and 0.2 mL of triethylamine in 20 mL of CH_2Cl_2 was refluxed until solution was complete. The solution was cooled to −5 °C and 1 mL (1.3 mmol) of a 10% (v/v) CH_2Cl_2 solution of methanesulfonyl chloride was added dropwise. The solution was stirred at −5 °C for 15 min, TLC (SiO_2, CH_2Cl_2/ether (4:1 v/v)) indicated the absence of **44** and the solution was cooled to −78 °C. A 4 M methanol solution of sodium methoxide (2 mL, 8 mmol) was added and the resulting solution was allowed to warm to room temperature. Water was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 10 g; eluent, CH_2Cl_2) gave as the major product band 150 mg (50%) of **16a** as a pink oil which crystallized upon standing: mp 80–82 °C, identical by NMR with authentic **16a**.

Method B. A mixture of 0.3 g (1 mmol) of **44** and 0.2 mL of triethylamine in 20 mL of CH_2Cl_2 was refluxed until solution was complete. The solution was cooled to −5 °C and 1.0 mL (1.3 mmol) of a 10% (v/v) CH_2Cl_2 solution of methanesulfonyl chloride was added dropwise. The solution was stirred for 10 min TLC (SiO_2; eluent, CH_2Cl_2/ether (4:1 v/v)) indicated the absence of **44**, and the solution was cooled to −78 °C. By means of a cannula, the solution was added to a solution of 1.5 mL of 40% aqueous NaOH and 2 mL of dioxane in 20 mL of MeOH. The mixture was stirred for 30 min, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 10 g; eluent, CH_2Cl_2) gave 60 mg (21%) of **16a** as a pink oil which crystallized upon standing, mp 80–82 °C. The material was identical in every respect by mp, mmp, and NMR with an authentic sample.

Acknowledgment. We thank our Physical Chemistry Department for mass spectra, HPLC analyses, elemental analyses, IR spectra, and NMR spectra.

Registry No. **1a**, 76049-54-2; **1b**, 76049-53-1; **1c**, 76049-52-0; **2a**, 76049-64-4; **2b**, 76049-63-3; **2c**, 76049-61-1; **3a**, 76049-70-2; **3a**·HBr, 101713-47-7; **5a**, 101713-15-9; **5b**, 81078-17-3; **5c**, 81078-16-2; **6a**, 101713-12-6; **6a** (free base), 81078-18-4; **6a**·CH_3SO_3H, 81078-19-5; **6b**, 101713-13-7; **6b** (free base), 89376-31-8; **6b**·CH_3SO_3H, 101713-45-5; **6c**, 101713-14-8; **8a**, 101713-16-0; **8b**, 81078-13-9; **8c**, 81078-12-8; **9a**, 101713-17-1; **9b**, 81078-15-1; **9c**, 81078-14-0; **10a**, 81078-25-3; **10b**, 81078-24-2; **10c**, 81078-23-1; **11a**, 101713-18-2; **11b**, 101713-20-6; **11b**·HCl, 101713-48-8; **12a**, 101713-19-3; **12b**, 101713-21-7; **13a**, 101713-22-8; **13b**, 101713-23-9; **13c**, 81078-28-6; **14a**, 81078-36-6; **14b**, 81078-35-5; **14c**, 81078-32-2; **15a**, 101713-24-0; **15b**, 101713-27-3; **16a**, 81078-37-7; **16b**, 101713-26-2; **16c**, 81078-34-4; **17**, 101713-28-4; **18**, 101713-29-5; **19c**, 81993-61-5; **20c**, 81993-60-4; **21c**, 101713-30-8; **21c** (free base), 101713-49-9; **22c**, 101713-31-9; **23c**, 101713-32-0; **24c**, 101713-33-1; **25a**, 89376-28-3; **25b**, 81993-72-8; **25c**, 81993-71-7; **25c** (dihydropyramidobenzazepine), 101713-46-6; **26b**, 81993-75-1; **27**, 81993-76-2; **28**, 81993-79-5; **29**, 81993-81-9; **30**, 81993-82-0; **30**·HCl, 89376-30-7; **31**, 81993-84-2; **33**, 101713-34-2; **34**, 101713-35-3; **35**, 101713-36-4; **36**, 101713-37-5; **37**, 101713-38-6; **38**, 101713-40-0; **42**, 101713-41-1; **43**, 101713-42-2; **44**, 101713-43-3; **45**, 101713-44-4; acetamidine hydrochloride, 124-42-5; guanidine carbonate, 100224-74-6; 3-(dimethylamino)propylamine, 109-55-7.

Supplementary Material Available: Table III, experimental details of crystals **13a**, **13b**, and **13c**; Table IV, the bond lengths in compounds **13a**, **13b**, and **13c**; Table V, the bond angles in compounds **13a**, **13b**, and **13c**; Tables VI and VII, the final atomic and ansiotropic thermal parameters for **13a**; Tables VIII and IX, the final atomic and anisotropic thermal parameters for **13b**; Table X the final atomic parameters for **13c** (8 pages). Ordering information is given on any current masthead page.

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Bridging from Nitrogen with Thiophene and an Olefin

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Novel 4-aryl-1,4-dihydropyridines, possessing 2-(3-thienyl)ethyl and 1-buten-4-yl nitrogen substitution, have been prepared by a titanium-promoted Hantzsch-type condensation. Treatment of these dihydropyridines with titanium tetrachloride catalyzes generation of the dihydropyridine/iminium ion. Subsequent trapping of this ion by either the thienyl or the olefinic moiety affords cyclic products derived respectively from elimination or addition pathways available to the intermediate cation. The stereochemistry of these cyclizations is discussed, and the scope of the process is evaluated in light of N-substituted dihydrohydropyridines that do not cyclize.

Several 4-aryl-1,4-dihydropyridines have recently gained clinical importance in the treatment of cardiovascular pathologies, such as angina and hypertension.[1,2] These compounds, which apparently operate by inhibiting the translocation of calcium through the cell membrane, have been termed calcium channel blockers.[3-5]

In addition to the extensive literature describing the chemistry of classical dihydropyridines,[6-11] more recently work has been published which centers on the preparation of novel, conformationally restricted dihydropyridine analogues. In an attempt to relate biological activity to

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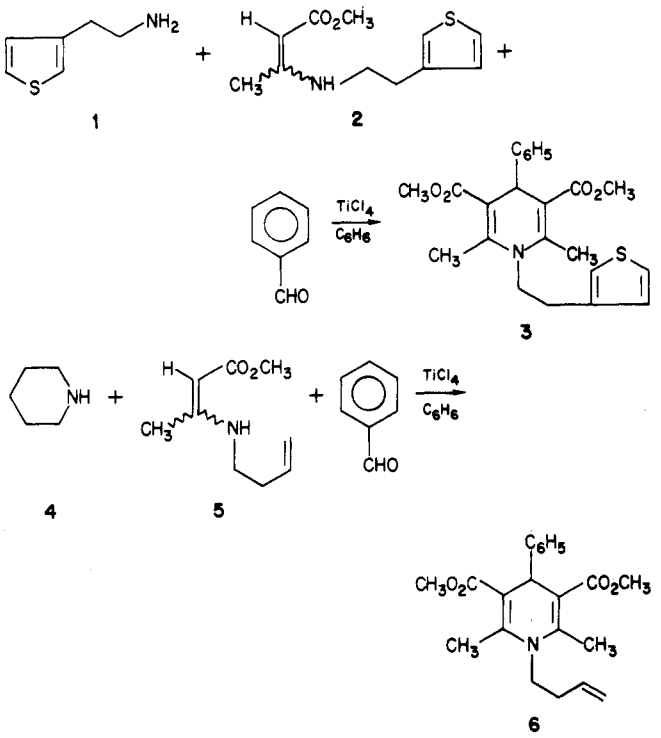
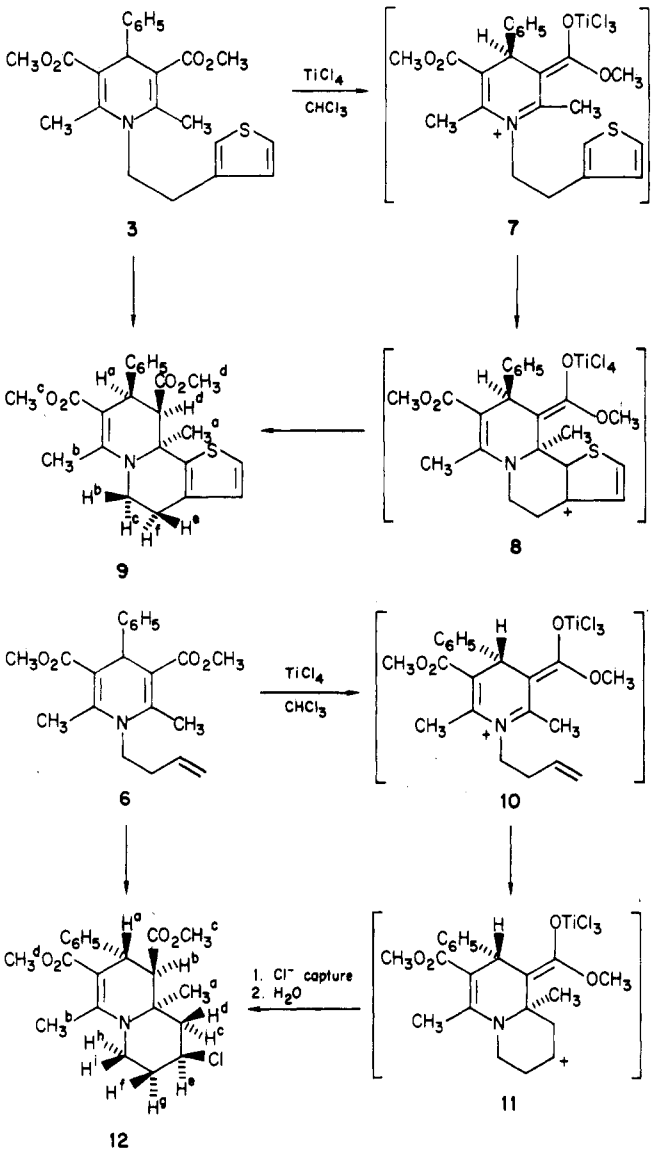
0022-3263/86/1951-2202$01.50/0

Scheme I



Scheme II



conformational preferences, these molecules have generally displayed bridging from the ortho position of the phenyl ring into either the C-3 ester function[12] or into C-2 or C-3 of the dihydropyridine ring.[13-17] These latter examples have exploited the generation and intramolecular capture of a dihydropyridine/iminium species by carbon–carbon double bonds, heteroatoms, and heterocycles. As a continuation of this approach, we wish to report the synthesis of dimethyl 2,6-dimethyl-4-phenyl-*N*-[2-(3-thienyl)-ethyl]-1,4-dihydropyridine-3,5-dicarboxylate (**3**) and dimethyl *N*-(1-buten-4-yl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**6**) via a novel titanium-mediated condensation procedure. Further, we show that with Lewis acid catalysis these molecules generate iminium ions which are trapped intramolecularly by the appropriate nucleophilic site of the nitrogen substituent in a stereospecific fashion.

On the basis of our earlier work[14] we anticipated that dihydropyridines **3** and **6** (Scheme I), for which a six-membered transition state would be required between the attacking atom and the electrophilic iminium carbon, would present favorable opportunities for cyclization. At the same time, we were concerned about the viability of this process since, unlike our previous work, the side chain bearing atom, i.e., nitrogen, would undergo important geometric changes during rehybridization to the iminium ion. The preparation[18] of **3** involved treatment of the adduct between 3-(2-aminoethyl)thiophene (**1**) and titanium tetrachloride with methyl 3-[*N*-(2-(3-thienyl)-ethyl)amino]crotonate (**2**) and benzaldehyde in benzene solution. These conditions were required to minimize the formation of cyclohexadiene side products.[18] In a similar fashion, **6** was synthesized by treatment of the adduct between piperidine and titanium tetrachloride with methyl 3-(*N*-1-buten-4-ylamino)crotonate (**5**) and benzaldehyde in benzene solution. The utilization of the titanium-assisted condensation sequence was of utmost importance since treatment of **1** or 4-amino-1-butene separately with methyl acetoacetate and benzaldehyde under normal Hantzsch conditions[6] failed to yield significant amounts of the desired dihydropyridines. Attempted preparation of **3** and **6** via alkylation of the requisite dihydropyridine anion[19-21] with the appropriate alkyl halide also failed to provide significant amounts of products because of competing elimination processes.

Treament of **3** with 3 equiv of titanium tetrachloride in chloroform for 24 h at room temperature produced 4,9,10,10a-tetrahydro-7,10aα-dimethyl-9β-phenyl-5*H*-

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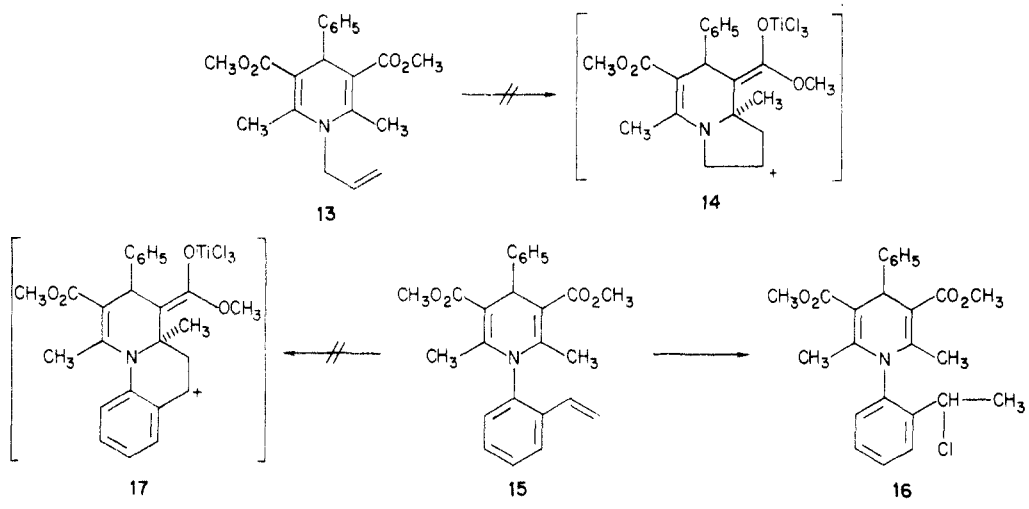
Scheme III



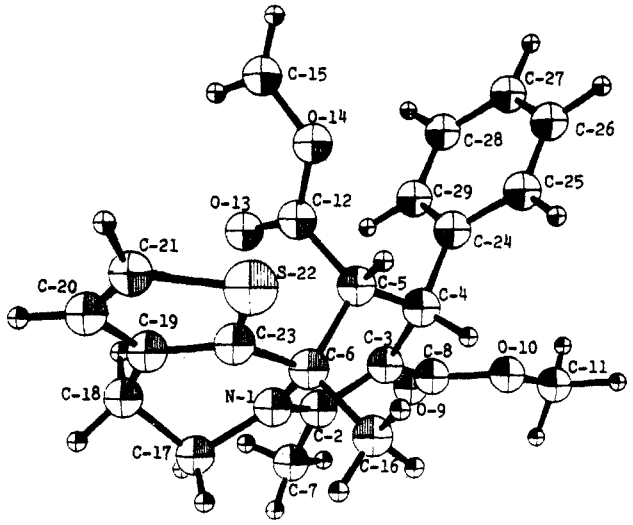


Figure 1. Ortep plot of compound **9**.

thieno[2,3-*a*]quinolizine-8,10β-dicarboxylate (**9**) as the major product in 73% yield. The structure of this compound was confirmed by single-crystal X-ray analysis, and an Ortep plot is shown in Figure 1. The mechanism (Scheme II) for formation of **9** most probably involves initial complexation of titanium on the ester function to give iminium ion **7**, followed by attack of C-2 of the thiophene with subsequent loss of a proton from cation **8**. This elimination pathway is analogous to previous examples[17] in which the dihydrothienyl cation undergoes rearomatization rather than bis cyclization via intramolecular attack of the crotonate double bond. This latter possibility is obviated by the geometrical constraints of cation **8**. Treatment of **3** with other protic or Lewis acid catalysts such as aluminum chloride or with varying amounts of titanium tetrachloride afforded complex product mixtures that contained diminished amounts of **9**. Similarly, treatment of **6** with hydrogen chloride gas in chloroform or methylene chloride or with titanium tetrachloride in chloroform at room temperature for 24 h gave a 61% isolated yield of dimethyl 8β-chloro-1,6,7,8,9,9a-hexahydro-4,9aα-dimethyl-2α-phenyl-2*H*-quinolizine-1β,3-dicarboxylate (**12**). This compound was identified by 360-MHz ^{1}H NMR and single-crystal X-ray analysis. Generation of **12** involves iminium ion formation followed by attack of the carbon–carbon double bond to give cation **11**, which captures chloride.

A number of features of this chemistry merit further discussion. First, these results indicate that dihydropyridine/iminium ions can be generated from N-alkylated precursors utilizing the same protic and Lewis acid catalysts that we previously described for cyclization of NH dihydropyridines.[14-17] Second, these cations can be trapped intramolecularly by thiophene and carbon–carbon double bonds, i.e., nucleophiles which also trap NH substituted dihydropyridine iminium ions, to afford in high stereochemical purity and in good yield the cycloadducts **9** and **12**. Third, intermediate cations **8** and **11** predictably undergo elimination and nucleophilic addition reactions, respectively, rather than participate in the bis cyclization pathways seen previously,[14] as a consequence of steric constraints at the N_1–C_2 bond.

We would anticipate this iminium ion mediated cyclization sequence for N-substituted dihydropyridines to have general utility, encompassing as the nucleophilic partner a wide variety of heteroatoms, reactive aromatic nuclei, and isolated carbon–carbon multiple bonds. However, we have found two cases which demonstrate limitations. Treatment of dimethyl *N*-allyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**13**) (Scheme III) with titanium tetrachloride in chloroform or with other protic and Lewis acids that generate iminium ions in analogous systems gave complex reaction mixtures rather than cyclized products which are derived from the expected intermediate cation **14**. Apparently, efficient iminium ion capture is prevented by the strain involved with forming, in the transition state, a five-membered ring by attack of the π electrons of the carbon–carbon double bond orthogonal to the plane of the iminium ion. The deleterious effect of increased strain in five-membered ring cyclizations, relative to their six-membered ring counterparts, has been previously noted and analyzed with respect to stereoelectronic requirements.[22-24]

A second case in which cyclization did not proceed as desired was that of dimethyl *N*-(2-ethenylphenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**15**) (Scheme III), which gave only **16** upon treatment with titanium tetrachloride in chloroform. Apparently, under these conditions the rate of iminium ion formation and subsequent cyclization is slower than that of simple addition of HCl to the double bond.

Finally, it is intriguing that cyclization of **3** and **6** produces in each case a single diastereomer as the major product, and that these two compounds, **9** and **12**, re-

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spectively, are formed via opposing stereochemical modes of cyclization. Thus, **3** cyclizes via cation **8** in which the thienyl moiety has entered syn to the 4-phenyl substituent, whereas **6** cyclizes thru **11** in which the carbon–carbon double bond attacked anti to the phenyl substituent. Experiments are under way to explore the basis of these cyclization preferences, as well as to extend the synthetic utility of this general procedure.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60, an EM-390, or a Nicolet NT-360 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a LKB-9000S mass spectrometer at 70 eV. Titanium tetrachloride, benzaldehyde, methyl 3-aminocrotonate, and methyl acetoacetate were purchased from commercial sources and used without purification.

Methyl 3-[*N*-(2-(3-Thienyl)ethyl)amino]crotonate (2). To 3.82 g (0.03 mol) of neat methyl acetoacetate under nitrogen was added dropwise 3.6 g (0.031 mol) of 3-(2-aminoethyl)thiophene (1),[25] and this was stirred at room temperature overnight. The reaction mixture was then diluted with ether and washed with brine and the dried ether phase stripped on the rotary evaporator to give 6.7 g (98%) of the desired product as a pale yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.80 (3 H, s, CH_3), 2.85 (2 H, t, CH_2), 3.38 (2 H, t, CH_2), 3.60 (3 H, s, CO_2CH_3), 4.40 (1 H, s), 6.80–7.35 (3 H, m, Ar), 8.60 (1 H, br s, NH).

Dimethyl 2,6-Dimethyl-4-phenyl-*N*-[2-(3-thienyl)-ethyl]-1,4-dihydropyridine-3,5-dicarboxylate (3). To a solution of 0.84 mL (7.5 mmol) of titanium tetrachloride in 45 mL of benzene under nitrogen was added dropwise 1.92 g (15 mmol) of 3-(2-aminoethyl)thiophene (1). A slight exotherm was observed as a red-orange precipitate formed. Then, a freshly prepared solution of 6.59 g (29.2 mmol) of **2** and 1.59 g (15 mmol) of benzaldehyde in 25 mL of benzene was added dropwise under N_2. The resulting yellow suspension was stirred at room temperature for 24 h. The reaction mixture was quenched by pouring into a stirred mixture of 150 mL of 2 N HCl/350 mL of methylene chloride. The organic layer was separated, and the aqueous phase was reextracted with two 100-mL portions of methylene chloride. The combined organic extracts were washed with brine and dried, and the solvent was removed to give a yellowish oil. Trituration of this oil with hexane/ether provided 1.7 g (28%) of **3** as a solid, mp 126.5–128 °C. Recrystallization from hexane gave analytically pure **3**, mp 127.5–128.5 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.50 (6 H, s, allylic CH_3), 2.58 (2 H, t, CH_2), 3.73 (6 H, s, CO_2CH_3), 3.86 (2 H, t, CH_2), 5.18 (1 H, s), 6.74 (1 H, br s), 6.80 (1 H, d), 7.10–7.30 (6 H, m, Ar). Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 67.01; H, 6.28; N, 3.58.

Dimethyl 4,9,10,10a-Tetrahydro-7,10aα-dimethyl-9β-phenyl-5*H*-thieno[2,3-*a*]quinolizine-8,10β-dicarboxylate (9). To a solution of 0.411 g (1.0 mmol) of **3** in 10 mL of chloroform under nitrogen at room temperature was added 0.57 g (3 mmol) of titanium tetrachloride. This was stirred at room temperature for 24 h and then poured into a mixture of 25 mL of chloroform/25 mL of H_2O. After neutralizing with saturated sodium bicarbonate solution, the phases were separated, and the aqueous was reextracted with three 50-mL portions of chloroform. The combined organic extracts were washed with brine and dried, and the solvent was removed in vacuo to give 0.3 g (73%) crude **9** as a brown foam. This was purified by flash chromatography in silica gel (230–400 mesh) to give pure **9** as a white solid, mp 198–201 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.55 (3 H, s, CH_3^a), 2.59 (3 H, d, CH_3^b), 2.63 (1 H, d of d of d, H^f, J = 2.7, 3.6, 15.3 Hz), 2.75 (1 H, d of d of d, H^e, J = 4.7, 11.2, 15.3 Hz), 2.83 (3 H, s, CH_3^c or CH_3^d), 3.20 (3 H, s, CH_3^c or CH_3^d), 3.21 (1 H, d, H^d, J = 8.5 Hz), 3.29 (1 H, d of d of d, H^c, J = 3.8, 11.1, 13.1 Hz), 4.18 (1 H, d of d of d, H^b, J = 2.5, 4.5, 13.1 Hz), 4.31 (1 H, d of q, H^a, J = 1.4, 8.5 Hz), 6.68 (1 H, d, J = 5 Hz), 7.1 (6 H, m, Ar). Anal. Calcd for $C_{23}H_{25}NO_4S\cdot0.5\ H_2O$: C, 65.69; H, 6.23; N, 3.33. Found: C, 65.73; H, 6.11; N, 3.05.

Methyl 3-(*N*-1-Buten-4-ylamino)crotonate (5). Methyl acetoacetate (1.42 g, 20.0 mmol) was added dropwise with stirring to 2.32 g (20.0 mmol) of 4-amino-1-butene cooled in an ice bath. The mixture was warmed to room temperature and a layer of H_2O formed. After 4 h the mixture was taken up in 50 mL of ether, the layers were separated, and the ether layer was dried and concentrated in vacuo to give 3.35 g (99%) of **5** as a pale yellow oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.8 (3 H, s), 2.3 (2 H, m), 3.3 (2 H, m), 3.6 (3 H, s), 4.4 (1 H, s), 5.1 (2 H, m), 5.8 (1 H, m), 8.6 (1 H, br s).

Dimethyl *N*-4-Butenyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (6). To a solution of 0.80 g (4.2 mmol) of titanium tetrachloride in 17 mL of benzene at room temperature was added dropwise 0.72 g (8.5 mmol) of piperidine with rapid stirring, resulting in a green mixture. To this was added dropwise a freshly prepared solution of 2.88 g (17.0 mmol) of **5** in 4 mL of benzene, resulting in a dark purple mixture. After 5 min a solution of 0.90 g (8.5 mmol) of benzaldehyde in 4 mL of benzene was added dropwise, and the resulting viscous mixture slowly became more fluid and gave a brown, gummy precipitate and a yellow solution. After 4 h at room temperature the reaction was quenched with 20 mL of 3 N HCl solution and extracted with three 75-mL portions of ether. The combined organic extracts were washed successively with 10 mL of 3 N HCl solution, 20 mL of saturated $NaHCO_3$ solution, and brine, dried, and concentrated in vacuo to give 2.52 g (83%) of crude product as a viscous, yellow oil. Trituration with ether gave 1.06 g of **6** as white crystalline solid, mp 108–110 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.05 (2 H, m), 2.48 (6 H, s), 3.69 (2 H, m), 3.72 (6 H, s), 4.97 (2 H, m), 5.16 (1 H, s), 5.5 (1 H, m), 7.2 (5 H, m). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.29; H, 7.38; N, 3.54.

Dimethyl 8β-Chloro-1,6,7,8,9,9a-hexahydro-4,9aα-dimethyl-2α-phenyl-2*H*-quinolizine-1β,3-dicarboxylate (12). To a solution of 0.36 g (1.0 mmol) of **6** in 10 mL of chloroform at room temperature under nitrogen was added dropwise 0.38 g (2.0 mmol) of titanium tetrachloride, and the resulting orange solution was stirred overnight. The reaction was then quenched with 3 mL of H_2O, and this was neutralized with saturated sodium bicarbonate solution. This was extracted with three 20-mL portions of chloroform, the combined organic extracts were dried, and the solvent was removed in vacuo to give 0.47 g of crude **12** as an oil. This was purified by flash chromatography on silica gel (230–400 mesh) by eluting with 3:1 hexane–ether, to give 0.35 g (89%) of **12** as an oil. This was dissolved in ether and allowed to stand to give 0.24 g of **12** as a white solid, mp 151–153 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.25 (3 H, s, CH_3^a), 1.64 (1 H, d of q, H^f, J = 5, 13 Hz), 2.1 (2 H, m, H^d, H^g), 2.33 (1 H, d of d of d, H^c, J = 1, 5, 13 Hz), 2.38 (3 H, d, CH_3^b, J = 1 Hz), 2.84 (1 H, d, H^b, J = 10 Hz), 3.19 (3 H, s, CH_3^c), 3.25 (1 H, d of t, H^h, J = 3, 15 Hz), 3.50 (3 H, s, CH_3^d), 3.81 (1 H, m, H^i), 4.10 (1 H, d of d, H^a, J = 1, 10 Hz), 4.28 (1 H, m, H^e), 7.15 (5 H, m); mass spectrum, m/e 391 (M^+). Anal. Calcd for $C_{21}H_{26}ClNO_4$: C, 64.36; H, 6.69; N, 3.57. Found: C, 64.38; H, 6.63; N, 3.65.

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Supplementary Material Available: Crystallographic data including tables of the atomic positional and thermal parameters, bond distances, and bond angles for **9** and **12** (14 pages). Ordering information is given on any current masthead page.

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