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3-(3-Pyrrolyl)thiopyrrolidones as Precursors of Benzo[1,2-*b*:4,3-*b*']dipyrroles. Synthesis of Structures Related to the Phosphodiesterase Inhibitors PDE-I and PDE-II

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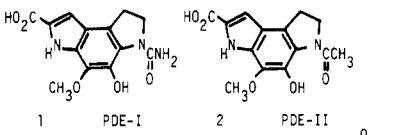
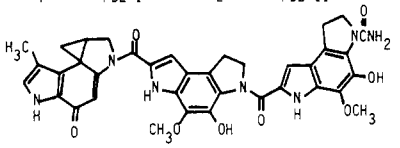
The possibility of conversion of 3-(3-pyrrolyl)thiopyrrolidones to benzo[1,2-*b*:4,3-*b*']dipyrrole derivatives which are structurally related to the naturally occuring benzodipyrroles PDE-I and PDE-II has been investigated. 3-(3-Pyrrolyl)pyrrolidone intermediates were prepared by addition of ethyl 4-lithio-5-(3-methylisoxazol-5-yl)-pyrrole-2-carboxylate to 1-benzylpyrrolidine-2,3-dione. The 3-methylisoxazole substituent was converted to a 1,3-dioxobutyl or a diazoacetyl group by appropriate manipulations and the lactam was converted to a thiolactam. These intermediates could be cyclized by aldol type condensations via *S*-alkyl thioiminium ions or by sulfur extrusion reactions of the Eschenmoser type. Ring contraction reactions leading to benzodipyrrole derivatives were also observed. Compounds which were prepared in good yield include ethyl 5-acetyl-6-benzyl-4-hydroxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate, ethyl 4-acetoxy-6-benzyl-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']-dipyrrole-2-carboxylate, and ethyl 4-acetoxy-5-(acetylthio)-6-benzyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']di-pyrrole-2-carboxylate. Ethyl 6-benzyl-4,5-diacetoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate was also obtained but only in modest yield.

The benzo[1,2-*b*:4,3-*b*']dipyrrole ring has only relatively recently been recognized in naturally occurring materials. Umezawa and co-workers first characterized structures **1** and **2**, known respectively as PDE-I and PDE-II, from streptomyces and demonstrated inhibitory activity of these compounds toward cyclic adenosine-3',5'-monophosphate phosphodiesterase.[1a] The structures were confirmed by synthesis.[1b,1c] The benzo[1,2-*b*:4,3-*b*']dipyrrole ring is also found in the antibiotic CC-1065, structure **3**.[2] The B and C rings are essentially the same structure as in the phosphodiesterase inhibitors, while the A ring is modified by inclusion of the spirocyclohexadienone feature but can be considered to be a derivative of the benzodipyrrole ring system.[3] The very high antitumor activity of CC-1065 has led to initiation of synthetic studies in several laboratories.[4] In this paper we report our investigation of 3-(3-pyrrolyl)thiopyrrolidones as precursors of benzo[1,2-*b*:4,3-*b*']dipyrroles having substitution patterns similar to those found in nature.



1 PDE-I 2 PDE-II



3 CC-1065

(1) (a) Enomoto, Y.; Furutani, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *Agric. Biol. Chem.* **1978**, *42*, 1331–1336. (b) Komoto, N.; Enomoto, Y.; Miyagaki, M.; Tanaka, Y., Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 555–557. (c) Komoto, N.; Enomoto, Y.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Argic. Biol. Chem.* **1979**, *43*, 559–561.

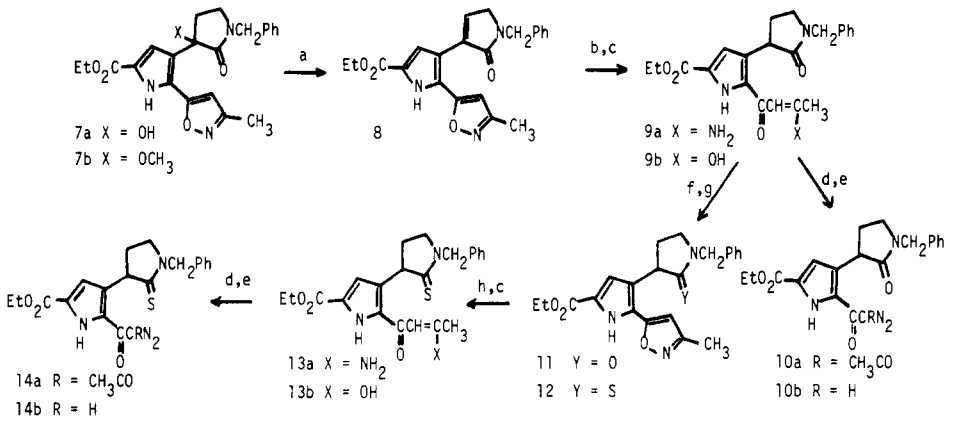
(2) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizsak, S. A. *J. Antibiot.* **1980**, *33*, 902–903. Martin, D. G.; Biles, C.; Gerpheide, S. A.; Hanka, L. J.; Krueger, W. C.; McGovren, J. P.; Mizsak, S. A.; Neil, G. L.; Stewart, J. C.; Visser, J. *J. Antibiot.* **1981**, *34*, 1119–1125. Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629–7635. Bhuyan, B. K.; Newell, K. A.; Crampton, S. L.; von Hoff, D. D. *Cancer Res.* **1982**, *42*, 3532–3537. McGovren, J. P.; Clarke, G. L.; Pratt, E. A.; De Koning, T. F. *J. Antibiot.* **1984**, *37*, 63–70.

(3) This structural relationship is well illustrated by the synthesis of the ring A skeleton from a substituted benzo[1,2-*b*:4,3-*b*']dipyrrole intermediate: Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621.

(4) In addition to ref 3, see: Magnus, P.; Or, Y.-S. *J. Chem. Soc., Chem. Commun.* **1983**, 26–27. Halazy, S.; Magnus, P. *Tetrahedron Lett.* **1984**, *25*, 1421–1424. Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389–390. Kraus, G. A.; Yue, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1198–1199. Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240–2245. Rawal, V. H.; Cava, M. P. "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, D.C., Aug 1983; American Chemical Society: Washington, D.C.; Abstract 241.

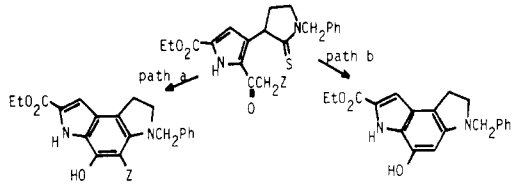
0022-3263/85/1950-0425$01.50/0

Scheme I[a]



[a] a, H^+; b, H_2/Pd-C; c, H^+, H_2O; d, $ArSO_2N_3$; e, C_4H_9N; f, NH_2OH; g, P_4S_{10}; h, $Mo(CO)_6$.

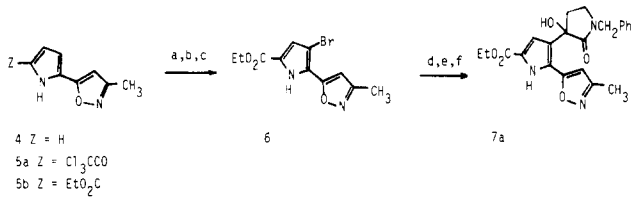
The choice of 3-(3-pyrrolyl)thiopyrrolidones as potential precursors of benzo[1,2-*b*:4,3-*b*']dipyrroles was based on the concept that these compounds could provide two possible cyclization routes. One route (path a) would depend on the potential electrophilic character of the thiopyrrolidone structure, which can be elicited by S-alkylation. The work of Hart provides a recent example of this type of reactivity.[5] The alternative mode of cyclization could be based on the Eschenmoser sulfur extrusion reaction (path b).[6] Thus, if Z is an electron withdrawing



substituent, cyclization following path a would proceed through enolate type condensation whereas with Z as a potential leaving group, the Eschenmoser process would be accessible. To examine the feasibility of these schemes we have synthesized compounds with both type of Z substituents.

Results

The key intermediate in the present study was ethyl 4-(1-benzyl-3-hydroxypyrrolidin-2-on-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate, **7a**. The known 2-(3-methylisoxazol-5-yl)pyrrole (**4**) was prepared by a modification of the method of Treibs.[7] This compound was converted to the ethyl ester **5b** via the trichloroacetyl derivative, **5a**, following the procedure of Harbuck and Rapoport.[8] Bromination of **5b** proceeded at C-4 of the pyrrole ring with good selectivity. The bromo ester **6** underwent halogen–metal exchange with *tert*-butyllithium after conversion to the pyrrole anion with sodium hydride. Very little addition at the ester carbonyl occurred when the halogen–metal exchange was done at −98 °C, although byproducts due to this competing process were identifiable, especially in reactions run at higher tempertures.[9] The molecular skeleton was completed by addition of the lithium reagent to 1-benzylpyrrolidine-2,3-dione[10] to give **7a** in 55% yield.



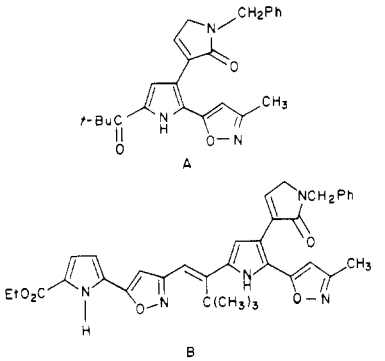
a, Cl_3CCOCl; b, EtO^-; c, Br_2; d, NaH; e, t-BuLi; f, 1-benzylpyrrolidin-2,3-dione.

Subsequent transformations of **7a** are shown in Scheme I.

As expected, the tertiary pyrrolyl carbinol **7a** is acid labile and could be dehydrated easily to **8**. In acidic methanol, substitution by a methoxy group took place to give **7b**. Catalytic reduction of **8** was accompanied by cleavage of the isoxazole ring to give enaminone **9a** which could be hydrolyzed to the β-diketone **9b**. Diazo transfer[11] with *p*-nitrobenzenesulfonyl azide followed by deacetylation with pyrrolidine gave **10b**. Compound **9b** could not be converted directly to the thiolactam **13b**. It was necessary to reform the isoxazole ring to give **11** which gave the thiolactam **12** on reaction with P_4S_{10}. Heating **12** with

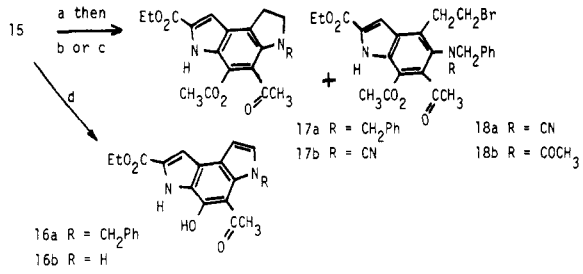
(5) Gugelchuk, M M.; Hart, D. J.; Tsai, Y. M. *J. Org. Chem.* **1981**, *46*, 3671–3675.
(6) Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868–1880.
(7) Treibs, A.; Michl, K.-H. *Liebigs Ann. Chem.* **1952**, *577*, 129–138. In contrast to the report of Treibs, we did not observe spontaneous reaction between pyrrole and diketene. We found pyridine bases catalyze the reaction and have surmised that a basic impurity in the pyrrole used by Treibs may have led to their observation.
(8) Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618–3622.

(9) On the basis of spectroscopic data given in the experimental section one of the two byproducts is believed to be the *tert*-butyl ketone analogous to **8** arising by addition of *tert*-butyllithium at the ester function, structure A. The second is more complex (M_r 605) and appears to result from addition of a second isoxazolypyrrole to the initial byproduct. The spectra suggest condensation has occurred at the isoxazole methyl group to give structure B.



(10) Southwick, P. J.; Crouch, R. T. *J. Am. Chem. Soc.* **1953**, *75*, 3413–3417.
(11) Regitz, M. *Chem. Ber.* **1966**, *99*, 3128–3147. Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 179–183.

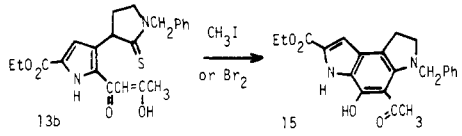
Scheme II[a]



[a] a, CH_3COCl; b, CNBr; c, CH_3COBr; d, Pd/C or Pd, H_2.

molybdenum hexacarbonyl[12] accomplished reductive cleavage of the isoxazole ring without interference with the thiolactam, giving **13a**. Hydrolysis afforded **13b**. Diazo transfer and deacylation gave the diazo ketone **14b**. The β-diketone **13b** provides a reactant which is suitable for type a cyclization whereas the diazo ketone **14b** provides a reagent suitable for examination of the Eschenmoser approach.

The initial cyclization studies were done with **13b**. Heating with methyl iodide in acetonitrile led to deposition of a white solid which on treatment with base provided an orange material characterized as **15**. The elemental analysis and mass spectrum were in agreement with the assigned composition and the expected structural features were evident in the ^1H NMR spectrum. Compound **15**

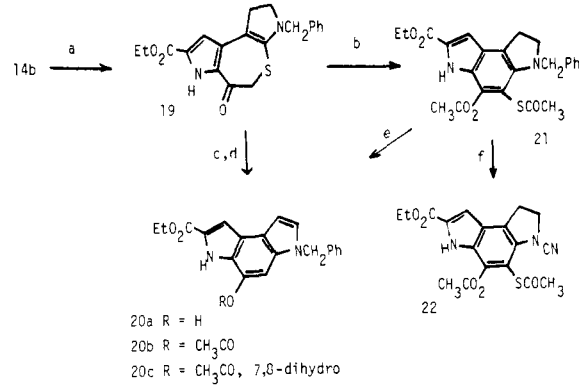


was also obtained in excellent yield by addition of 1 equiv of Br_2 to a solution of **13b**. The mechanistic basis of the bromine-induced cyclization is uncertain. The reaction can be formulated as a bromination of the enol followed by an Eschenmoser reaction[13] or as an enolate type cyclization initiated by bromination at the sulfur atom.

Attempted debenzylation of **15** with either Pearlman's catalyst or with Pd/C leads to mixtures of **16a** and **16b**, both compounds being aromatized dihydrobenzodipyrroles (Scheme II). The cyclization product **15** was readily acetylated to give **17a**, but resisted methylation with diazomethane. This behavior is characteristic of tightly hydrogen-bonded *o*-acetylphenols.[14] The acetate **17a** reacted with cyanogen bromide to give mainly **17b** (30% yield) but a small amount of ring-opening also occurred to give **18a**. With acetyl bromide ring opening was dominant and gave rise to **18b** as the only characterizable product in 18% yield.

To investigate the path b cyclization, the diazo ketone **14b** was treated with hydrogen bromide. The rationale was to generate an α-bromo ketone that could be expected to eventually cyclize under Eschenmoser conditions. In fact the thiolactam undergoes cyclization directly and after neutralization with base, the thiepinone **19** was isolated. The same compound could be obtained nearly quantitatively by treatment of **14b** with BF_3. Compound **19** was characterized spectroscopically and was obtained analytically pure.

Scheme III[a]



[a] a, HBr or $BF_3 \cdot OEt_2$; b, CH_3CO_2H, $(CH_3CO)_2O$; c, 100 °C; d, Ac_2O, DMAP; e, Raney nickel; f, CNBr.

Subsequent transformations of **19** are shown in Scheme III. On heating in acetonitrile, **19** was converted to the unstable phenol **20a**, which was characterized as the acetate **20b**. This oxidative ring contraction occurs by loss of H_2S. In the presence of tributylphosphine disappearance of **19** was *slower* and **20b** was accompanied by an approximately equal amount of the tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole **20c**. This is the expected product of Eschenmoser ring contraction. We interpret this result to indicate that the H_2S liberated in the thermal reaction may catalyze the ring contraction. A related ring contraction occurred when **19** was heated in acetic acid containing acetic anhydride. The *O*,*S*-diacetate **21** was obtained in excellent yield. Although the mechanistic details can not be completely specified, it is clear that aromatization under these conditions occurs without elimination of the sulfur substituent and thereby preserves the desired tetrahydro level of the ring system. Raney nickel desulfurization of **21** provided **20b**, confirming the relationship between the two cyclization processes. The accompanying aromatization was not unexpected in view of other results which demonstrate that the tetrahydro system is easily aromatized when the N-6 nitrogen is of the amine type. Debenzylation of **21** by cyanogen bromide gave **22** in fair yield.

The transformation of **19** to **21** was an intriguing one in terms of possible access to the 4,5-dihydroxy substitution which is found in PDE-I and PDE-II. The possibility of observing an analogous transformation of the diazoacetyl lactam **10b** was therefore investigated. Treatment of **10b** with $BF_3 \cdot OEt_2$ led to immediate evolution of nitrogen and formation of a polar substance. Treatment of the resulting solution with organic or aqueous base led to formation of solutions of a red orange compound presumed by analogy with **19** to be **23b**. In contrast to **19**, **23b** was not very stable and the orange color disappeared rapidly from methylene chloride or chloroform solutions. It was found that the orange material was not very soluble in acetonitrile. It could be isolated by treating the diazo compound **10b** with $(CH_3)_3O^+ BF_4^-$ in dichloromethane–nitromethane and evaporating to leave a residual salt, presumably the tetrafluoroborate salt of cation **23a**.[15] When this salt was

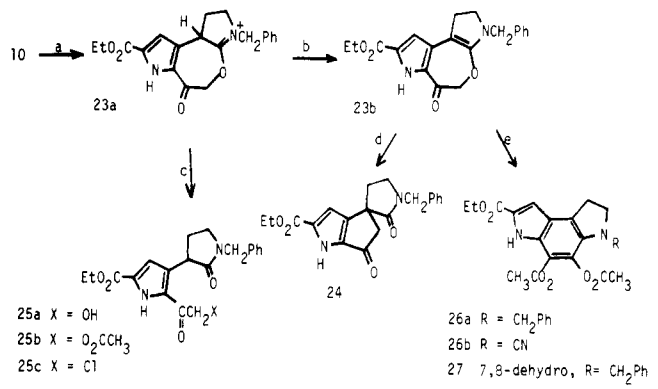
(12) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877–880.

(13) Bromodicarbonyl compounds are known to undergo sulfur extrusion without the use of phosphorus reagents: Singh, H.; Gandhi, C. S. *Synth Commun.* **1978**, *8*, 469–472. Bachi, M. D.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439–1444.

(14) Schonberg, A.; Mustafa, A. *J. Chem. Soc.* **1946**, 746–748.

(15) The trimethyloxonium ion was used with the goal of effecting decomposition of the diazo ketone by O-methylation. No evidence of O-methyl products were found. Protons may be generated by solvolysis of $(CH_3)_3O^+$ by traces of water although standard techniques for maintenance of anhydrous conditions were used. Alternatively, there may be some reversible O-methylation of nitromethane which might serve as a proton source; cf: Olah, G. A.; Fung, A. P.; Rowdah, F. N. *J. Org. Chem.* **1980**, *45*, 4149–4153. The decomposition initiated by $(CH_3)_3O^+BF_4^-$ was smoother than that with $BF_3 \cdot O(C_2H_5)_2$.

Scheme IV[a]



[a] a, BF_3·OEt_2 or $Me_3O^+BF_4^-$; b, aqueous base or DMAP; c, HX; d, 25 °C; e, Ac_2O, DMAP.

redissolved in acetonitrile and treated with (dimethylamino)pyridine **23b** precipitated and could be isolated. The NMR spectrum recorded before extensive decomposition provided confirmation of the assigned structure. Decomposition of **23b** in chloroform or acetonitrile led to an array of products but the major one (~50% yield) was the spirolactam **24** (Scheme IV). A key feature in the recognition of the identity of this material was the unusually large geminal coupling constant for the methylene group in the cyclopentanone ring (J = 18 Hz).[16] In contrast to **19**, **23b** and its conjugate acid **23a** were not stable in hydroxylic solvents. A series of products of general structure **25** were isolated when either **23a** or **23b** was exposed to acidic hydroxylic solvents. These can be accounted for as arising from nucleophilic ring opening on the iminoether linkage in **23a**.

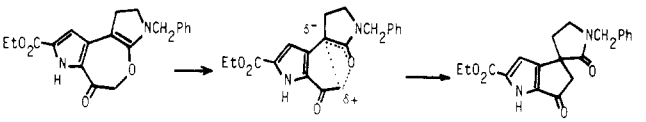
The limited stability of **23b** precluded the reaction conditions used for conversion of **19** to **21**. Under modified conditions, a 30% yield for conversion of **23b** to the diacetate **26a** was achieved by decomposing **10b** with trimethyloxonium tetrafluoroborate to give a crude salt of **23a**, which was immediately neutralized with (dimethylamino)pyridine. In acetonitrile at ~100 °C in the presence of acetic anhydride, ring contraction occurs and **26a** is obtained. This oxygen-sensitive compound was accompanied by the aromatized **27** after chromatographic purification, but samples of sufficient purity for spectroscopic verification of its structure were obtained. Variable amounts of **24** and **25b** were also formed under these conditions. Numerous modifications of the reaction conditions failed to improve the yield and in other solvents tried (dichloroethane, nitromethane) no **26a** could be found. Crude **26a** gave **26b** on reaction with cyanogen bromide.

Discussion

This work has established that the ring construction processes depicted as paths a and b are operative routes to benzo[1,2-*b*:4,3-*b*']dipyrrole derivatives. In particular, **15**, **20b**, and **21** can be obtained in good yield. Subsequent transformations to the naturally occurring *N*-acetyl or *N*-carbamoyl derivatives will need to take into account the ease of oxidative aromatization of those intermediates. It may, in fact, be preferable to modify the cyclizations to provide intermediates with stabilizing electron-attracting substituents on nitrogen, and this approach is currently under investigation.

(16) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113–116; they report J = 18–19 Hz in a somewhat related structure.

The oxepin intermediate **23b**, although tantalizing similar to **19**, has proven to be much less stable and although ring contraction to a 4,5-diacetoxybenzo[1,2-*b*:4,3-*b*']dipyrrole has been observed, the reaction will not be practical for synthesis of CC-1065 analogues unless the yield can be substantially improved. The difference in stability between **19a** and **23b** reflects the greater reactivity of the protonated iminoether moiety present in **23a**. The thermal stability of **23b** is also severely restricted by the facile rearrangement to **24**. This reaction occurs spontaneously at room temperature in solution and seems best formulated as a formal 1,3-shift, presumably occurring through a polarized transition state or an intermediate with dipolar character.



Experimental Section

General Methods. Extracts were generally dried by shaking with aqueous NaCl and then stirring over solid sodium sulfate. All of the tetrahydrobenzodipyrroles were air sensitive and became discolored at room temperature but could be stored in a freezer. All reactions involving tetrahydro species were run with strict exclusion of air, preferably in sealed ampules. Flash chromatography was done with E. Merck Kieselgel 60, 230–400 mesh. Infrared spectra were recorded with a Perkin-Elmer 1430 ratio recording infrared spectrophotometer. ^1H NMR spectra were recorded on either a Varian EM-390 (90 MHz) or a Nicolet NT-360 (360 MHz). The chemical shifts from Me_4Si, multiplicity, and integration ratios are stated for individual compounds. Low-resolution mass spectra were obtained on a Finnigan Model 3200 quadrupole mass spectrometer. Samples with spectra designated EI were ionized by electron impact at 70 eV and spectra designated CI were obtained with CH_5^+ as the reagent ion at 0.5 torr CH_4. The high-resolution molecular ion (HRMI) data were provided by Harvey Labs, Charlottesville, VA. Microanalyses were done by Atlantic Microlabs, Atlanta, GA.

2-(1,3-Dioxobutyl)pyrrole.[7] A well-stirred mixture of freshly distilled pyrrole (0.2 mol, 13.9 mL) and freshly distilled diketene (0.22 mol, 17.3 mL) was cooled to −5 °C. Pyridine (50 drops) was slowly added to the cooled solution at such a rate that the temperature did not rise above 50–60 °C. After the pyridine had been added and the reaction was no longer exothermic, the solution was stirred overnight at room temperature. The volatile components were removed at 50 °C (0.1 mm). The solid material was purified by flash chromatography (2:3 ether:hexanes) to give 2-(1,3-dioxobutyl)pyrrole, 10.83 g, 36% yield. Pale yellow needles were obtained by crystallization from hexanes, mp 85–90 °C (lit.[7] mp 89 °C).

2-(3-Methylisoxazol-5-yl)pyrrole (4). 2-(1,3-Dioxobutyl)-pyrrole (0.124 mol, 18.70 g) in methanol (200 mL) was added to a solution prepared from hydroxylamine hydrochloride (0.128 mol, 8.86 g) and triethylamine (0.136 mol, 19.9 ml) in methanol (60 mL). The solution was refluxed for 40 min, at which time TLC showed complete conversion to a more polar material, which is presumably the oxime. The methanol solution was made just acidic by the addition of *p*-toluenesulfonic acid. The solution was heated and the cyclization to the less polar isoxazole was rapid. The solution was poured into water and extracted with methylene chloride. Evaporation and recrystallization from ether–hexanes gave **4** (17.47 g, 95%) as pale tan needles, mp 128–131 °C (lit.[7] mp 133 °C sublimed).

2-(3-Methylisoxazol-5-yl)-5-(trichloroacetyl)pyrrole (5a). 2-(3-Methylisoxazol-5-yl)pyrrole (0.117 mol, 17.4 g) was dissolved in 150 mL of 1,2-dichloroethane. Trichloroacetyl chloride (0.351 mol, 39.3 mL) was added to the solution and it was heated to reflux for 2 h. The deep purple solution was reduced to about one-half volume and 400 mL of hexanes was added, causing **5a** (31.2 g) to precipitate as dark purple crystals. Three recrystallizations from chloroform–hexanes gave 20.7 g of **5a** as colorless plates, mp 155–156 °C. The mother liquors were eluted through a flash

column (CH_2Cl_2) to give an additional 9.40 g of **5a**: mp 155.5–156 °C; total yield, 30.15 g, 88%; IR (KBr) 3200, 1670, 1630, 1400, 1260, 1055, 820, 750, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 6.38 (s, 1 H), 6.69 (m, 1 H), 7.39 (m, 1 H), 9.98 (br s, 1 H). Anal. Calcd for $C_{10}H_7N_2O_2Cl_3$: C, 40.92; H, 2.40; N, 9.54. Found: C, 40.87; H, 2.44; N, 9.51.

Ethyl 5-(3-Methylisoxazol-5-yl)pyrrole-2-carboxylate (5b). Sodium (.0122 mol, 0.28 g) was allowed to dissolve in 400 mL of anhydrous ethanol. The trichloromethyl ketone **5a** (0.102 mol, 29.9 g) was added to the sodium ethoxide solution. The reaction was complete after 30 min. Acetic acid (0.02 mol, 1.16 mL) was added and the solution was poured into water and extracted with chloroform. Recrystallization of the product from chloroform–hexanes gave, in several crops, **5b** (22.3 g, 99%) as beautiful colorless needles: mp 142–143 °C; IR (KBr) 3300, 2990, 1690, 1635, 1415, 1327, 1203, 800, 763 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37, (t, J = 7.5 Hz, 3 H), 2.30 (s, 3 H), 4.34 (q, J = 7.5 Hz, 2 H), 6.22 (s, 1 H), 6.58 (m, 1 H), 6.90 (m, 1 H), 9.70 (br s, 1 H). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.52; N, 12.69.

Ethyl 4-Bromo-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (6). The ester **5b** (0.023 mol, 5.0 g) and sodium acetate trihydrate (0.023 mol, 3.2 g) were dissolved in 60 mL of acetic acid. Dichloromethane (40 mL) was added and the solution was cooled to 5 °C. Bromine (0.023 mol, 3.4 g) was added as an acetic acid solution (30 mL). A precipitate formed soon after the addition of bromine was complete. The mixture was stirred for 5 min at 5 °C and 20 min at room temperature and then poured into water (300 mL). The product was extracted into methylene chloride, dried, and evaporated to give a solid. TLC showed one major spot and a slightly less polar spot, corresponding to the minor product ethyl 5-(4-bromo-3-methylisoxazol-5-yl)pyrrole-2-carboxylate. Repeated recrystallizations (six total) from ethanol gave **6**, 4.93 g, 73%, as colorless needles, mp 186–187 °C. The remaining crude material was estimated by NMR integration to contain 1.01 g of **6**, 605 mg of the byproduct, and 135 mg of recovered **5b**. Total yields: 6, 5.95 g, 87%; isomeric bromoisoxazole, 605 mg, 9%; recovered **5b**, 135 mg, 2.7%. **6**: IR (KBr) 3260, 2990, 1705, 1620, 1410, 1320, 1205, 1018, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.35 (s, 3 H), 4.35 (q, J = 7.5 Hz, 2 H), 6.72 (s, 1 H), 6.97 (d, J < 2 Hz, 1 H), 9.74 (br s, 1 H). Anal. Calcd for $C_{11}H_{11}N_2O_3Br$: C, 44.17; H, 3.71; N, 9.36. Found: C, 44.29; H, 3.72; N, 9.35.

Ethyl 4-(1-Benzyl-3-hydroxy-2-oxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (7a). The sodium salt of **6** (10.6 mmol, 3.18 g) was prepared in dry THF (170 mL) by the addition of sodium hydride (11.7 mmol, 469 mg of 60% NaH dispersion in oil). The mixture was stirred for 10 min at room temperature and then cooled to −98 °C. A solution of *tert*-butyllithium (2.6 M in pentane, 21.8 mmol, 8.40 mL) was added at −98 °C, giving a red solution. After stirring for 3 min, a solution of 1-benzylpyrrolidine-2,3-dione (13.9 mmol, 2.62 g) in 30 mL of THF precooled to −78 °C was added. The reaction mixture was then allowed to warm to −78 °C and was stirred at that temperature for 30 min. The reaction mixture was stirred an additional 30 min at room temperature and then quenched with acetic acid (22.4 mmol, 1.3 mL). The mixture was poured into water (300 mL) giving a dark solution. Dilute hydrochloric acid was added until the dark color lightened to a pale brown (pH 5). The product was extracted into ethyl acetate. The crude product was purified by flash chromatography (3:2 hexanes:ethyl acetate, 1:1 hexanes:ethyl acetate). The major fraction was crystallized from chloroform–hexanes to give 2.16 g (5.3 mmol) of **7a** as white crystals, mp 168–169 °C. Also recovered from the column was **5b** (2.62 mmol, 577 mg) and a mixture (413 mg) containing alcohol **7a** and two byproducts. The byproducts were more easily separated after the subsequent elimination step, which provided an additional 0.6 mmol of **8**, making the total yield of **7a** 55%. **7a**: IR (KBr) 3440, 2995, 1720, 1417, 1205 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 2.20 (s, 3 H), 2.35 (m, 2 H), 3.34 (m, 3 H), 4.33 (q, J = 7.5 Hz, 2 H), 4.64 (s, 2 H), 6.47 (s, 1 H), 6.72 (s, 1 H), 7.37 (s, 5 H), 11.28 (br s, 1 H). Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.53; H, 5.70; N, 10.21.

Ethyl 4-(1-Benzyl-2-oxo-Δ^3-pyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (8). Alcohol **7a** (5.26 mmol, 2.15 g) was dissolved in 50 mL of concentrated hydrochloric acid (warming slightly, <40 °C, if necessary), giving a pale yellow solution. The mixture was stirred for 20 min at room temperature and then poured into water. The product was extracted into ethyl acetate. The organic layer was washed with aqueous $NaHCO_3$ and NaCl, dried, and evaporated to leave a solid material, 1.97 g. Recrystallization from chloroform–hexanes gave **8**, 1.20 g, as colorless needles, mp 185–186 °C. The crude material remaining was purified by flash chromatography (3:2 hexanes:ethyl acetate) to give an additional 720 mg of **8**; total yield 1.92 g, 93%. Trace amounts (~4%) of two less polar olefins, A, colorless crystals from ether–hexanes, mp 174–176 °C, and B, yellow crystals from chloroform–hexanes, darkens and softens at 212 °C, melts at 220–222 °C, were also recovered.[9] **8**: IR (KBr) 3320, 2950, 1700, 1687, 1463, 1422, 1237, 1040 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.30 (s, 3 H), 3.93 (d, J < 2 Hz, 2 H) 4.32 (q, J = 7.5 Hz, 2 H), 4.71 (s, 2 H) 6.26 (s, 1 H), 7.16 (d, J = 2 Hz, 1 H) 7.13 (s, 6 H), 9.74 (br s, 1 H). Anal. Calcd for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.36; H, 5.44; N, 10.69. Byproduct A: ^1H NMR (90 MHz, $CDCl_3$)[9] δ 1.38 (s, 9 H), 2.28 (s, 3 H), 3.90 (d, J = 2 Hz, 2 H), 4.68 (s, 2 H), 6.24 (s, 1 H), 7.30 (m, 6 H), 7.49 (d, J < 2 Hz, 1 H), 9.69 (br s, 1 H). Byproduct B: ^1H NMR (90 MHz, $CDCl_3$)[9] δ 1.20 (s, 9 H), 1.31 (t, J = 7.5 Hz, 3 H), 2.19 (s, 3 H), 3.68 (d, J = 2 Hz, 2 H), 4.28 (q, J = 7.5 Hz, 2 H), 4.59 (s, 2 H), 5.17 (s, 1 H), 5.93 (s, 1 H), 6.03 (m, 1 H), 6.43 (m, 1 H), 6.62 (m, 1 H), 6.73 (s, 1 H), 7.3 (m, 5 H), 9.27 (br s, 1 H), 9.62 (br s, 1 H); mass spectrum (EI) 605, 581, 337, 268, 256 amu.

Ethyl 4-(1-Benzyl-3-methoxy-2-oxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (7b). Alcohol **7a** (0.51 mmol, 207 mg) was dissolved in 25 mL of dry methanol containing 30 mg of anhydrous *p*-toluenesulfonic acid. After refluxing 1.5 h, the methanol was evaporated and the crude product was purified by preparative layer chromatography (3:2 hexanes:ethyl acetate), 4 elutions. Obtained in increasing polarity were **7b**, 157 mg, mp 162–164 °C, 73% (83% based on recovered **7a**), **8** (16.7 mg, 8.4%), and **7a** (24.8 mg). **7b**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3 H), 2.32 (s, 3 H), 2.37 (m, 2 H), 3.20 (m, 2 H), 3.32 (s, 3 H), 4.32 (q, J = 7.5 Hz, 2 H), 4.50 (ABq, 2 H), 6.80 (s, 1 H), 6.95 (d, J = 3 Hz, 1 H), 7.27 (s, 5 H), 9.77 (br s, 1 H).

Ethyl 4-(1-Benzyl-2-oxopyrrolidin-3-yl)-5-(3-amino-1-oxo-2-butenyl)pyrrole-2-carboxylate (9a) and Ethyl 4-(1-Benzyl-2-oxopyrrolidin-3-yl)-5-(1,3-dioxobutyl)pyrrole-2-carboxylate (9b). A solution of **8** (7.94 mmol, 3.10 g) in 200 mL of ethanol, containing 2 g of 5% Pd/C, was hydrogenated under 100 psi of hydrogen at 50 °C for 9 h. The Pd/C was filtered off and the ethanol was removed to give a solid residue (3.29 g). The product was purified by flash chromatography (1:1 hexanes:ethyl acetate, 7:3 ethyl acetate:hexanes, ethyl acetate). Enaminone **9a** (2.57 g, 82%) was obtained as a pale yellow foam. **9a**: IR (KBr) 3380, 2980, 1700, 1640, 1545, 1230, 1040 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.03 (s, m, 4 H), 2.50 (m, 1 H), 3.30 (d of d, J = 6, 7 Hz, 2 H), 4.38 (t, J = 9 Hz, 1 H), 4.40 (q, J = 7.5 Hz, 2 H) 4.54 (s, 2 H), 5.33 (br s, 1 H), 5.50 (s, 1 H), 6.72 (d, J < 2 Hz, 1 H), 7.32 (s, 5 H), 9.68 (br s, 1 H), 10.04 (br s, 1 H).

Enaminone **9a** (0.22 mmol, 87 mg) was dissolved in 10 mL of THF. An equal volume of 5% hydrochloric acid was added and the mixture was heated at 50 °C for 20 min. The solution was poured into water and the product was extracted into ethyl acetate. Evaporation left a white solid which was recrystallized from chloroform–hexanes to give **9b** (72.4 mg, 83%): mp 170–171 °C; IR (KBr) 3460, 1740, 1675, 1300, 1230 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3 H), 2.0–2.1 (m, 1 H), 2.11 (s, 3 H), 2.48 (m, 1 H), 3.31 (d of d, J = 7 Hz, 5 Hz, 2 H), 4.28–4.50 (m, 5 H), 6.05 (s, 1 H), 6.72 (s, 1 H), 7.32 (s, 5 H), 9.96 (br s, 1 H), 16.12 (v br s, 1 H). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.49; H, 6.12; N, 7.06.

Ethyl 4-(1-Benzyl-2-oxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (11). Enaminone **9a** (5.08 mmol, 2.02 g) and hydroxylamine hydrochloride (5.23 mmol, 364 mg) were heated to reflux in 30 mL of ethanol for 1 h. The solution was poured into water and the product was extracted into methylene chloride and recovered by evaporation. Recrystallization of the solid (1.92 g, 96%) from chloroform–hexanes

gave an analytical sample of **11** as white microneedles, mp 164–165 °C. **11**: IR (KBr) 3420, 1695, 1660, 1205 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3 H), 1.9–2.6 (m, 2 H), 2.30 (s, m, 3 H), 3.34 (d of d, J = 6, 7 Hz, 2 H), 4.03 (t, J = 9 Hz, 1 H), 4.30 (q, J = 7.5 Hz, 2 H), 4.31, 4.47, 4.51, 4.68 (ABq, 2 H), 6.40 (s, 1 H), 6.72 (d, J < 2 Hz, 1 H), 7.34 (s, 5 H), 9.88 (br s, 1 H). Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 66.98; H, 5.93; N, 10.65.

Ethyl 4-(1-Benzyl-2-thioxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (12). A mixture of isoxazole **11** (3.08 mmol, 1.21 g) and P_4S_{10} (0.46 mmol, 206 mg) was heated under reflux in 100 mL of dry toluene for 30 min. TLC showed mostly **12** along with some starting material **11**. An additional 0.09 mmol, 41 mg, of P_4S_{10} was added and the solution was heated for 30 min to complete conversion of **11** to **12**. The toluene was decanted and the red gummy residue was triturated with additional hot toluene (25 mL). The toluene extracts were combined and evaporated to leave a crude solid residue. Recrystallization from chloroform–hexanes gave **12** (839 mg) as pale yellow crystals, mp 186–187 °C. Flash chromatography of the mother liquors (ethyl acetate:hexanes) gave an additional 264 mg of **12**: total yield, 1.10 g, 88%; IR (KBr) 3285, 2990, 1690, 1630, 1510, 1250, 1225, 1030 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 2.30 (m, 2 H), 2.34 (s, 3 H), 3.67 (t, J = 9 Hz, 2 H), 4.32 (q, J = 7.5 Hz, 2 H), 4.43 (t, J = 9 Hz, 1 H), 5.05 (ABq, 2 H), 6.46 (s, 1 H), 6.75 (d, J < 2 Hz, 1 H), 7.40 (s, 5 H), 9.57 (br s, 1 H). Anal. Calcd for $C_{22}H_{23}N_3O_3S$: C, 64.53; H, 5.66; N, 10.26. Found: C, 64.58; H, 5.69; N, 10.21.

Ethyl 4-(1-Benzyl-2-thioxopyrrolidin-3-yl)-5-(3-amino-1-oxobut-2-enyl)pyrrole-2-carboxylate (13a). Thiolactam **12** (2.61 mmol, 1.07 g) and molybdenum hexacarbonyl (1.31 mmol, 345 mg) were dissolved in 25 mL of wet acetonitrile (20 drops of H_2O). The mixture was heated to reflux for 1.5 h. The acetonitrile was evaporated, leaving a black gum. Flash chromatography (hexanes, 1:1 ethyl acetate:hexanes) removed the black material and gave 1.16 g of a brown solid. Recrystallization from chloroform:hexanes gave **13a**, 701 mg, as tan crystals, mp 164–165 °C. An additional 187 mg of **13a** and 84 mg of diketone **13b** were obtained after flash chromatography of the mother liquors (hexanes:ethyl acetate). The total yield of **13a** was 91%. A second recrystallization from chloroform–hexanes provided an analytical sample, mp 164–165 °C, as light tan crystals. **13a**: IR (KBr) 3390, 3270, 2997, 1710, 1614, 1535, 1303, 1220, 1030 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 1.9–2.1 (m, 1 H), 2.04 (s, 3 H), 2.3–2.7 (m, 1 H), 3.60 (t, J = 7 Hz, 2 H), 4.28 (q, J = 7.5 Hz, 2 H), 4.84 (t, J = 7 Hz, 1 H), 4.82, 5.01, 5.04, 5.22 (ABq, 2 H), 5.59 (s, 1 H), 6.65 (s, 1 H), 7.38 (s, 5 H), 9.62 (br s, 1 H), 10.03 (br s, 1 H). Anal. Calcd for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21. Found: C, 63.97; H, 6.14; N, 10.15.

Ethyl 4-(1-Benzyl-2-thioxopyrrolidin-3-yl)-5-(1,3-dioxobutyl)pyrrole-2-carboxylate (13b). Enaminone **13a** (2 mmol, 821 mg) was dissolved in 15 mL of the THF and an equal volume of 5% HCl was added. The mixture was stirred at 55 °C for 20–25 min. The mixture was poured into water (200 mL) and the product was extracted into ethyl acetate. The solid residue was recrystallized from chloroform–hexanes to give **13b**, quantitative yield, as lemon yellow crystals: mp 151–153 °C; IR (KBr) 3300, 2997, 1715, 1610 1515, 1260, 1220, 1032, 710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.14 (s, 3 H), 2.50 (m, 2 H), 3.60 (t, J = 7.5 Hz, 2 H), 4.30 (q, J = 7.5 Hz, 2 H), 4.70 (t, J = 7.5 Hz, 1 H), 5.04 (ABq, 2 H), 6.00 (s, 1 H), 6.70 (d, J < 2 Hz, 1 H), 7.37 (s, 5 H), 9.59 (s, 1 H), 16.03 (br s, 1 h). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 63.80; H, 5.90; N, 6.69.

Ethyl 4-(1-Benzyl-2-thioxopyrrolidin-3-yl)-5-(2-diazo-1,3-dioxobutyl)pyrrole-2-carboxylate (14a) and Ethyl 4-(1-Benzyl-2-thioxopyrrolidin-3-yl)-5-(diazoacetyl)pyrrole-2-carboxylate (14b). Thiolactam **13b** (1.26 mmol, 521 mg), *p*-nitrobenzenesulfonyl azide (1.5 mmol, 346 mg), and triethylamine (1.5 mmol, 0.21 mL) were dissolved in 35 mL of THF and stirred for 5.5 h at room temperature. The mixture was poured into water (100 mL) and extracted with ethyl acetate. The extract was evaporated at <50 °C and the crude material was run through a flash column (hexanes:ethyl acetate). A yellow foam was obtained which was triturated with chloroform, giving rise to a pale yellow precipitate (201.4 mg), mp 178–180 °C, which is *p*-nitrobenzenesulfonamide. Evaporation of the chloroform gave 610 mg, 110%, of **14a** as a yellow foam: IR (KBr) 2950, 2140, 1710, 1640, 1250 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.02 (m, 1 H), 2.48 (s, 3 H), 2.50 (m, 1 H), 3.58 (t, J = 7.5 Hz, 2 H), 4.34 (q, J = 7.5 Hz, 2 H), 4.90 (m, 1 H), 4.80, 4.98, 5.10, 5.26 (ABq, 2 H), 6.80 (d, J < 2 Hz, 1 H), 7.34 (s, 5 H), 13.55 (br s, 1 H).

To an ethanol solution (40 mL) of **14a** (610 mg) was added pyrrolidine (40 drops) and the mixture was stirred 20 min at room temperature. The ethanol was removed by evaporation (<50 °C) and the crude solid was purified by flash chromatography (hexanes:ethyl acetate). Recrystallization from chloroform–hexanes gave **14b**, 422 mg, as lemon yellow crystals, which shrinks and darkens at 135 °C and melts at 172–175 °C with gas evolution. An additional 80 mg of slightly less pure **14b** was recovered from the mother liquors, making the overall yield of **13b** from dione quantitative. **14b**: IR (KBr) 2980, 2100, 1720, 1600, 1315, 1250, 1212 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3 H), 2.15–2.50 (m, 2 H), 3.64 (m, 2 H), 4.29 (q, J = 7.5 Hz, 2 H, 4.61 (t, J = 9 Hz, 1 H), 4.80, 4.97, 5.04, 5.21, (ABq, 2 H), 6.65 (d, J < 2 Hz, 1 H), 6.70 (s, 1 H), 7.31, (s, 5 H), 9.82 (br s, 1 H).

Ethyl 5-Acetyl-6-benzyl-4-hydroxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (15). A. Cyclization of 13b with Methyl Iodide. To a solution of **13b** (0.243 mmol, 100 mg) in 2 mL of dry THF was added methyl iodide (0.73 mmol, 0.045 mL), and the mixture was sealed under nitrogen in a Pyrex tube. The tube was heated at 80 °C for 15 h during which the pale yellow solution deposited white crystals. The tube was cooled to −78 °C and opened, and the contents were poured into water (25 mL). A strong odor of methanethiol was noticed. The aqueous solution was made slightly basic (aqueous $NaHCO_3$) and the product was extracted into methylene chloride. The deep yellow-orange extract was dried and evaporated, leaving an orange solid. Recrystallization from methylene chloride–hexanes gave **15**, 89.3 mg, 97%, as a yellow-orange crystalline powder, mp 158–160 °C. Recrystallization from ethanol gave orange needles, mp 162–163 °C. **15**: IR (KBr) 3320, 2995, 1703, 1615, 1380, 1290, 1260, 1108, 747 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 2.78 (s, 3 H), 2.89 (t, J = 7.5 Hz, 2 H), 3.51 (br t, J = 7.5 Hz, 2 H), 4.0 (s, 2 H), 4.37 (q, J = 7.5 Hz, 2 H), 6.89, (d, J < 2 Hz, 1 H), 7.28 (s, 5 H), 9.27 (br s, 1 H), 13.44 (br s, 1 H); mass spectrum (EI) 378, 287, 241, 313, 149, 91 amu. Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.57; H, 5.88; N, 7.33.

B. Cyclization with Bromine. To a solution of **13b** (0.049 mmol, 20 mg) in 1 mL of 1,2-dichloroethane at 0 °C was added bromine (0.05 mmol, 8 mg) in 1 mL of dichloroethane. The mixture was stirred for 5 min at 0 °C and 30 min at room temperature. The solution was poured into water, made basic with aqueous $NaHCO_3$, and extracted with dichloroethane. The deep red-orange dichloroethane extract was heated for several minutes with a heat gun. This procedure initiates a distinct color change from red-orange to orange. Evaporation gave 20 mg of an orange solid which was nearly pure **15** by TLC and NMR. Elution through a flash column gave pure **15**, 15 mg, 81%, identical with **15** from reaction of **13b** and methyl iodide by IR, ^1H NMR, and TLC.

Ethyl 5-Acetyl-6-benzyl-4-hydroxy-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (16a) and Ethyl 5-Acetyl-4-hydroxy-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (16b). A. By Reaction with Palladium/Carbon. A solution of **15a** (0.039 mmol, 14.9 mg) was dissolved in 3 mL of toluene. Palladium on carbon (10%), 5 mg, was added and the toluene solution was heated to reflux for 2 h, at which time TLC showed a trace of **15a** along with two more polar products. The solution was filtered and the toluene was evaporated to leave a crude residue. Flash chromatography (4:1 hexanes:ethyl acetate then 2:1 hexanes:ethyl acetate) resulted in the isolation of two products which were assigned structures **16a** (4.6 mg, 31%) and **16b** (2.4 mg, 22%). **16a**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.44 (t, J = 7.5 Hz, 3 H), 2.63 (s, 3 H), 4.44 (q, J = 7.5 Hz, 2 H), 5.24 (s, 2 H), 6.79 (d, J = 3 Hz, 1 H), 6.92 (m, 3 H), 7.25 (m, 3 H), 7.33 (d, J = 2 Hz, 1 H), 9.42 (br s, 1 H), 12.15 (s, 1 H); mass spectrum (EI) 376, 334, 285, 239, 211, 91 amu; HRMI calcd for $C_{22}H_{20}N_2O_4$ 376.1421, found 376.1420. **16b**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.44 (t, J = 7.5 Hz, 3 H), 2.86 (s, 3 H), 4.44 (q, J = 7.5 Hz, 2 H),

6.81 (d of d, J = 3, 2 Hz, 1 H), 7.18 (t, J = 3 Hz, 1 H), 7.34 (d, J = 2 Hz, 1 H), 8.49 (br s, 1 H), 9.43 (br s, 1 H), 14.25 (s, 1 H); mass spectrum (EI) 286, 240, 212, 197, 184 amu; HRMI calcd for $C_{15}H_{14}N_2O_4$ 286.0951, found 286.0957.

B. From Attempted Hydrogenolysis. An ethanol solution (5 mL) of **15a** (11.5 mg) was shaken in a pressure bottle with 5 mg of Pearlman's catalyst[17] at 55 psi H_2 for 1 h. Two more polar products were recovered in low mass balance (3 mg). The 360-MHz NMR specrum of the mixture is a superposition of the spectra for the compounds assigned structures **16a** and **16b**.

Ethyl 4-Acetoxy-5-acetyl-6-benzyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-3-carboxylate (17a). An unpurified sample of **15** (prepared from 0.243 mmol of **13b**) was dissolved in 8 mL of methylene chloride and the solution was cooled to −5 °C. Triethylamine (2 drops) and acetyl chloride (2 drops) were added to the solution of **15**. TLC showed mostly **17a** along with some **15**. An additional drop of triethylamine and acetyl chloride were added and the solution was stirred another 30 min at −5 °C. The solvent was evaporated and the product was purified by flash chromatography (1:1 ethyl acetate:hexanes) to give **17a** as a yellow foam, 100.1 mg, 98%. Crystals could not be obtained and the compound darkened rapidly on storage. **17a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.37 (s, 3 H), 2.57 (s, 3 H), 3.06 (t, J = 7.5 Hz, 2 H), 3.44 (t, J = 7.5 Hz, 2 H), 4.04 (s, 2 H), 4.36 (q, J = 7.5 Hz, 2 H), 6.93 (d, J < 2 Hz, 1 H), 7.28 (s, 5 H), 8.80 (br s, 1 H).

Ethyl 4-Acetoxy-5-acetyl-6-cyano-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (17b). A Pyrex tube (8 mm) containing **17a** (0.12 mmol, 50 mg) and cyanogen bromide (0.48 mmol, 50 mg) dissolved in 1.5 mL of 1,2-dichloroethane was sealed under vacuum and heated at 92 °C for 3 h. The tube was cooled and opened. The contents were poured into water and extracted with methylene chloride. The residue from evaporation was subjected to flash chromatography (hexanes:ethyl acetate increasing from 4:1 to 1:1) to give **17b** (14.2 mg, 34%), mp 150–152 °C, after recrystallization from ethyl acetate:hexane. A small amount of **18a** (2.4 mg, 3.8%) was also isolated. **17b**: IR (KBr) 3220, 2990, 2200, 1770, 1700, 1390, 1170, cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.42 (t, J = 7.5 Hz, 3 H), 2.43 (s, 3 H), 2.64 (s, 3 H), 3.40 (t, J = 10 Hz, 2 H), 4.26 (t, J = 10 Hz, 2 H), 4.43 (q, J = 7.5 Hz, 2 H), 7.06 (d, J = 2 Hz, 1 H), 8.89 (br s, 1 H); MS (EI) 355, 313, 267, 251, 239. **18a**: IR (KBr) 3260, 2985, 2200, 1775, 1705, 1340, 1260, 1175, 1015, 740 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45 (t, J = 7.5 Hz, 3 H), 2.44 (s, 3 H), 2.67 (s, 3 H), 3.26 (m, 2 H), 3.28 (m, 1 H), 3.64 (m, 1 H), 4.27, 4.32, 4.53, 4.58 (ABq, 2 H), 4.45 (q, J = 7.5 Hz, 2 H), 7.24 (d, J < 2 Hz, 1 H), 7.32–7.40 (m, 5 H), 9.11 (br s, 1 H); mass spectrum (EI) 485, 483, 463, 390, 279, 256, 240, 205, 149, 91 amu.

Ethyl 7-Acetoxy-6-acetyl-5-(*N*-benzylacetamido)-4-(2-bromoethyl)indole-2-carboxylate (18b). A 1,2-dichloroethane solution (3 mL) containing **15** (0.02 mmol, 10 mg) and acetyl bromide (10mg) was refluxed for 1 h. TLC showed one more polar spot in addition to unchanged **15a**. Additional acetyl bromide (5 mg) was added and the solution was heated for another hour. The solvent was evaporated and the crude residue was purified by flash chromatography (2:1 hexanes:ethyl acetate). A compound assigned structure **18b**, 2.3 mg, 18%, was obtained as the only characterizable product. **18b**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.44 (t, J = 7.5 Hz), 1.93 (s), 2.23 (s), 2.42 (s), 3.04 (m, 2 H), 3.28 (m, 1 H), 4.23, 4.27, 5.25, 5.29 (ABq, 2 H), 4.44 (q, J = 7.5 Hz, 2 H), 7.20–7.25 (m), 9.06 (br s); mass spectrum (EI) 544, 542, 502, 500, 463, 421, 379, 287, 241, 149, 132, 91 amu.

Ethyl 7-Benzyl-4-oxo-3,4,5,7,8,9-hexahydrothiepino[2,3-*b*:5,4-*b*']dipyrrole-2-carboxylate (19). A solution of **14b** (0.70 mmol, 280 mg) in dry methylene chloride (30 mL) was treated with boron trifluoride etherate (0.70 mmol, 100 mg) dissolved in methylene chloride (5 mL). Vigorous evolution of nitrogen occurred and after stirring for 15 min the solution was poured into aqueous Na_2CO_3 solution. The solution was extracted with additional methylene chloride to give a bright orange solution. After evaporation, 260 mg (100%) of **19** was obtained. Recrystallization from chloroform–hexane gave orange needles, mp 158–159 °C. Alternatively, the decomposition could be done in acetic acid by adding 48% hydrobromic acid. The yield was quantitative on a 0.3-mmol scale but neutralization of the excess acetic acid was inconvenient on a larger scale. **19**: IR (KBr) 3300, 2980, 2850, 1710, 1640, 1580, 1250, 1180, 760 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.87 (t, J = 9 Hz, 2 H), 3.30 (t, J = 9 Hz, 2 H), 2.45 (s, 2 H), 4.31 (s, 2 H), 4.34 (q, J = 7.5 Hz, 2 H), 6.63 (d, J < 2 Hz, 1 H), 7.29 (s, 5 H), 9.68 (br s, 1 H). Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.21; H, 5.57; N, 7.54.

Ethyl 4-Acetoxy-6-benzyl-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (20b). A. By Thermolysis of 19 in Acetonitrile. A solution of **19** (.027 mmol, 10 mg) in 2 mL of acetonitrile was heated in a sealed tube to 100 °C for 6 h, during which time the orange color faded. The tube was opened and treated with (dimethylamino)pyridine (2 mg) and acetic anhydride (0.1 mL). After 1 h the mixture was evaporated to dryness and purified by flash chromatography to give 8 mg (80%) of **20b**, mp 160–161 °C after recrystallization from ethyl acetate:hexane. **20b**: IR (KBr) 3280, 1755, 1675, 1290, 1200, 748 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3 H), 2.30 (s, 3 H), 4.32 (q, J = 7.5 Hz, 2 H), 5.25 (s, 2 H), 6.67 (d, J = 2 Hz, 1 H), 7.0–7.35 (m, 7 H), 7.42 (d, J = 1 Hz, 1 H), 8.95 (br s, 1 H). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.19; H, 5.36; N, 7.44. Found: C, 70.18; H, 5.41; N, 7.44.

B. By Thermolysis of 19 in the Presence of Tributylphosphine. A solution of **19** (.022 mmol, 8 mg) in 1 mL of acetonitrile containing 10 mg of tributylphosphine was heated to 110 °C for 20 h. The orange color slowly disappeared. When the color had faded to yellow the tube was opened and the acylation was effected as above. After flash chromatography a 1:1 mixture of **20b** and the dihydro derivative **20c** was obtained in about 70% yield. **20c**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz), 2.27 (s), 3.10 (t, J = 8 Hz), 3.36 (t, J = 8 Hz) 4.21 (s), 4.30 (q, J = 7.5 Hz), 6.60 (s), 7.1–7.5 (m), 8.6 (br s).

C. By Raney Nickel Desulfurization of 21. A solution of **21** (0.081 mmol, 30 mg) was dissolved in ethanol (4 mL) and Raney nickel (~100 mg) was added. The tube was cooled, degassed, and sealed. It was then heated to 100 °C for 6 h. The contents were centrifuged and the solution evaporated. Purification by flash chromatography gave 18 mg (60%) of **20b**.

Ethyl 4-Acetoxy-5-(acetylthio)-6-benzyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (21). A Pyrex tube containing **19** (0.068 mmol, 25 mg) and 0.5 mL of acetic anhydride in 1.5 mL of acetic acid was sealed under vacuum and then heated at 132 °C for 1.5 h. The tube was cooled and opened, and the contents were poured into water. The product was extracted into methylene chloride. Purification of the crude product by flash chromatography (2:1 hexanes:ethyl acetate) provided **21** as a yellow gum (27 mg, 88%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.21 (s, 3 H), 2.34 (s, 3 H), 3.08, (t, J = 7.5 Hz, 2 H), 3.46 (t, J = 7.5 Hz, 2 H), 4.35 (q, J = 7.5 Hz, 2 H), 4.47 (s, 2 H), 6.94 (d, J < 2 Hz, 1 H), 7.28 (s, 5 H), 8.64 (br s, 1 H).

Ethyl 4-Acetoxy-5-(acetylthio)-6-cyano-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (22). The debenzylation procedure described for **17b** was followed with **21** (0.11 mmol, 50 mg). The product was purified by flash chromatography (hexanes:ethyl acetate) to give **22** (33 mg, 77%). Recrystallization of **22** from ethyl acetate–hexanes gave colorless needles: mp 132–133 °C; IR (KBr) 3290, 2990, 2200, 1770, 1700, 1300, 1190 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 2.36 (s, 3 H), 2.47 (s, 3 H), 3.33 (t, J = 8 Hz, 2 H), 4.17 (t, J = 8 Hz, 2 H), 4.38 (q, J = 7.5 Hz, 2 H), 6.98 (s, 1 H), 9.00 (br s, 1 H); mass spectrum (CI) 388, 374, 360, 345, 330, 314, 304 amu. Anal. Calcd for $C_{18}H_{17}N_3O_5S$: C, 55.80; H, 4.42; N, 10.84. Found: C, 55.37; H, 5.06; N, 10.43.

Ethyl 4-(1-Benzyl-2-oxopyrrolidin-3-yl)-5-(2-diazo-1,3-dioxobutyl)pyrrole-2-carboxylate (10a) and Ethyl 4-(1-Benzyl-2-oxopyrrolidin-3-yl)-5-(diazoacetyl)pyrrole-2-carboxylate (10b). A solution of **9b** (3.00 mmol, 1.20 g) in tetrahydrofuran (60 mL) was treated with *p*-nitrobenzenesulfonyl azide (3.5 mmol, 0.82 g). Triethylamine (400 mg) was added and the solution was stirred at room temperature for 3 h. The mixture was poured into water and extracted with ethyl acetate. The crude product obtained by evaporation was stirred with chloroform,

(17) Hiskey, R. G.; Northrop, R. C. *J. Am. Chem. Soc.* **1961**, *83*, 4798–4800.

which led to crystallization of most of the *p*-nitrobenzenesulfonamide. The chloroform solution was concentrated and purified by flash chromatography to give **10a** (0.923 g, 71%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 1.4–2.1 (m, 3 H), 2.40 (s, 3 H), 3.2 (d of d, J = 5, 8 Hz, 2 H), 4.0–4.6 (q, J = 7.5 Hz + m, 6 H), 6.7 (d, J = 2 Hz, 1 H), 7.22 (s, 5 H).

The solid was dissolved in ethanol (30 mL) and pyrrolidine (700 mg) was added. The solution was stirred at room temperature and precipitation of the product began soon after mixing. After 30 min the product **10b** (0.60 g) was collected by filtration and an additional 70 mg (total yield 84%) was obtained on concentration of the mother liquors. **10b**: IR (KBr) 2090, 1710, 1650, 1590, cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 1.7–2.7 (m, 2 H), 3.3 (m, 2 H), 4.1–4.7 (q, J = 7.5 Hz + ABq, J = 1.4 Hz, 4 H), 6.64 (overlapping d, J = 1 Hz and s, 2 H).

Cyclization of 10b and Ring Contraction to 26a. Diazo ketone **10b** (65 mg) was dissolved in 3 mL of dichloromethane and 2 mL of nitromethane. There was syringed into this solution over 2–3 min a solution of trimethyloxonium tetrafluoroborate (0.21 mmol, 30 mg) dissolved in 0.5 mL of nitromethane. Nitrogen evolution was observed and after 30 min TLC indicated complete conversion of the diazo compound to polar material. The yellow solution was quickly evaporated with minimal exposure to air to give a solid residue. This was dissolved in 4 mL of acetonitrile and (dimethylamino)pyridine (0.36 mmol, 45 mg) and 0.2 mL of acetic anhydride were added. The bright red-orange solution was placed in a reaction tube, frozen in dry ice–acetone, degassed, and sealed. The solution was then immediately heated to 100–110 °C for 2 h. The cooled tube was opened and rapidly evaporated. The residue was dissolved in dichloromethane, washed with water, dried, evaporated, and subjected to flash chromatography with 2:1:1 hexane–ethyl acetate–dichloromethane for elution. The major fraction (27 mg) consisted of **26a** and **27**. When 1:1:1 hexane–ethyl acetate–dichloromethane was used for TLC development, **26a** was very slightly less polar than **27**. The spot for **26a** was moderately fluorescent (yellow orange) while **27** has a very strong blue fluorescence. The NMR spectra were assigned by comparison of fractions of varying composition. **26a**: ^{1}H NMR (360 MHz $CDCl_3$) δ 1.41 (t, J = 7.5 Hz, 3 H), 2.07 (s, 3 H), 2.37 (s, 3 H), 3.14 (t, J = 8 Hz, 2 H), 3.45 (t, J = 8 Hz, 2 H), 4.38 (overlapping s + q, J = 7.5 Hz, 4 H), 6.99 (d, J = 2 Hz, 1 H), 7.05–7.40 (m), 8.56 (br s, 1 H). **27**: (360 Hz $CDCl_3$) δ 1.47 (t, J = 7.5 Hz, 3 H), 1.98 (s, 3 H), 2.36 (s, 3 H) 4.42 (q, J = 7.5 Hz 2 H), 5.03 (s, 2 H), 6.80 (d, J = 2 Hz, 1 H), 6.99 (d, J = 6 Hz, 2 H), 7.10 (d, J = 2 Hz, 1 H), 7.2–7.4 (m, 3 H), 7.45 (d, J = 2 Hz, 1 H), 8.83 (br s, 1 H).

The mass spectrum (EI) also showed the presence of both components with the **26a** spectrum appearing somewhat before the **27** spectrum in successive scans, although the **26a** spectrum always contains peaks from the **27** spectrum. **26a**: MS (EI) 436, 394, 352, 287, 276, 215, 91 amu. **27**: MS (EI) 434, 392, 350, 303, 276, 213, 91 amu. Pure **27**, mp 220–222 °C, was obtained after reaction of the mixture with cyanogen bromide (see below).

Ethyl 4,5-Diacetoxy-6-cyano-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (26b). A sample of **26a** containing about 20% of **27** (25 mg) was dissolved in dichloroethane (2.0 mL) containing cyanogen bromide (30 mg). The solution was sealed in an ampoule and heated to 100 °C for 3 h. TLC indicated incomplete reaction and additional cyanogen bromide (30 mg) was added. The tube was resealed and heated an additional 6 h. After evaporation two major spots were evident by TLC and pure samples of **26b** (9 mg) and **27** (8 mg) containing a small amount of unreacted **26a** was obtained after flash chromatography. Compound **26b** was obtained in crystalline form, mp 261–262 °C, by recrystallization from ethyl acetate:hexane. **26b**: ^{1}H NMR (360 MHz $CDCl_3$) δ 1.42 (t, J = 7.5 Hz, 3 H), 2.40, 2.41 (2 s, 6 H), 3.40 (t, J = 8 Hz, 2 H), 4.22 (t, J = 8 Hz, 2 H), 4.41 (q, J = 7.5 Hz, 2 H), 7.03 (d, J = 1 Hz, 1 H), 8.84 (br s, 1 H); mass spectrum (EI) 371, 329, 287, 241, 213 amu; HRMI calcd for $C_{18}H_{17}N_3O_6$ 371.1115, found 371.1122. Pure **27**, mp 220–222 °C, was obtrained by recrystallization from ethyl acetate:hexanes. NMR and MS as above. HRMI calc for $C_{24}H_{22}N_2O_6$ 434.1475, found 434.1494.

Isolation and Rearrangement of 23b. Diazo ketone **10b** (60 mg) was treated with trimethyloxonium tetrafluoroborate as in the cyclization procedure. The total polar product remaining after removal of solvent was dissolved in 1 mL of acetonitrile and treated at 0 °C with a solution of 45 mg of 4-(dimethylamino)-pyridine dissolved in 0.5 mL of CH_3CN. There was rapid precipitation of an orange solid which was collected by centrifuging and drying (~50% yield). A sample in chloroform-*d* was observed by NMR. Over 2–3 h the color faded and several new peaks arose. Those which were most prominent were assignable to **24**.

Similar reactions on a 20-mg scale led to isolation of **24** in about 50% yield after flash chromatographic purification; mp 180–182 °C after recrystallization from ethyl acetate:hexane. **24**: IR (KBr) 3200, 1750, 1720, 1670, 1660, 1230 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 2.2–2.4 (m, 2 H), 2.74 (d, J = 18 Hz, 1 H), 3.33 (d of t, J = 11, 4 Hz, 1 H), 3.42 (d, J = 18 Hz, 1 H), 3.45 (m, 1 H), 4.36 (d of q, J = 7.5 Hz, 2 H), 4.43, 4.65 (ABq, J = 15 Hz, 2 H), 6.60 (d, J = 1 Hz, 1 H), 7.25–7.40 (m, 5 H), 9.52 (br s, 1 H); MS (EI) 352, 324, 310, 296, 261, 232, 91 amu. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.02; H, 5.75; N, 7.91.

Solvolysis of 23a. A. Acetic Anhydride–Acetic Acid. A sample of **10b** (25 mg) was cyclized by reaction with $(CH_3)_3O^+$ BF_4^- under the usual conditions and the solvents removed under vacuum to leave a residue of **23a**. This was dissolved in 10:1 acetic acid–acetic anhydride and heated at 110 °C in a sealed tube for 3 h. The reaction solution was then diluted with water, made slightly alkaline with sodium hydroxide solution and extracted with chloroform. Separation by flash chromatography gave **25a** (5 mg, 20%) and **25b** (15 mg, 60%). **25a** was crystallized from ethyl acetate:hexanes, mp 154–155 °C. **25a**: IR (KBr) 3450, 2900, 1710, 1650 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.31 (t, J = 7.5 Hz, 3 H), 1.8–2.8 (m, 2 H), 3.35 (d of d, J = 5, 7 Hz, 2 H), 4.20 (m, 1 H), 4.30 (q, J = 7.5 Hz, 2 H), 4.50 (s, 2 H), 4.65 (bs, 2 H), 6.65 (d, J = 1 Hz, 1 H), 7.28 (s, 5 H); MS (CI) 371, 355, 313. Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.92; H, 6.04; N, 7.53. **25b** was crystallized from ethyl acetate-hexane, mp 173–175 °C. **25b**: IR (KBr) 3200, 3000, 2940, 1755, 1720, 1680, 1660, 1230 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 1.8–2.6 (m, 2 H), 2.18 (s, 3 H), 3.30 (d of d, J = 8, 6 Hz, 2 H), 4.30 (q, J = 7.5 Hz + m, 3 H), 4.40 (s, 2 H), 5.20 (s, 2 H), 6.70 (d, J = 1 Hz, 1 H), 7.27 (s, 5 H), 10.4 (bs, 1 H). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.06; H, 5.86; N, 6.79. Found: C, 64.15, H, 5.89; N, 6.75.

B. Dilute Hydrochloric Acid. A sample of **10b** (8 mg) was cyclized in dry CH_2Cl_2 with BF_3·OEt_2. The solution was then stirred for 15 min with 5% HCl. The products were extracted into chloroform and separated by flash chromatography and identified as **25a** and **25c**. **25a**: Spectroscopic data given in previous experiment. **25c**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3 H), 1.6–2.7 (m, 2 H), 3.32 (d of d, J = 8, 6 Hz, 2 H), 4.32 (q, J = 7.5 Hz + m, 3 H) 4.50 (m, 2 H), 4.65 (s, 2 H), 6.72 (d, J = 1 Hz, 1 H), 7.30 (s, 5 H), 10.3 (br s, 1 H); MS (CI) 391, 389, 355, 342.

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