transformation and 1-Hz line broadening was applied.

Two-dimensional COSY and J-resolved NMR spectra were obtained on a Bruker WM-300 spectrometer. 2K × 2K data points cover 2400 × 2400 Hz resulting in about 2.4 Hz/pt digital resolution. Data was collected for 256 T_1 values and then zero-filled to 1K; 96 scans were accumulated for each T_1.

The NOE experiments were conducted on a Bruker WM-500 NMR spectrometer. Peak irradiation was conducted at a power level below saturation of the signal in an 8-s time period and was followed after a 15 ms delay by a 90° observe pulse and 3 s of data acquisition with an additional 1-s delay between cycles. Sixteen transients were collected per multiplet irradiated. On-resonance transients were interleaved with off-resonance transients. The 32K point FID of the off resonance control experiment was subtracted from that of the on resonance experiment and Fourier transformed with 0.5-Hz line broadening.

High Resolution Mass Spectrometry. High resolution electron impact mass spectra were obtained with a VG 79S mass spectrometer using a DCI probe, 70 eV electron energy and 180 °C source block, 10^{-8} accuracy, 0.3-s response time, 100-μA trap current, and 6.6K/1000 resolution.

FTIR Analysis. IR spectra were acquired on a Nicolet Fourier transform IR Model 20DX spectrophotometer containing a IIIb HeNe laser with 4.0 cm^{-1} resolution. The photoadducts were dissolved in benzene-d_6 and placed in sodium chloride cells with 0.015-mm spacers. Interference from benzene-d_6 absorbance was minimized by spectral subtraction after Fourier transformation.

Flash Photolysis Experiments. Flash photolysis experiments were performed with the help of Dr. T. George Truscott at the Department of Chemistry, Paisley College of Technology, Scotland. The experimental system used the frequency doubled (347 nm) output from a J. K. Laser Ruby laser with data analysis using a digitiser/Apple computer system. Samples were dissolved in ethanol and bubbled with oxygen-free argon or nitrogen prior to measurements.

Molecular Mechanics Calculations. Molecular mechanics energy minimization calculations were performed by using Allinger's MM2 program available as program no. 395 from QCPE, Department of Chemistry, Indiana University, Bloomington, IN. A fragment of the tmPso–OAME adducts containing the cyclobutane ring fused to the six-membered lactone ring portion of tmPso, including the 4-CH_3 group was used. The benzofuran ring that is fused to the lactone ring in the furocoumarin was not included to simplify calculations. This benzofuran ring would be expected to decrease the pucker of the cyclobutyl ring due to the constraint it would impose on the flexibility of the lactone ring and therefore the absence of the benzofuran ring should lead to an overestimation of the ring pucker. Calculations were performed for the molecules with methyl groups representing the fatty acid chains in all four of the possible configurations. The presence of methyl groups instead of long alkyl chains should not dramatically alter the results in terms of the pucker of the cyclobutyl ring. To check this assumption, we also performed calculations with the same molecules with hydrogens in place of the methyl groups. The results of these calculations showed that the methyl group caused the ring to flatten relative to the H-substituted analogues (data not shown) and, therefore, the larger alkyl substituents of the fatty acids at these positions would not be expected to cause a large increase in cyclobutyl ring pucker relative to the methyl-substituted models.

Acknowledgment. We thank Prof. George Truscott, Department of Chemistry, Paisley College of Technology, Scotland, for his valuable assistance in the flash photolysis studies of psoralen triplet quenching by OAME and the use of his equipment. We are also grateful to Prof. George Clemans of the Department of Chemistry, Bowling Green State University, for performing the molecular mechanics calculations and expert advice. We acknowledge the use of the following facilities: high resolution EI mass spectra obtained by Dr. Joseph L. Kachinski, Jr. in the Department of Chemistry, Johns Hopkins University, Baltimore, MD; 300-MHz 2D COSY and J-resolved ^{1}H NMR spectra obtained at the Johns Hopkins University Biophysics NMR Facility established by NIH grant GM27512 guided by Facility Coordinator, Prof. Lou-Sing Kan; 400-MHz ^{1}H NMR spectra obtained at the Johns Hopkins Chemistry Department NMR Facility established by NIH grant SIO RR01934 and NSF grant PCM 83-03176, and 500-MHz ^{1}H NOE NMR experiments performed at the Chemical Instrument Center of the Ohio State University Chemistry Department in Columbus, OH, expertly assisted and advised by Center Director, Dr. Chuck Cottrell. We are grateful for financial support from NIH grants ES03841 and ES02300. This is publication 49 from the Center for Photochemical Sciences, Bowling Green State University.

Supplementary Material Available: More details on the ^{1}H NMR assignments of trimethylpsoralen and the coumarin model compounds, the FTIR results, and the kinetic derivation and analysis (6 pages). Ordering information is given on any current masthead page.

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Regio- and Stereoselective Intermolecular Cycloaddition Reactions

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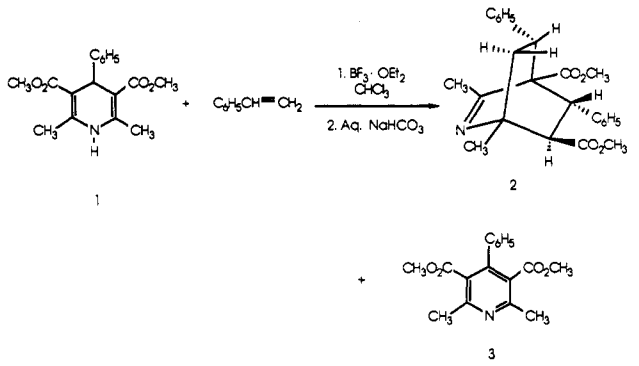
Cyclopentadiene and furan undergo efficient regio- and stereoselective intermolecular inverse electron demand cycloaddition to the dihydropyridine iminium ion under Lewis acid conditions. However, the reaction is quite sensitive to both steric and electronic factors in the nucleophilic component. Synthetically useful cyclization is restricted to unhindered styrenes, cyclopentadiene, and reactive aromatic compounds such as furan. The initial example of an intermolecular cycloaddition in this series involving a thioether is described.

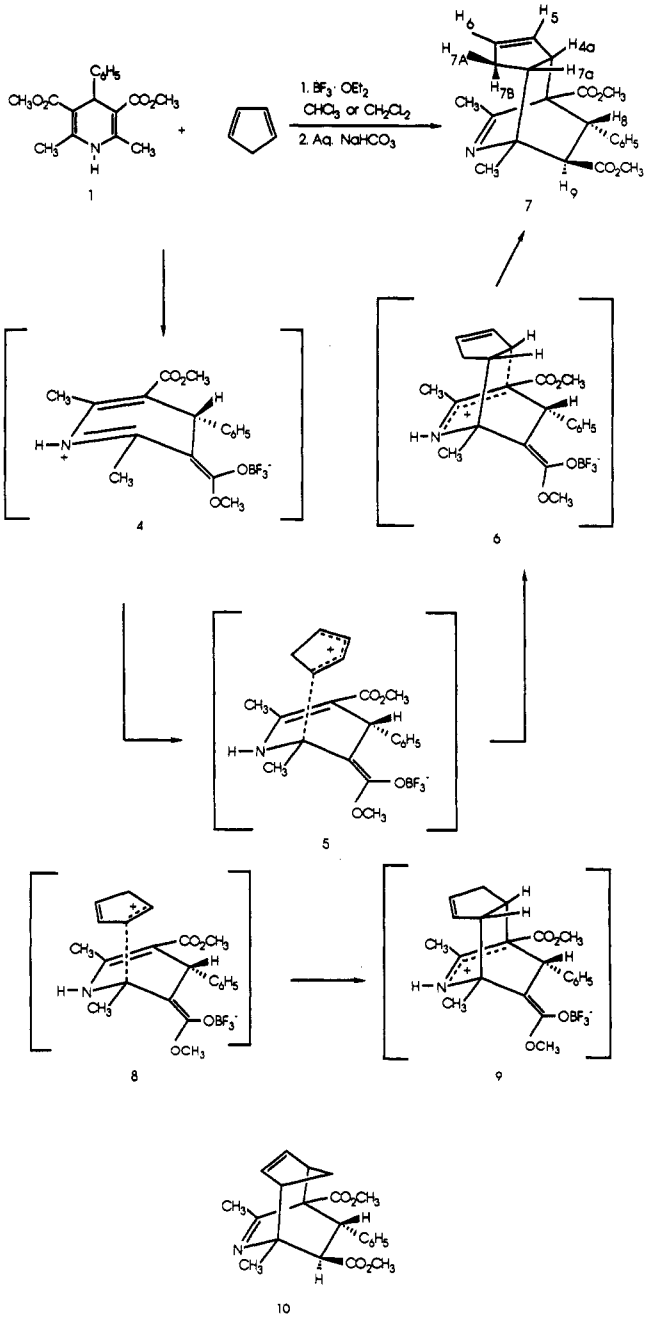
We and others have reported a variety of novel intramolecular cycloaddition processes of appropriately substituted 4-aryl-1,4-dihydropyridines.[1] Similar imminium ion mediated processes have been shown by Wenkert,[2]

0022-3263/89/1954-4134$01.50/0

Scheme I



Scheme II



Overman,[3] and Grieco,[4] among others, to effect formation of key carbon–carbon bonds, leading to a variety of nitrogen-containing natural products. More recently, we have reported the initial *intermolecular* variant wherein the dihydropyridine iminium species is trapped by either styrene or allyltrimethylsilane.[5] We now report the results of studies that probe the scope of this bimolecular process by appraising the corresponding intermolecular reactivity of selected monoolefins, dienes, and heterocycles.

Our initial studies[5] showed that treatment of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1) with 20 equiv of styrene in chloroform solution at 0–10 °C and 3 equiv of boron trifluoride etherate afforded the cycloadduct **2** in 84% yield along with 10% of pyridine **3** (Scheme I). However, treatment of **1** under similar Lewis acid conditions with α-methylstyrene, β-methylstyrene, cyclohexene, or methylenecyclopentane gave product mixtures containing little if any cycloadduct. Under these conditions, dihydropyridine **1** was generally consumed slowly over the course of 24–48 h to provide pyridine **3** as the sole major product. This contrasts sharply with the facile reaction of **1** with styrene (6 h at 0–10 °C) and signifies the requirement for both a benzylic (or allylic) stabilized cationic intermediate, as well as a minimum of sterically encumbering groups at the reactive olefin centers.

Mindful of the above limitations we next chose to study the reactivity of cyclopentadiene, which we anticipated would accommodate the cited steric and electronic factors. Treatment of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1**) with excess cyclopentadiene at room temperature in either chloroform or methylene chloride solution in the presence of boron trifluoride etherate resulted in the disappearance of **1** over 16 h. The sole cyclized product was dimethyl 1,4a,7,7a-tetrahydro-1,3-dimethyl-8-phenyl-1,4-ethano-4*H*-2-pyrindine-4,9-dicarboxylate (**7**) (Scheme II), obtained in 58% isolated yield after chromatography. The structure of **7**, which is an oil, was established by extensive NMR studies (see Experimental Section for details). The same product was also formed when titanium tetrachloride was used as the catalyst; however, the yield was lower and the product mixture more complex.

Although no conclusive evidence is available on the question of the synchronous/stepwise nature of this reaction, several mechanistic points are noteworthy. Activation of **1** by the Lewis acid to afford the dihydropyridine iminium species **4**[1,2] was followed by a regio- and stereoselective cycloaddition with cyclopentadiene. The syn relationship existing between the cyclopentene ring and the imine bond of **7** is precisely the result that one expects from an endo addition in a typical synchronous Diels–Alder process.[6,7] However, the observed stereoselectivity should not be construed as proof of this type of mechanism, as it is reasonable that a stepwise process,[3] relying

(1) (a) Claremon, D. A.; Hirshfield, J.; Lumma, P. K.; McClure, D. E.; Springer, J. P. *Synthesis* **1986**, 144. (b) Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1985**, *50*, 2423. (c) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1985**, *50*, 2427. (d) Hartman, G. D.; Halczenko, W.; Cochran, D. W. *Can. J. Chem.* **1985**, *64*, 556. (e) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1986**, *51*, 142. (f) Hartman, G. D.; Halczenko, W.; Phillips, B. T.; Pitzenberger, S. M. *J. Org. Chem.* **1986**, *51*, 2202.

(2) Wenkert, E.; Porter, B.; Simmons, D. P. *J. Org. Chem.* **1984**, *49*, 3733. Wenkert, E.; Orito, K.; Simmons, D. P. *J. Org. Chem.* **1983**, *48*, 5006.

(3) McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6107 and references cited therein.

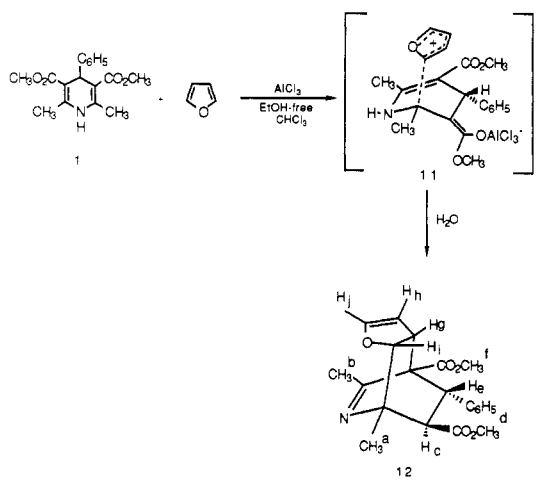
(4) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 3512.

(5) Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1987**, *52*, 1136.

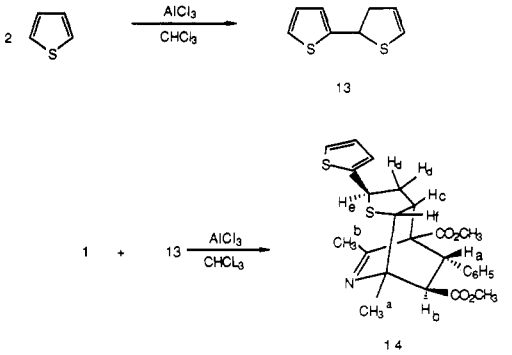
(6) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(7) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.

Scheme III



Scheme IV



on the steric influence of the bulky phenyl ring, would also generate an adduct with the orientation shown in **7**.

Two other olefin regioisomers, **9** and **10**, are possible from the above cyclization mode. The exclusive formation of **7** indicates that the terminus of the olefinic system interacts with the electrophilic iminium carbon to give intermediate **5**, rather than isomer **8** derived from attack at an internal position of the diene. This selectivity is apparently associated with the contribution in the transition state for formation of the stabilized allylic cation **5** as compared to the simple secondary cation **8**. Although the lack of products such as **10** would argue against a discrete allylic cation that could be trapped at either allylic terminus, the present data does not exclude the operation of a nonconcerted pathway[3,7] utilizing zwitterionic intermediates. The final stereochemical aspect of adduct formation arises from stereoselective protonation during workup of the boron enolate **6** from the less hindered α-face to orient the C-9 ester function trans with respect to the phenyl group.

The extension of this reaction to other cyclic dienes was problematic. For example, treatment of **1** with 1,3-cyclohexadiene under the normal Lewis acid conditions afforded pyridine **3** as the major product along with several unidentified minor components. The failure of 1,3-cyclohexadiene to generate cycloadducts reflects subtle rate-retarding electronic and steric factors. We observed qualitatively a reduction in reaction rate in going from styrene to cyclopentadiene and a corresponding increase of the amount of pyridine **3** formed. Cyclization of 1,3-cycloheptadiene is apparently slower yet and thus cannot compete with the acid-catalyzed aromatization reaction.

Since reactive heterocycles such as furan and thiophene had previously been shown[1e,f] to be efficient intramolecular nucleophiles toward the dihydropyridine iminium ion, we investigated analogous utility in the intermolecular sense. Treatment of **1** in ethanol-free chloroform at room temperature with 20 equiv of furan and 3 equiv of aluminum chloride resulted in the disappearance of **1** over the course of 18 h. Following the standard alkaline workup and extraction procedure, the major product was dimethyl 7,7a-dihydro-5,7-dimethyl-9(*S*)-phenyl-4,7-ethanofuro-[2,3-*c*]pyridine-4,8(*R*)-dicarboxylate (**12**) (Scheme III), formed in 67% yield. This product is derived by attack of C-2 of furan on the aluminum analogue of **4**, followed by internal capture in **11** as was previously reported.[1b,c,f] Interestingly, furan attacked the immium ion via the endo mode, trans to the 4-aryl substituent in analogy with all previous intermolecular dihydropyridine cyclizations. Also, the generation of **12** constitutes formal trapping of an intermediate of heterocyclic electrophilic aromatic substitution, which is not well documented in the literature.[1c] Attempted utilization of boron trifluoride etherate as catalyst gave **3** as the only major product, while titanium tetrachloride caused spontaneous decomposition at 0–10 °C.

Attempted cycloaddition of **1** with thiophene under similar conditions followed a much different course. When **1** was treated with 20 equiv of thiophene and 3 equiv of aluminum chloride in chloroform solution at room temperature, the starting dihydropyridine was consumed slowly over 24 h. Alkaline workup generated a complex product mixture that contained a single major product, dimethyl 3,3a,7,7a-tetrahydro-5,7-dimethyl-9(*S*)-phenyl-2-(2-thienyl)-4,7-ethanothieno[2,3-*c*]pyridine-4,8(*R*)-(2*H*)-dicarboxylate (**14**) (Scheme IV), formed in 34% yield. Initial ^{1}H NMR analysis of this compound showed enough similarity to **12** to suggest that cyclization had occurred; however, the spectrum was more complex than expected for simple thiophene addition. The structure of **14** was ultimately determined by single-crystal X-ray analysis.[8] Apparently, thiophene underwent initial dimerization[9] to afford 2-[2-(2,3-dihydrothienyl)]thiophene (**13**), which participated in a regio- and stereoselective cycloaddition to **4**. This result illustrates that thiophene itself was not reactive enough to initiate cycloaddition and points out the potential synthetic utility of thioethers in similar intermolecular reactions.

In summary, the present results suggest that only highly reactive olefins, such as unhindered styrenes, cyclopentadiene, and aromatic compounds that possess furan-like electrophilic aromatic substitution reactivity, will participate in synthetically useful cycloadditions with **1**. Successful reaction, however, in each of these classes was found to be similarly regio- and stereoselective, thus allowing excellent predictability of configurational relationships and access to precisely defined aza polycyclics.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were recorded on an EM-360 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. Cyclohexadiene, α-methylstyrene, β-methylstyrene, and aluminum chloride were obtained from Aldrich and were used without purification. Thiophene, furan, and 2-methylfuran were obtained from Aldrich and were distilled just prior to use.

Dimethyl 1,4a,7,7a-Tetrahydro-1,3-dimethyl-8-phenyl-1,4-ethano-4*H*-2-pyrindine-4,9-dicarboxylate (7). Generation of Cyclopentadiene. Dicyclopentadiene was heated under ni-

(8) Private communication from J. Hirshfield, MSDRL, Rahway, NJ.
(9) Wynberg, H.; Logothetis, A.; VerPloeg, D. *J. Am. Chem. Soc.* **1957**, *79*, 1972.

trogen at 180 °C in a flask equipped with a distillation column and condenser. As it distilled, cyclopentadiene was collected in a flask cooled in dry ice/acetone and was used immediately. To a solution of 0.6 g (2.0 mmol) of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxyate (1)[10] and 1.32 g (20.0 mmol) of cyclopentadiene (freshly distilled) in 30 mL of chloroform at room temperature under nitrogen was added 0.85 g (6.0 mmol) of boron trifluoride etherate dropwise over 5 min to afford a light brown solution. This was stirred overnight at room temperature. The reaction was then cooled in an ice bath and quenched with the addition of 5 mL of water followed by 5 mL of saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was reextracted with chloroform. The combined organic phase was washed with brine and dried over sodium sulfate. Solvent removal on the rotary evaporator gave a yellow oil, which had on TLC (silica gel, 2% methanol/chloroform) two major components at R_f 0.9, 0.5, and one minor component at R_f 0.2. The product at R_f 0.5 was separated from the others by flash chromatography on silica gel (Merck, 230–300 mesh), eluting with chloroform to provide homogeneous material as a slightly yellow oil which did not crystallize. The yield of this material (7) was 0.42 g (58%). Spectroscopic (NMR) evaluation of the impurities showed that the faster moving material was dicyclopentadiene and that the slower moving material was not a cyclized product. 7 had ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.57 (3 H, s), 2.25 (3 H, s), 2.37 (1 H, m H_{7A}, J = 2, 2, 2 Hz), 2.39 (1 H, m, H_{7B}, J = 2,2,2 Hz), 2.59 (1 H, d, H_9, J = 7 Hz) 2.95 (1 H, m, H_{7a}, J = 9.4, 7.5, 7.5 Hz), 3.52 (3 H, s, CO_2CH_3), 3.65 (1 H, m, H_{4a}, J = 9, 2, 2, 2, 2 Hz), 3.66 (1 H, d, H_8 J = 7 Hz), 3.67 (3 H, s, CO_2CH_3), 5.35 (1 H, m, H_5, J = 6, 2, 2, 2 Hz), 5.66 (1 H, m, H_6, J = 6, 2, 2, 2, 2 Hz), 7.0–7.21 (5 H, m, aromatic); exact mass determination, calcd for $C_{22}H_{25}NO_4$ 367.1783, found 367.1781. 2D J-correlated spectroscopy (COSY) of a $CDCl_3$ solution of 7 revealed two nonaromatic spin systems, one consisting of a vicinal set of protons (3.66 and 2.59 ppm; 7.0 Hz coupling) and the other consisting of six protons that interact in a complicated fashion. Of the six protons, the ones that resonate at 5.66 and 5.35 ppm are clearly olefinic. The connectivities (COSY) and the splitting patterns of the six resonances showed that they were all part of a 3,4-disubstituted-cyclopentene. The orientation of the five-membered ring is syn to the imine bond in 7 since H_{7a} is not W-coupled to H_9, as it would be in the event of the opposite regiochemistry.

The methine proton that resonates at 3.65 ppm must be adjacent to the olefin, and the methine at 2.95 ppm must be adjacent to the methylene. Thus, the regiochemistry of the olefin can be determined by identification of the two methines. Since the two nonaromatic spin systems are isolated with respect to scalar coupling, we looked for dipolar couplings via difference NOE experiments. Unfortunately, selective irradiation of H_8 was not possible due to nearly coincidental chemical shifts of H_8 and the methine at 3.65 ppm. The alternate experiment was to irradiate the methine at 2.95 ppm. If the 2.95 ppm methine is H_{4a}, then NOE's were expected in H_{7a}, H_8, and one of the methylene protons, while if the 2.95 ppm methine is H_{7a}, the NOE's were expected in only H_{4a} and one of the methylene protons. Initial results of this experiment were ambiguous as an intense methyl ester peak partially obscurred the resonances at 3.66 and 3.65 ppm. This methyl ester peak did not completely cancel during the difference NOE experiment, making it difficult to distinguish any NOE's in resonances underneath. It was possible to shift the methyl ester peak upfield by adding about 20% C_6D_6 to the sample. When the difference NOE experiment was repeated, NOE's were observed in one of the methylene protons and in the other methine, but not in H_8. The olefin, therefore, had the regio- and stereochemistry shown in 7. In addition, the olefinic protons were assigned on the basis of a difference NOE experiment, in which the methylene protons were irradiated.

Dimethyl 7,7a-Dihydro-5,7-dimethyl-9(*S*)-phenyl-4,7-ethanofuro[2,3-*c*]pyridine-4,8(*R*)-dicarboxylate (12). To a stirred solution of 0.3 g (1.0 mmol) of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1) and 1.36 g (20 mmol) of furan in 7 mL of ethanol-free chloroform cooled to 0–10 °C under nitrogen was added in one portion 0.4 g (3.0 mmol) of aluminum chloride. The reaction mixture, which discolored somewhat, was a free-stirring suspension. After 2 h the ice bath was removed and the reaction mixture was stirred at ambient temperature. After 16 h the cooled reaction mixture was quenched with 20 mL of saturated sodium bicarbonate solution (foaming) and this was extracted with 2 × 50 mL portions of ether. The combined organic extracts were dried and concentrated and the residue was purified by flash chromatography on silica gel, eluting with 25% acetone/hexane. This afforded 0.214 g (58%) of the product 12 as a clear oil (R_f 0.4): mass spectrum, m/e calcd 369.42116, found 369.42110; NMR ($CDCl_3$, 360 MHz) δ 1.71 (3 H, s, CH_3^a), 2.29 (3 H, s, CH_3^b), 2.64 (1 H, dd, J = 7, 1 Hz, H_c), 3.51 (3 H, s, CH_3^d or CH_3^f), 3.55 (1 H, d, J = 7 Hz, H_e), 3.68 (3 H, s, H_f), 3.90 (1 H, dt, H_g), 4.67 (1 H, m, H_h), 5.03 (1 H, dd, J = 12, 2 Hz, H_1), 6.24 (1 H, m, H_j), 6.99 and 7.24 (5 H, m (aromatic)).

Dimethyl 3,3a,7,7a-Tetrahydro-5,7-dimethyl-9(*S*)-phenyl-2-(2-thienyl)-4,7-ethanothieno[2,3-*c*]pyridine-4,8-(*R*)(2*H*)-dicarboxylate (14). To a solution of 150 mg (0.5 mL) of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1) under nitrogen in 4 mL of chloroform (dried over sieves) was added 0.42 g (5.0 mmol) of thiophene, followed by 0.10 g (0.75 mmol) of aluminum chloride, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched by adding a mixture of 10 mL of water, 10 mL of $CHCl_3$, and 10 mL of a saturated sodium bicarbonate solution. The organic layer was separated, and the aqueous phase was reextracted with four 15-mL portions of chloroform. The combined organic extracts were washed with brine and dried, and the solvent was removed to give a viscous, amber-colored oil. This was purified by flash chromatography on silica gel (230–400 mesh) by eluting with 3:2 hexane–ether, to give 140 mg (63%) of a viscous gum. Trituration of this gum with 2 mL of 2:1 hexane/ether provided 76 mg (34%) of 14 as a white solid, mp 141.5–143.5 °C: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.64 (3 H, s, CH_3^a), 2.05 (1 H, m, H_d), 2.40 (1 H, m, H_d), 2.49 (3 H, s, CH_3^b) 2.65 (1 H, d, H_d), 3.49 (4 H, s and m, CO_2CH_3 and H_c), 3.67 (4 H, s, H_a and CO_2CH_3), 4.35 (1 H, d, H_f), 4.50 (1 H, t, H_e), 6.87–7.40 (8 H, m, aromatic); mass spectrum, m/e calcd 469.62624 found 469.62631.

(10) Loev, B.; Goodman, M. M.; Snador, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956.