63 (s, 2 H), 7.30 (m, 3 H), 10.76 (br s, 1 H); IR (KBr) 3422, 2950, 1696, 1470, 1414, 1308, 1132, 1034, 928 cm^{-1}.

A mixture of (3,4-dichlorophenyl)acetic acid (20.5 g, 100 mmol), *N*-bromosuccinimide (21.36 g, 120 mmol; crystallized from water), 2,2′-azobis(2-methylpropanenitrile) (25 mg), and carbon tetrachloride (250 mL) was irradiated with a tungsten lamp at 35 °C for 15 h. The mixture was filtered and the filtrate concentrated in vacuo to give an orange gum that was treated with aqueous methylamine solution (250 mL, 40% solution) at 0 °C. The mixture was stirred at 65 °C for 18 h, and the excess methylamine was removed in vacuo. Sodium bicarbonate (16.8 g, 200 mmol)

was then added, and the aqueous solution was stirred at 65 °C for 1 h. The mixture was concentrated to dryness under reduced pressure to give a yellow powder that was dissolved in formic acid (200 mL). Acetic anhydride (50 mL) was added dropwise at 0 °C. After the addition was complete, the solution was stirred for 18 h at 25 °C and cooled to 0 °C, and water (75 mL) was added dropwise. The solvents were removed under reduced pressure to give an orange gum that was stirred with acetic anhydride (250 mL) and dimethyl acetylenedicarboxylate (16.34 g, 115 mmol) at 65 °C for 4 h. The mixture was concentrated in vacuo to give a brown gum that was dissolved in hot ethyl acetate (500 mL) and filtered and the filtrate concentrated under reduced pressure to give a brown oil that was chromatographed (silica gel eluted with 95:5 dichloromethane–ethyl acetate) to yield a yellow gum that was crystallized from acetone–isopropyl ether to give **18d** as white needles: 15.62 g (46%); mp 117–120 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.50 (s, 3 H), 3.70 (s, 3 H), 3.83 (s, 3 H), 7.40 (m, 4 H); IR (KBr) 3133, 2992, 1710, 1541, 1470, 1442, 1393, 1231, 1203, 1182, 1069, 907 cm^{-1}. Anal. ($C_{15}H_{13}NO_4Cl_2$) C, H, N.

1-Methyl-2-(4-methoxyphenyl)-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]pyrrole (19a). A solution of the diester **18a** (4.55 g, 15 mmol) and tetrahydrofuran (50 mL; distilled from sodium–benzophenone ketyl) was added dropwise to a stirred suspension of lithium aluminum hydride (1.25 g, 33 mmol) and tetrahydrofuran (200 mL) at 0 °C under argon. After the addition was complete, the mixture was stirred at 25 °C for 15 h and cooled to 0 °C, and water added slowly to hydrolyze the salts. The salts were filtered and washed with acetone and the combined filtrates dried (sodium sulfate). The solvent was removed under reduced pressure to give 1-methyl-2-(4-methoxyphenyl)-3,4-bis(hydroxymethyl)pyrrole as a white powder: 3.44 g (93%); ^{1}H NMR ($CDCl_3/Me_4Si$) δ 2.82 (br s, 2 H), 3.43 (s, 3 H), 3.83 (s, 3 H), 4.53 (s, 4 H), 6.63 (s, 1 H), 6.90 (d, 2 H, J = 8 Hz), 7.23 (d, 2 H, J = 8 Hz); IR (KBr) 3337, 3260, 2957, 2914, 1534, 1386, 1252, 1182, 1041, 851 cm^{-1}.

A solution of isopropyl isocyanate (5.93 g, 70 mmol), diol (3.44 g, 14 mmol), dibutyltin diacetate (50 mg), and dichloromethane (250 mL, distilled from sodium hydride) was stirred at reflux for 15 h. The solvent was removed in vacuo to give a white solid that was crystallized from dichloromethane–hexanes to yield **19a** as a white powder: 5.04 g (86%); mp 128–132 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.13 (d, 12 H), 3.40 (s, 3 H), 3.76 (s, 3 H), 4.50 (br s, 2 H), 4.96 (d, 4 H), 6.73 (s, 1 H), 6.93 (d, 2 H, J = 8 Hz), 7.26 (d, 2 H, J = 8 Hz); IR (KBr) 3310, 2978, 1682, 1611, 1534, 1252, 1083, 935 cm^{-1}. Anal. ($C_{22}H_{31}N_3O_5$) C, H, N.

1-Methyl-2-phenyl-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]pyrrole (19b). The compound was prepared by the method described for **19a**. The diester **18b** was reduced to the diol (92%) that was isolated as a white powder: ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.20 (br s, 2 H), 3.46, (s, 3 H), 4.57 (d, 4 H), 6.67 (s, 1 H), 7.33 (s, 1 H); IR (KBr) 3288, 2922, 2872, 1492, 1449, 1182, 1005, 801 cm^{-1}.

The diol was converted to the bis(carbamate) **19b**: 82%; white powder; mp 134–136 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.16 (d, 12 H, J = 6 Hz), 3.50 (s, 3 H), 3.83 (m, 2 H), 4.50 (br s, 2 H), 4.96 (s, 2 H), 5.05 (s, 3 H), 6.76 (s, 1 H), 7.36 (s, 5 H); IR (KBr) 3344, 2971, 1703, 1671, 1528, 1495, 1462, 1244, 1177, 1067 cm^{-1}; UV (ethanol) λ_{max} 270 nm (ε 8900). Anal. ($C_{21}H_{29}N_3O_4$) C, H, N.

1-Methyl-2-(4-fluorophenyl)-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]pyrrole (19c). The compound was prepared by the procedure described for **19a**. The diester was converted to the diol (96%), isolated as an opaque oil: ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.40 (s, 3 H), 4.50 (d, 4 H), 6.59 (s, 1 H), 7.19 (m, 4 H).

The diol was converted to **19c**: 91%; white powder; mp 133–137 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.13 (d, 12 H, J = 6 Hz), 3.43 (s, 3 H), 3.79 (m, 2 H), 4.53 (br, 2 H), 4.90 (s, 2 H), 5.03 (s, 2 H), 6.69 (s, 1 H), 7.13 (m, 4 H); IR (KBr) 3372, 2971, 1717, 1673, 1532, 1507, 1247, 1081, 1058, 941 cm^{-1}. Anal. ($C_{21}H_{28}N_3O_4F$) C, H, N.

1-Methyl-2-(3,4-dichlorophenyl)-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]pyrrole (19d). The diester **18d** was converted to the diol that was obtained as a white oil: 95%; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 3.53 (s, 3 H), 4.56 (d, 4 H), 6.69 (s, 1 H), 7.43 (m, 3 H).

The diol was converted to **19d**, isolated as a white powder: 95%; mp 132–135 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.10 (d, 12 H, J = 6 Hz), 3.43 (s, 3 H), 3.73 (m, 2 H), 4.53 (br, 2 H), 4.83 (s, 2 H), 5.00 (s, 2 H), 6.69 (s, 1 H), 7.26 (m, 3 H); IR (KBr) 3358, 2978, 1717, 1689, 1470, 1386, 1322, 1252, 1231, 1062, 942 cm^{-1}. Anal. ($C_{21}H_{27}N_3O_4Cl_2$) C, H, N.

1,5-Dimethyl-2-phenyl-3,4-bis[[(*N*-2-propylcarbamoyl)oxy]methyl]pyrrole (20). A solution of 1,5-dimethyl-2-phenyl-3,4-bis(hydroxymethyl)pyrrole[4b] (1.15 g, 5 mmol), isopropyl isocyanate (1.70 g, 20 mmol), dibutyltin diacetate (50 mg), and dichloromethane (150 mL, distilled from sodium hydride) was stirred at 25 °C for 24 h under argon. The solvent was removed under reduced pressure to give a white solid that was crystallized (dichloromethane–hexanes), yielding **20** as a white powder: 1.69 g (98%); mp 65–67 °C; ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.10 (d, 12 H, J = 6 Hz), 2.29 (s, 3 H), 3.33 (s, 3 H), 3.83 (quint, 2 H, J = 6 Hz), 4.50 (br, 2 H), 4.90 (s, 2 H), 5.09 (s, 2 H), 7.33 (s, 5 H); IR (KBr) 3323, 2978, 1682, 1456, 1259, 1076, 935, 703 cm^{-1}; UV (ethanol) λ_{max} 281 nm (ε 7800).

NBP Alkylating Assay.[32] The compound to be tested was dissolved in absolute ethanol (2.0 μmol/10 mL), and 0.5-mL aliquots of this solution were added to tubes containing an NPB solution (1.0 mL, 10% w/v in dimethoxyethane) and a water solution (1.0 mL, 1:1 v/v water–dimethoxyethane). The tubes were stoppered and heated at 50 °C for the specified times. The tube was removed and cooled in an ice bath, and a base solution (1.0 mL, 1:1 v/v triethylamine–ethanol) was added. The contents were mixed on a Vortex type mixer for 3 s, cooled to 0 °C for 30 s, and diluted with acetone (7.0 mL). The absorbance was read immediately at 570 nm on a Bausch & Lomb (Spectronic 20) spectrophotometer. The instrument had previously been calibrated to 0% absorbance against a solution containing NBP solution (1.0 mL), water solution (1.0 mL), absolute ethanol (0.5 mL), base solution (1.0 mL), and acetone (7.0 mL).

The rate constant, k', was calculated from the slope of the line resulting from a plot of absorbance vs. time. The slope was obtained by linear regression, and the correlation coefficients were >0.99.

Registry No. **2a**, 104156-36-7; **2b**, 104156-37-8; **3a**, 104156-39-0; **3b**, 104156-41-4; **3c**, 104156-43-6; **3d**, 104156-45-8; **4**, 104156-47-0; **5**, 104156-35-6; **6a**, 104156-38-9; **6b**, 104156-40-3; **6c**, 104156-42-5; **6d**, 104156-44-7; **7**, 104156-46-9; **8**, 104156-48-1; **9a**, 104156-49-2; **9b**, 72090-97-2; **9c**, 104156-55-0; **9d**, 104156-58-3; **10**, 104156-50-5; **11**, 104156-51-6; **12a**, 13114-23-3; **12b**, 622-29-7; **12c**, 104156-56-1; **12d**, 17947-66-9; **13a**, 104156-53-8; **13b**, 104156-73-2; **13c**, 104156-75-4; **13d**, 104156-77-6; **14**, 87576-94-1; **15a**, 104156-54-9; **15b**, 57402-97-8; **15c**, 104156-57-2; **15d**, 104156-59-4; **16**, 14491-02-2; **17**, 61728-55-0; **18a**, 52705-21-2; **18b**, 19611-52-0; **18c**, 104156-60-7; **18d**, 104156-61-8; **19a**, 104156-63-0; **19a** (diol), 104156-62-9; **19b**, 104156-65-2; **19b** (diol), 104156-64-1; **19c**, 104156-67-4; **19c** (diol), 104156-66-3; **19d**, 104172-28-3; **19d** (diol), 104156-68-5; **20**, 104156-69-6; **20** (diol), 70889-04-2; **21a**, 104156-70-9; **21d**, 104156-71-0; DMAD, 762-42-5; (trimethylsilyl)methyl acetate, 2917-65-9; (trimethylsilyl)methanol, 3219-63-4; (trimethylsilyl)-methyl trifluoromethanesulfonate, 64035-64-9; isopropyl isocyanate, 1795-48-8; methyl isocyanate, 624-83-9; methyl trifluoromethane sulfonate, 333-27-7; *trans*-stilbene, 103-30-0; *trans*-stilbene oxide, 1439-07-2; methylamine, 74-89-5; *erythro*-1,2-diphenyl-2-(*N*-methylamino)ethanol, 20616-52-8; 4-methoxybenzaldehyde, 123-11-5; benzaldehyde, 100-52-7; 4-fluorobenzaldehyde, 459-57-4; 3,4-dichlorobenzaldehyde, 6287-38-3; isobutyrophenone, 611-70-1; 1,1-dimethylhydrazine, 57-14-7; isobutyrophenone dimethylhydrazone, 61852-68-4; isobutyrophenone dimethylhydrazone methiodide, 56062-73-8; (4-methoxyphenyl)acetic acid, 104-01-8; α-(bromophenyl)acetic acid, 4870-65-9; 2-phenylsarcosine, 74641-60-4; (4-fluorophenyl)acetic acid, 405-50-5; (3,4-dichlorophenyl)acetonitrile, 3218-49-3; (3,4-dichlorophenyl)acetic acid, 5807-30-7; 4-(*p*-nitrobenzyl)pyridine, 1083-48-3.