Carbon–Carbon Bond-Forming Additions to 1-Alkyl-3-acylpyridinium Salts

Ernest Wenkert,* E. Charles Angell, Josef Drexler, Peter D. R. Moeller, Jan St. Pyrek, Yao-Jun Shi, Mumtaz Sultana, and Yashwant D. Vankar

Departments of Chemistry, Rice University, Houston, Texas 77001, and University of California—San Diego, La Jolla, California 92093

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An important side reaction in the first stage of the two-step alkaloid synthesis scheme, involving the addition of carbon nucleophiles to 1-alkyl-3-acylpyridinium salts and acid-catalyzed cyclization of the resultant 1,4-dihydropyridines, is shown to be the formation of 1,6-dihydropyridines, followed by pyridine ring opening. The dimer (or oligomer), prepared by the reaction of base with the salt from the N-alkylation of methyl β-(β-pyridyl)acrylate with tryptophyl bromide, produces a 6-(trichloromethyl)-1,6-dihydropyridine and a 4-(trichloromethyl)-1,4-dihydropyridine on reaction with chloroform. Heating converts the former product into the latter, which on acid treatment undergoes ring closure. The two-step alkaloid synthesis procedure is shown to work well with the use of the lithio salt of methylthioacetic esters acting as the initial carbon nucleophile.

The two-step reaction sequence of the addition of carbon nucleophiles to 1-alkyl-3-acylpyridinium salts or their equivalents and the acid-induced cyclization of the resultant 1,4-dihydropyridines has been the foundation stone of total syntheses of a variety of indole alkaloids (Scheme I, path A).[1] Whereas despite the structural complexity of the natural bases their syntheses were composed of a few, high-yielding reactions, the yields of the early two-step sequence were always low. Since the nucleophile–pyridine interaction, in principle, could take place at α- or γ-carbon sites on the pyridine nucleus, it had been assumed that, to the extent a kinetic α-addition product had been an intermediate, its equilibration with the thermodynamic γ-addition product had been blocked (partly or fully) by a competitive, irreversible side reaction of an undesirable decomposition mode. Whereas thus the major, albeit unwanted, products of the two-reaction procedure never had been characterized (being polar, difficulty purifiable substances), their formation always had been assumed to be associated with an elimination of the α-addition product, leading to the unraveling of the pyridine ring (Scheme I, path B). Recent data now corroborate this hypothesis and shed more light on the pyridine addition process.

The first indication of the α-addition being responsible for undesired side reactions was the observation of the formation of an α-addition–oxidation product from the interaction of the vinylogous β-acylpyridinium salt 1 with the salt of Meldrum's acid (substituting the heretofore generally used anion of dimethyl malonate[1]), followed by acid-catalyzed methanolysis (scheme II, path C).[2] However, the first direct observations of both the α-addition and ring-opening processes came from reactions of β-acylpyridinium salts **2a,b** with the lithio salt of ethyl(methylthio)acetate, followed by treatment with acid. The products proved to be vinylogous amides **3a,b**, respectively.[3] Interaction of the same nucleophile with salt 1 and subsequent reaction with acid led to a mixture of the desired γ-addition product **4**[4] and α-pyridone **5**,[3] a product of α-addition, ring scission, and cyclization. Thus path B (Scheme I) appears to be a major contributor to the derailing of the synthetically useful reactions of path A (Scheme I).

Careful observation of the interaction of dimethyl sodiomalonate with salt 1, the first step in the syntheses of yohimboid[1b] and corynantheoid[1c] alkaloids, had revealed an early formation of an insoluble material which disappeared after longer reaction. Superficial examination of the precipitate showed it to be a dihydropyridine without a malonic ester side chain, indicative of the possibility of the malonate enolate having acted upon salt 1 as a base instead of nucleophile and the resultant zwitterion (indole anion, pyridinium cation) having undergone dimerization or oligomerization.[5] This surmise proved to be correct, when it could be shown that the substance was produced in 90% yield on exposure of salt 1 to sodium hydride in tetrahydrofuran for 2 days. The ultraviolet, infrared, and ^{1}H NMR spectral data suggested structure **6** (probably in *d,l* and meso forms) for the material,[5] although no rigorous structure proof could be established. When a suspension of the material in a dimethyl sulfoxide–chloroform mixture was stirred at room temperature for an extended period of time, it dissolved, and after 8 days led to a ca. 1:1 mixture of dihydropyridines **7** and **8** in 95% yield. When a solution of the mixture in chloroform (presumably containing hydrogen chloride) was maintained at room temperature for 3 days, there ensued precipitation of cyclized product **9a** (52% yield, based on used "dimer" **6**) and the highly unstable dihydropyridine 7 (33% yield, based on used "dimer" **6**) was recovered. Maintenance of the latter in a dimethyl sulfoxide–chloroform solution for 3 weeks at room temperature converted it into isomer **8**,[6] whose cyclization in chloroform produced a 47% yield of tetracycle **9a**.[4] In view of the ease of isomerization of the α-trichloromethyl compound **7** it was of interest to force the decomposition of "dimer" **6** in the direction of exclusively chloroform adduct **8** and hence ultimately to the production of tetracycle **9a**. This idea proved feasible, as shown by the isolation of dihydropyridine **8** in 89% yield on

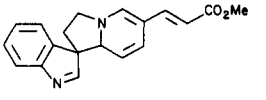
(1) (a) Wenkert, E.; Chang, C-J.; Chawla, H. P. S; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645; **1982**, *104*, 6166. (b) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *Ibid.* **1979**, *101*, 5370; **1982**, *104*, 6166. (c) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *Ibid.* **1980**, *102*, 7971.

(2) Wenkert, E.; Michelotti, E.; Pyrek, J. St. *J. Org. Chem.* **1984**, *49*, 1982.

(3) The stereochemistry of the double bond of the α-(methylthio)-acrylic ester unit remains unknown.

(4) The stereochemistry was assigned by analogy with products of related cyclization reactions.[1]

(5) The structure of the intramolecular interaction product, e.g. i, was incompatible with the physical data.

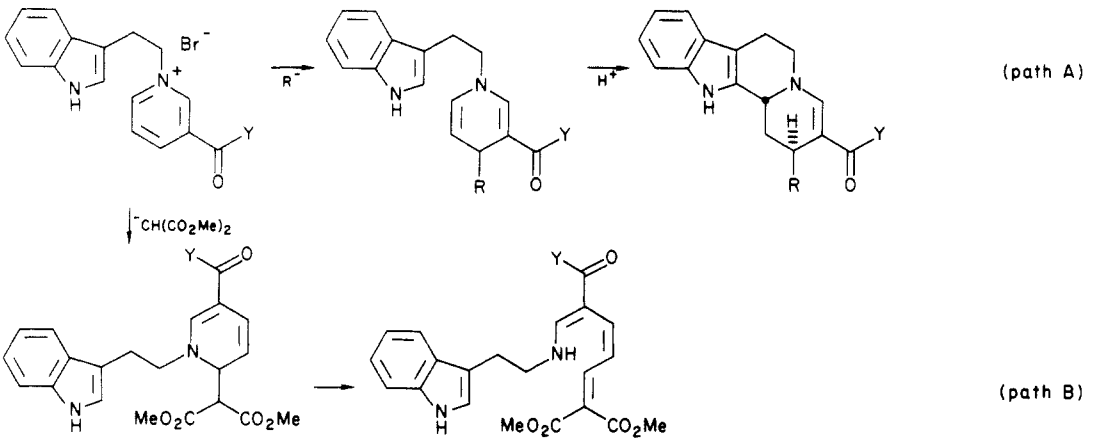


i

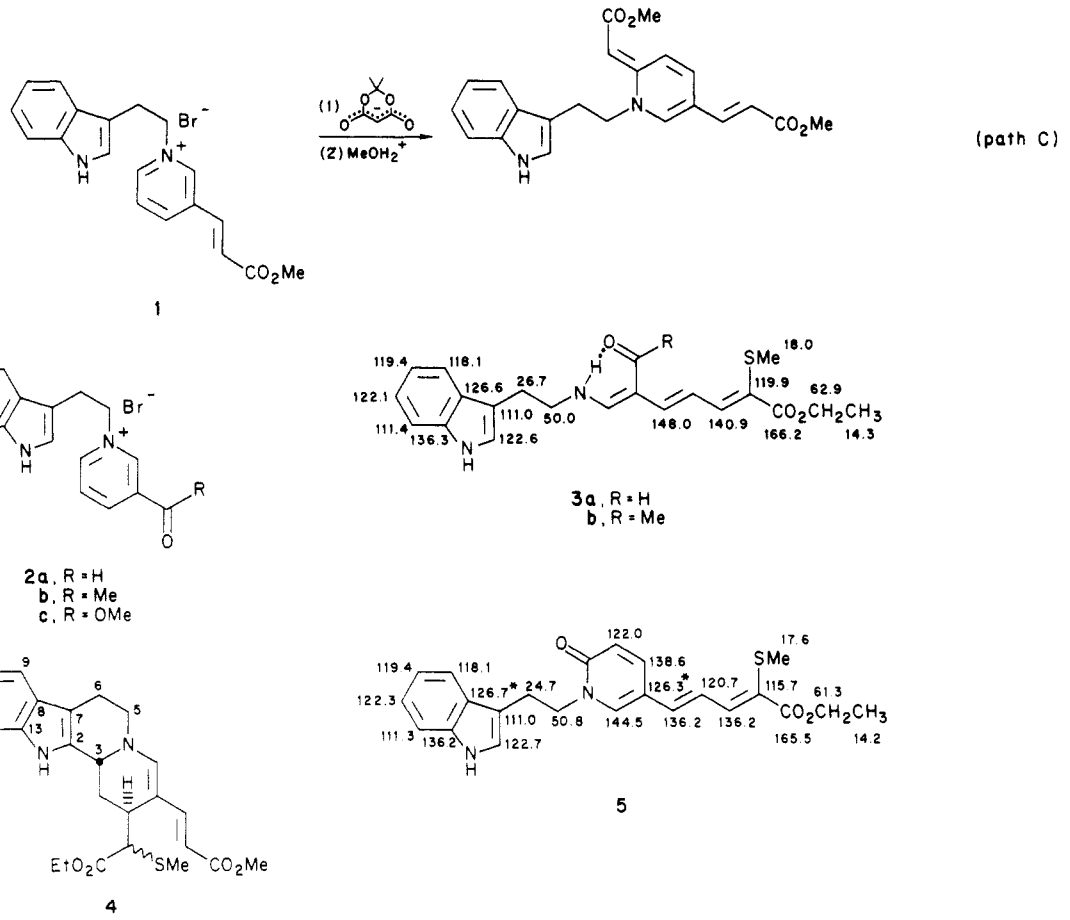
(6) For earlier examples of transformations of 1-alkyl-2-(trichloromethyl)-1,2-dihydropyridines into 1-alkyl-4-(trichloromethyl)-1,4-dihydropyridines, albeit without β-acyl functions, see: Kröhnke, F.; Duchardt, K. H. *Chem. Ber.* **1977**, *110*, 2669.

0022-3263/86/1951-2995$01.50/0

Scheme I



Scheme II



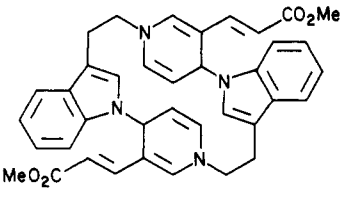
refluxing a dimethyl sulfoxide–chloroform suspension of "dimer" **6** for 0.5 h.

The simplest explanation of the above unusual results involves the homolysis of the carbon–nitrogen bond at the dihydropyridine γ-carbon site of "dimer" **6** and interaction of the resultant indolyl pyridyl radical pair with chloroform, leading to chloroform adducts **7** and **8**.[7] The **7** → **8** transformation can be visualized as a homolysis and restructuring of the resultant trichloromethyl pyridyl radical pair complex leading to the most stable product.

It is most worthy of note that the three-step conversion of salt **1** into tetracycle **9a** constitutes the highest yielding transformation conceptually of the path A (Scheme I) type observed thus far. To prepare substance **9a** for future use in alkaloid synthesis, it was exposed to the following two reactions. Treatment of the compound with silver nitrate in aqueous methanol produced ester **9b**. Hydrolysis and decarboxylation of the vinylogous amide **9a** with aqueous acid and subsequent sodium borohydride reduction yielded amine **10**.[1c]

The above experience led to the notion of the carbanion addition to pyridinium salts (Scheme I, path A) proceeding probably by single electron transfer prior to carbon–carbon bond formation and hence the regioselectivity and product yield increasing with the augmentation of the lifetime of the radical created from the carbanion. In view of the

(7) Whereas this interpretation represents the most likely reaction path, the data do not preclude a heterolysis of the carbon–nitrogen bond and the interaction of chloroform with the resultant zwiterionic pyridinium indolate. Furthermore, there exists the possibility of full unraveling of the "dimer" by homolytic or heterolytic means prior to interaction with chloroform.



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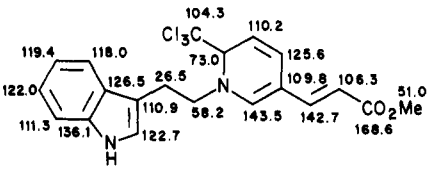

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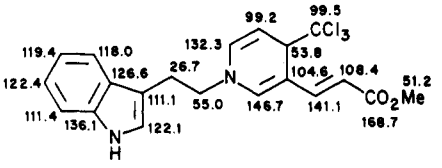

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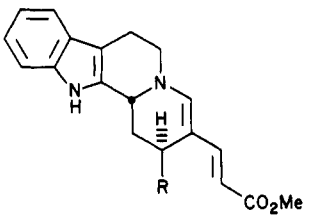
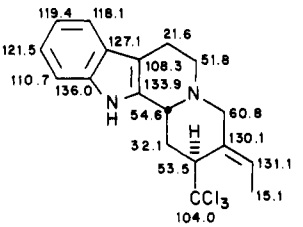


9a, R = CCl_3
b, R = CO_2Me



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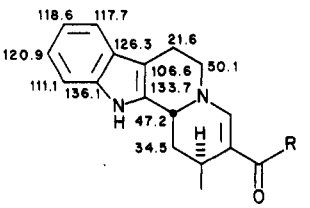
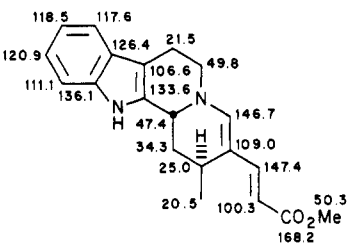


11a, R = Me
b, R = OMe



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known propensity of lithium dialkylcuprates to undergo addition reactions by prior single electron transfers[8] it was of interest to investigate the behavior of 1-alkyl-3-acylpyridinium salts toward these reagents.[9] Exposure of lithium dimethylcuprate to salts **2b**, **2c**, and **1** and subsequent acid-induced cyclization of the resultant dihydropyridines produced tetracycles **11a**,[4] **11b**,[10] and **12**,[4] respectively, in 43%, 53%, and 40% yields, respectively. Thus the reactions with the organometallic reagent had yielded exclusively γ-addition products in yields double those obtained in earlier malonic ester additions.[1]

Were the single electron transfer step in the carbanion addition reaction and the stability of the carbanion-derived radical important features in the success of path A (Scheme I), nucleophiles would have to be chosen with substituents that not only stabilize the carbanion but, more importantly, also the radical created therefrom. In recent times there has arisen the idea of the enhancement of radical stability being connected with the carbon center holding the free electron being substituted by both electron-donating and electron-accepting groups.[11] In this context the earlier use of malonic ester anion as the nucleophile in the pyridinium salt addition reactions[1] was inefficient in view of the intermediate dicarbomethoxymethyl radical holding no electron-donating substituent. In accord with this argument the reaction of the lithio salt of ethyl (trimethylsilyl)acetate with salt **2c** (the initial step in the synthesis of the indole alkaloid vallesiachotamine[12]) and subsequent acid-catalyzed cyclization of the intermediate dihydropyridine had produced a tetracycle of structure type **11b** in 47% yield, i.e., once again, much higher than the yields in the malonic ester additions.[1] In order to broaden the base of understanding of the behavior of the nucleophiles in the pyridinium salt additions, the chemistry of (alkylthio)acetic esters, substances expected to accomodate a free electron on the α-carbon exceedingly well,[11] now came under scrutiny. Exposure of salt **2c** to the lithio salt of ethyl (methylthio)acetate, followed by acid-promoted cyclization, led to a ca. 1:1 stereoisomer mixture of ester **13** in 64% yield. Their nuclear stereochemistry was assured by the transformation of one of the isomers into the known ester **14a**[12] (90% yield) on Raney nickel desulfurization. Interaction of salt **1** with methyl (methylthio)lithioacetate and subsequent acid-induced cyclization produced the ester stereoisomer mixture **15** (28% yield), the establishment of whose nuclear stereochemistry came from its conversion into the known ester **14b**[1b] (66% yield) on reduction with Raney nickel. In an attempt to convert the (methylthio)methine into a carbonyl group the ester **15** was treated with *N*-chlorosuccinimide, but prior to being given a chance to undergo hydration the material had cyclized into pentacycle **16** (70% yield). The intermediate carbonium ion thus had been trapped by the neighboring nucleophilic dienamine. Oxidation of sulfide **15** with *m*-chloroperbenzoic acid and pyrolysis of the resultant sulfoxides led to the vinylogous diurethane **17**[13] (54% yield).

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Ultraviolet spectra of methanol solutions were recorded on Cary 17 and IBM 9420 spectrophotometers and infrared spectra on Beckman IR-9 and Perkin-Elmer 1320 spectrophotometers. ^1H NMR spectra of deuteriochloroform solutions were obtained on a Varian EM-390 spectrometer and a 360-MHz instrument equipped with a highly modified Varian HR-220 console, an Oxford magnet, and a Nicolet 1180-E com-

(8) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128.

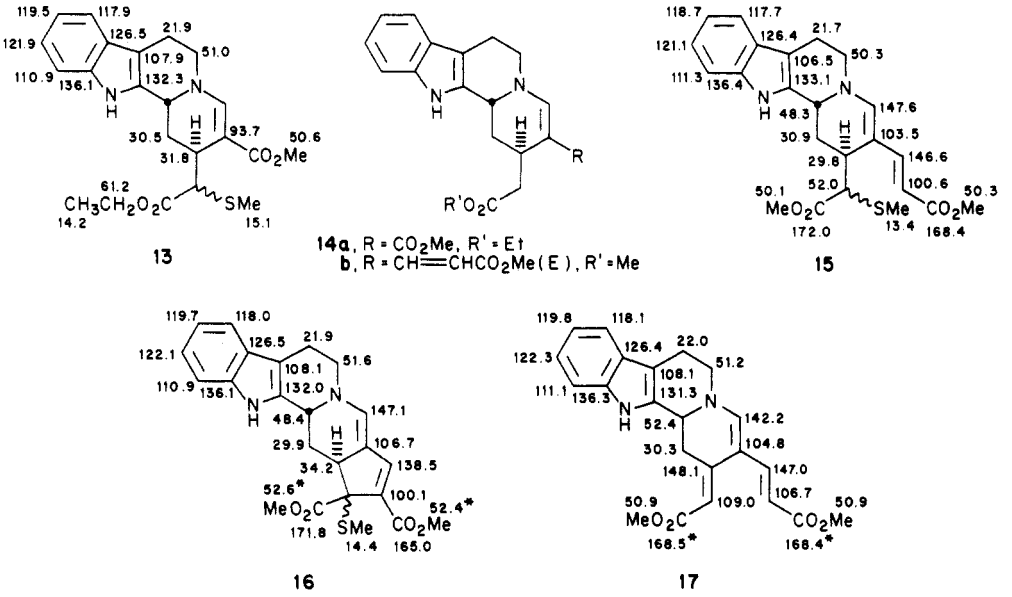
(9) For γ-additions of 1-acylpyridinium salts with alkylcopper reagents see: Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3563. Akiba, K.; Iseki, Y.; Wada, M.; *Tetrahedron Lett.* **1982**, 429.

(10) Lounasmaa, M.; Johansson, C.-J. *Tetrahedron* **1977**, *33*, 113.

(11) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917. Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.

(12) Spitzner, D.; Wenkert, E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 984.

(13) Assignment of the stereochemistry of the new exocyclic double bond is only tentative.



puter system. ^{13}C NMR spectra of $CDCl_3$ or Me_2SO-d_6 solutions were taken on a Nicolet NT-200 wide-bore, broad-band spectrometer (with Oxford magnet), operating at 50.31 MHz in the Fourier transform mode. The carbon shifts are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9 = \delta(Me_2SO\text{-}\delta\ d_6) + 39.7$. The shifts asterisked on formulas **5**, **15**, and **16** may be interchanged. Chromatography (both TLC and column) was performed on Merck silica (HF-254+366 type 60), and extracts of crude products were dried over anhydrous sodium sulfate.

Vinylogous Amides 3a,b. A hexane solution of *n*-butyllithium (2.56 mL, 3.84 mmol) was added slowly to a stirring solution of 0.54 mL (3.84 mmol) of diisopropylamine in 15 mL of anhydrous tetrahydrofuran under nitrogen at −78 °C and the stirring continued for 0.3 h. A solution of 603 mg (4.50 mmol) of ethyl (methylthio)acetate in 10 mL of tetrahydrofuran was added dropwise and the stirring then continued for 1 h. The salt **2a** (990 mg, 3.00 mmol) was added in one portion at −78 °C and the stirring mixture brought slowly to 0 °C. Enough of a saturated benzene solution of hydrogen bromide was added dropwise to bring the pH to 5 and the stirring continued at 0 °C for 1 h. The mixture was poured into 100 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine solution, dried, and evaporated. Chromatography of the residue on Florisil (60–100 mesh) and elution with 1.5:1 hexane–ether yielded 494 mg (43%) of vinylogous amide **3a** as amorphous foam: UV λ_{max} 221 nm (log ϵ 4.58), 291 (4.10), 3.78 (4.30); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1690 (m), 1645 (s), [C=C] 1592 (s), 1560 (s), 1555 (s) cm^{-1}; ^1H NMR δ 1.30 (t, 3, J = 7 Hz, Me), 2.25 (s, 3 SMe), 3.06 (t, 2, J = 7 Hz, CH_2), 3.60 (dt, 2, J = 7, 6 Hz, NCH_2), 4.25 (q, 2, J = 7 Hz, OCH_2), 6.3–7.6 (m, 9, olefinic, aromatic Hs), 9.41 (d, 1, J = 3 Hz, CHO), 10.60 (br s, 1, amide NH); ^{13}C NMR ($CDCl_3$) δ 106.1 (α-formyl C), 113.9 (C γ to ester), 154.3 (NCH), 188.9 (CHO); exact mass: m/e (M − 132) 252.1255 (calcd for $C_{16}H_{16}ON_2$ m/e 252.1262).

The same procedure was utilized for the reactions of *n*-butyllithium (5.00 mL, 7.10 mmol) with diisopropylamine (1.05 mL, 7.50 mmol) in 30 mL of anhydrous tetrahydrofuran, the resultant lithium diisopropylamide with ethyl (methylthio)acetate (1.20 g, 8.94 mmol) and the produced carbanion with salt **2b** (1.28 g, 3.71 mmol). This produced 515 mg (35%) of vinylogous amide **3b**: mp 157 °C; UV λ_{max} 264 nm (log ϵ 3.90), 289 (3.05), 366 (4.27), 3.80 (4.28); IR ($CHCl_3$) [NH] 3480 (m), [C=O] 1690 (m), 1637 (s), [C=C] 1598 (s), 1585 (s), 1555 (s) cm^{-1}; ^1H NMR δ 1.34 (t, 3, J = 7 Hz, Me), 2.23 (s, 3, SMe), 2.26 (s, 3, $COCH_3$), 3.07 (t, 2, J = 6 Hz, CH_2), 3.65 (dt, 2, J = 7, 6 Hz, NCH_2), 4.27 (q, 2, J = 7 Hz, OCH_2), 6.54 (dd, 1, J = 15, 11 Hz, H γ to ester), 6.92 (d, 1, J = 15 Hz, H δ to ester), 7.04 (d, 1, J = 3 Hz, indole α-H), 7.13 (dt, 1, J = 8, 1 Hz, H-10), 7.21 (dt, 1, J = 8, 1 Hz, H-11), 7.28 (d, 1, J = 14 Hz, NCH), 7.36 (d, 1 J = 8 Hz, H-12), 7.56 (d, 1, J = 8 Hz, H-9), 7.59 (d, 1, J = 11 Hz, H β to ester), 8.38 (br s, 1, indole NH), 10.90 (m, 1, NH); ^{13}C NMR ($CDCl_3$) δ 27.3 (acetyl Me), 105.3 (α-acetyl C), 114.6 (C γ to ester), 196.4 (C=O).

Anal. Calcd for $C_{22}H_{24}O_3N_2S$: C, 66.30; H, 6.57; N, 7.03. Found: C, 66.41; H, 6.55; N, 6.63.

Ester 4 and Pyridone 5. The same procedure was used for the reactions of *n*-butyllithium (5.00 mL, 7.50 mmol) with diisopropylamine (1.05 mL, 7.50 mmol) in 15 mL of anhydrous tetrahydrofuran, the resultant lithium diisopropylamide with ethyl (methylthio)acetate (1.18 g, 8.79 mmol), and the thus-formed carbanion with salt **1** (1.92 g, 4.96 mmol). Chromatography of the crude product on Florisil and elution with 9:1 hexane–ethyl acetate afforded 450 mg (21%) of a solid mixture of ester 4 diastereomers, whose chromatography on silica gel and elution with chloroform gave a single crystalline diastereomer: mp 205–206 °C (MeOH); UV λ_{max} 222 nm (log ϵ 4.32), 270 (3.77), 290 (3.64), 356 (4.42); IR ($CHCl_3$) [NH] 3470 (w), [C=O] 1720 (m), 1682 (m), [C=C] 1575 (s) cm^{-1}; ^1H NMR δ 1.32 (t, 3, J = 7 Hz, Me), 2.19 (s, 3, SMe), 3.55 (d, 1, J = 8 Hz, SCHCO), 3.70 (s, 3, OMe), 4.19 (q, 2, J = 7 Hz, OCH_2), 4.87 (d, 1, J = 8 Hz, H-3), 5.44 (d, 1, J = 15 Hz, acrylic ester α-H), 6.73 (s, 1, olefinic NCH), 7.12 (t, 1, J = 8 Hz, H-10), 7.24 (t, 1, J = 8 Hz, H-11), 7.26 (d, 1, J = 15 Hz, acrylic ester β-H), 7.34 (d, 1, J = 8 Hz, H-12), 7.49 (d, 1, J = 8 Hz, H-9); ^{13}C NMR ($CDCl_3$) δ 13.8 (Me), 14.4 (SMe), 21.7 (C-6), 30.0 (CH_2), 31.5 (allyl CH), 48.9 (C-3), 49.9 (OMe), 50.7 (C-5), 51.4 (SCH), 61.5 (OCH_2), 101.6 (acrylic ester α-C), 103.3 (enamine β-C), 107.2 (C-7), 110.9 (C-12), 117.6 (C-9), 119.0 (C-10), 121.4 (C-11), 126.2 (C-8), 132.3 (C-2), 136.2 (C-13), 146.7 (enamine α-C), 146.8 (acrylic ester β-C), 169.6 (acrylic C=O), 172.2 (C=O); exact mass m/e 440.1736 (calcd for $C_{24}H_{28}O_4N_2S$ m/e 440.1770).

Anal. Calcd for $C_{24}H_{28}O_4N_2S$: C, 65.43; H, 6.41; N, 6.36. Found: C, 64.81; H, 6.45; N, 6.02.

Further elution of the Florisil chromatogram with 1.5:1 hexane–ethyl aceate gave 300 mg (15%) of crystalline pyridone **5**: mp 124–125 °C (MeOH); IR ($CHCl_3$) [NH] 3480 (m), [C=O] 1697 (s), 1665 (s), [C=C] 1598 (s), 1580 (s), 1558 (m), 1531 (m) cm^{-1}; ^1H NMR δ 1.34 (t, 3, J = 7 Hz, Me), 2.30 (s, 3, SMe), 3.20 (t, 2, J = 6 Hz, CH_2), 4.21 (t, 2, J = 6 Hz, NCH_2), 4.27 (q, 2, J = 7 Hz, OCH_2), 6.36 (d, 1, J = 15 Hz, δ-H on dienoic ester), 6.61 (d, 1, J = 9 Hz, pyridone α-H), 6.86 (m, 2, indole α-H, pyridone δ-H), 7.03 (dd, 1, J = 15, 11 Hz, γ-H on dienoic ester), 7.12 (t, 1, J = 7 Hz, H-10), 7.19 (t, 1, J = 7 Hz, H-11), 7.36 (d, 1, J = 7 Hz, H-12), 7.48 (d, 1, J = 11 Hz, β-H on dienoic ester), 7.26 (d, 1, J = 7 Hz, H-9), 7.62 (d, 1 J = 9 Hz, pyridone β-H); ^{13}C NMR ($CDCl_3$) δ on formula **5**; exact mass m/e 408.1504 (calcd for $C_{23}H_{24}O_3N_2S$ m/e 408.1508).

Anal. Calcd for $C_{23}H_{24}O_3N_2S$: C, 67.62; H, 5.92. Found: C, 67.48; H, 6.04.

"Dimer" 6 and Its Reactions. Salt **1** (860 mg, 2.22 mmol) was added to a stirring suspension of 151 mg (6.29 mmol) of 99% sodium hydride in 15 mL of anhydrous tetrahydrofuran and the mixture stirred at room temperature under nitrogen for 48 h. The suspension was brought to pH 6 by the addition of 1 N methanolic

hydrochloric acid and filtered. The precipitate was filtered, washed with aqueous methanol and then with ether and dried at 80 °C under vacuum. The led to 614 mg (90%) of amorphous, pale yellow, solid "dimer" **6**: mp 220 °C dec; UV λ_{max} (CH_2Cl_2) 237 nm (log ϵ 4.91), 287 (4.18), 372 (4.57), λ_{min} 275 nm (log ϵ 4.16), 320 (3.94) (extinction coefficients based on dimer structure); IR (KBr) [C=O] 1700 (s), 1670 (s), [C=C] 1610 (s), 1580 (s) cm^{-1}; ^1H NMR δ [major component] 2.95 (m, 1, H of benzyl CH_2), 3.20 (m, 1, other H of benzyl CH_2), 3.63 (s, 3, OMe), ca. 3.7 (m, 2, NCH_2), 4.84 (dd, 1, J = 8, 4 Hz, enamine β-H), 5.22 (d, 1, J = 15 Hz, acrylic ester α-H), 5.25 (dd, 1 J = 8, 2 Hz, enamine α-H), 6.00 (d, 1, J = 4 Hz, dihydropyridine γ-H), 6.75 (d, 1, J = 2 Hz, olefinic NCH), 6.86 (s, 1, indole α-H), 7.32 (d, 1, J = 15 Hz, acrylic ester β-H), [minor component] 2.85 (m, 1, H of benzyl CH_2), ca. 3.0 (m, 1, other H of benzyl CH_2), 3.57 (s, 3, OMe), ca. 3.7 (m, 2, NCH_2), 4.57 (dd, 1, J = 8, 4 Hz, enamine β-H), 5.20 (d, 1, J = 15 Hz, acrylic ester α-H), 5.73 (dd, 1, J = 8, 2 Hz, enamine α-H), 6.05 (d, 1, J = 4 Hz, dihydropyridine γ-H), 6.91 (s, 1, indole α-H), 6.91 (d, 1, J = 2 Hz, olefinic NCH), 7.02 (d, 1, J = 15 Hz, acrylic ester β-H).

A suspension of 2.28 g (3.72 mmol) of "dimer" **6** in 100 mL of chloroform and 100 mL of dimethyl sulfoxide was stirred at room temperature for 192 h. The mixture was diluted with 250 mL of methylene chloride, washed with water, dried, and filtered through a Florisil pad. Evaporation of the filtrate gave 3.01 g (95%) of a yellow solid, spectrally consistent with a ca. 1:1 mixture of dihydropyridine **7** and **8**: ^1H NMR δ 2.94 (t, 2, J = 7 Hz, CH_2), 3.57 (t, 2, J = 7 Hz, NCH_2), 3.69 (s, 3, OMe), 4.27 (d, 1, J = 6 Hz, dihydropyridine γ-H), 5.05 (dd, 1, J = 7, 6 Hz, enamine β-H), 5.90 (d, 1, J = 15 Hz, acrylate α-H), 6.23 (d, 1, J = 7 Hz, enamine α-H), 6.58 (s, 1, olefinic NCH), 6.89 (d, 1, J = 2 Hz, indole α-H), 7.0–7.4 (m, 4, aromatic Hs), 7.34 (d, 1, J = 15 Hz, acrylate β-H); ^{13}C NMR ($CDCl_3$) δ on formula **8**. A solution of the solid in 50 mL of chloroform was kept at room temperature for 72 h and the resultant precipitate filtered. The filtrate was evaporated under vacuum. Chromatography of its residue on Florisil and elution with methylene chloride led to 1.05 g (33%) of sensitive dihydropyridine **7**: UV λ_{max} 277 nm (log ϵ 3.90), 287 (3.97), 334 (4.36), 354 (4.34); IR ($CHCl_3$) [NH] 3480 (m), [C=O] 1691 (s), 1634 (s), 1609 (s), [C=C] 1563 (s) cm^{-1}; ^1H NMR δ 3.02 (t, 2, J = 7 Hz, CH_2), 3.73 (s, 3, OMe), 3.83, 4.01 (quint, 1 each, J = 7 Hz, NCH_2), 4.54 (d, 1, J = 6 Hz, dihydropyridine γ-H), 5.51 (dd, 1, J = 9, 6 Hz, dihydropyridine β-H), 5.70 (d, 1, J = 15 Hz, acrylate α-H), 6.57 (s, 1, olefinic NCH), 6.64 (d, 1, J = 9 Hz, NCH), 6.87 (s, 1, indole α-H), 7.17 (d, 1, J = 15 Hz, acrylate β-H), 7.1–7.3 (m, 2, H-10, H-11), 7.36 (d, 1, J = 8 Hz, H-12), 7.54 (d, 1, J = 8 Hz, H-9); ^{13}C NMR ($CDCl_3$) δ on formula **7**. The precipitate (1.64 g, 52%) proved to be tetracycle **9a**: mp 150 °C dec; UV λ_{max} 279 nm (log ϵ 3.94), 286 (3.91), 345 (4.65); IR (KBr) [NH] 3310 (w), [C=O] 1673 (s), 1561 (s), [C=C] 1540 (m) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6–4.0 (m, 7, CH, 3 CH_2), 3.56 (s, 3, OMe), 5.11 (dm, 1, J = 11 Hz, H-3), 5.53 (d, 1, J = 12 Hz, acrylate α-H), 6.98, 7.07 (t, 1 each, J = 8 Hz, H-10, H-11), 7.2–7.6 (m, 2, H-9, H-12), 7.37 (d, 1, J = 12 Hz, acrylate β-H), 7.56 (s, 1, olefinic NCH); ^{13}C NMR (Me_2SO-d_6) δ 21.9 (C-6), 31.2 (CH_2), 48.2 (C-3), 50.4 (C-5), 50.5 (OMe), 51.1 (CH), 99.0 (CCl_3), 102.1 (acrylate α-C), 105.3 (enamine β-C), 106.5 (C-7), 111.4 (C-12), 118.0 (C-9), 118.9 (C-10), 121.3 (C-11), 126.3 (C-8), 133.0 (C-2), 136.4 (C-13), 148.3 (acrylate β-C), 149.9 (enamine α-C), 168.4 (C=O); exact mass m/e 424.0517 (calcd for $C_{20}H_{19}O_2N_2Cl_3$ m/e 424.0512).

A variant of the cyclization, in the event of low hydrogen chloride concentration in the chloroform, was as follows. A mixture of the trichloromethyl compounds **7** and **8** and 4 mL of 6 N hydrochloric acid in 20 mL of methanol and 60 mL of chloroform was stirred at room temperature for 5 min. Chloroform (200 mL) was added and the mixture washed with water, dried, and evaporated. Extraction of the residue with chloroform left 1.44 g (51%) of tetracycle **9a**.

A solution of 300 mg (0.70 mmol) of dihydropyridine **7** in 20 mL of chloroform and 20 mL of dimethyl sulfoxide was stirred at room temperature for 504 h. Workup as above and cyclization of thus-formed dihydropyridine **8** in chloroform led to 140 mg (47%) of tetracycle **9a**. A suspension of 568 mg (0.93 mmol) of "dimer" **6** in 20 mL of chloroform and 20 mL of dimethyl sulfoxide was refluxed with stirring for 0.5 h. Workup as above gave 700 mg (89%) of dihydropyridine **8**, which was transformed into tetracycle **9a** by the aforementioned procedures.

Ester 9b. A solution of 510 mg (3.00 mmol) of silver nitrate in 1 mL of deionized water was added to a suspension of 212 mg (0.50 mmol) of chloride **9a** in 10 mL of methanol and the mixture stirred at room temperature under nitrogen until TLC showed the absence of starting chloride (ca. 5 h). Water (10 mL) was added and the mixture extracted exhaustively with methylene chloride. The extract was dried and evaporated. Thick-layer chromatography of the residue on silica gel gave 73 mg (40%) of colorless crystalline **9b**: mp 248–250 °C (MeOH); IR (KBr) [NH] 3280 (m), [C=O] 1725 (s), 1665 (s), [C=C] 1570 (s) cm^{-1}; ^1H NMR δ 1.83 (dt, 1, J = 7, 6 Hz, H of CH_2), 2.62 (dm, 1, J = 11 Hz, other H of CH_2), 2.7–2.9 (m, 2, α-keto H, H-6), 3.5–3.8 (m, 3, H-6, 2 H-5), 3.72, 3.75 (s, 3 each, 2 OMe), 4.82 (dm, 1, J = 11 Hz, H-3), 5.48 (d, 1, J = 15 Hz, acrylic ester α-H), 6.78 (s, 1, olefinic NCH), 7.12 (t, 1, J = 8 Hz, H-10), 7.19 (t, 1, J = 8 Hz, H-11), 7.33 (d, 1, J = 8 Hz, H-9), 7.36 (d, 1, J = 15 Hz, acrylic ester β-H), 7.49 (d, 1, J = 8 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 21.9 (C-6), 30.6 (CH_2), 36.9 (CH), 48.9 (C-3), 50.8 (C-5), 50.9 (acrylic ester OMe), 52.3 (OMe), 100.7 (enamine β-C), 103.9 (acrylic ester α-C), 108.5 (C-7), 110.9 (C-12), 118.1 (C-9), 119.7 (C-10), 122.1 (C-11), 126.6 (C-8), 131.8 (C-2), 136.2 (C-13), 146.2 (enamine α-C), 146.7 (acrylic ester β-C), 169.1 (acrylic ester C=O), 174.7 (C=O); exact mass m/e 366.1576 (calcd for $C_{22}H_{22}O_4N_2$ m/e 366.1579).

Chloride 10. A suspension of 212 mg (0.50 mmol) of chloride **9a** in 10 mL of 4 N hydrochloric acid and 1 mL of methanol was refluxed under nitrogen for 5 h and then evaporated under vacuum. The residue was dissolved in 5 mL of methanol, 100 mg of sodium borohydride added, and the solution stirred for 2 h. Water (5 mL) was added and the mixture extracted exhaustively with methylene chloride. The extract was dried and evaporated. Thick-layer chromatography of the residue on silica gel gave 80 mg (44%) of crystalline chloride **10**: mp 108–110 °C (EtOH); IR ($CHCl_3$) [NH] 3465 (m), [C=C] 1590 (w) cm^{-1}; ^1H NMR δ 1.73 (d, 3, J = 6 Hz, Me), 1.8–3.7 (m, 8, 2 CH, 3 CH_2), 3.7–4.0 (m, 2, allyl NCH_2), 4.2–4.5 (m, 1, H-3); ^{13}C NMR ($CDCl_3$) δ on figure **10**; exact mass m/e 368.0615 (calcd for $C_{18}H_{19}N_2Cl_3$ m/e 368.0614).

Lithium Dimethylcuprate Reactions. A 1.5 M ethereal methyllithium solution (14.0 mL) was added dropwise over a 5-min period to a stirring suspension of 2.04 g (10.7 mmol) of cuprous iodide in 80 mL of anhydrous tetrahydrofuran under nitrogen at −15 °C and the stirring continued for 0.5 h. Solid pyridinium salt (3.6 mmol) **2b**, **2c**, or **1** was added in one portion to the stirring mixture, creating a clear, deeply red solution. The latter was permitted to reach slowly 0 °C (causing a precipitate to form), and a saturated benzene solution of hydrogen bromide gas, enough to attain pH 5, was added. After being stirred at 0 °C for 1 h the mixture was brought to room temperature and poured into a saturated sodium bicarbonate solution. It was extracted exhaustively with ether and the extract washed with brine, dried (Na_2SO_4), and evaporated. Crystallization of the residue from methanol gave a 43% yield of tetracycle **11a** (mp 266–267 °C), 53% of **11b** [mp 238–240 °C (lit.[10] mp 238–240 °C)] and 40% of **12** (mp 241–242 °C) respectively.

Tetracycle **11a**: UV λ_{max} 221 mm (log ϵ 3.99), 303 (4.44); IR (KBr) [NH] 3450 (m), [C=O] 1578 (s), [C=C] 1550 (m) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.16 (d, 3, J = 6 Hz, Me), 1.5–2.6 (m, 3, CH_2, CH), 2.14 (s, 3, COMe), 2.7–3.1 (m, 2, benzyl Hs), 3.4–3.9 (m, 2, NCH_2), 4.60 (br d, 1, J = 11 Hz, H-3), 7.00 (t, 1, J = 7 Hz, H-10), 7.07 (t, 1, J = 7 Hz, H-11), 7.31 (d, 1, J = 7 Hz, H-9), 7.41 (d, 1, J = 7 Hz, H-12), 7.52 (s, 1, olefinic NCH); ^{13}C NMR (Me_2SO-d_6) δ 21.7 (Me), 23.8 (acetyl Me), 23.8 (allyl CH), 106.5 (α-keto C), 148.1 (olefinic NCH), 191.1 (C=O); exact mass m/e 280.1563 (calcd for $C_{18}H_{20}ON_2$ m/e 280.1562).

Tetracycle **12**: UV λ_{max} 235 nm (log ϵ 2.63), 283 (0.66), 299 (0.55), 360 (4.56); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1682 (m), 1578 (s), [C=C] 1558 (m), 1540 (m) cm^{-1}; ^1H NMR (Me_2SO-d_6) 1.18 (d, 3, J = 6 Hz, Me), 1.6–3.8 (m, 7, methylenes, CH), 3.40 (s, 3, OMe), 4.65 (br d, 1, J = 11 Hz, H-3), 5.30 (d, 1, J = 12 Hz, acrylic α-H), 6.9–7.5 (m, 4, aromatic Hs), 7.10 (s, 1, olefinic NCH), 7.20 (d, 1, J = 12 Hz, acrylic β-H); ^{13}C NMR (Me_2SO-d_6) δ on formula **12**; exact mass m/e 322.1669 (calcd for $C_{20}H_{22}O_2N_2$ m/e 322.1668).

Tetracyclic Ester 13. The procedure used above for the preparation of the lithio salt of ethyl (methylthio)acetate and its interaction with salts **1** and **2** was carried out in the following

manner: reaction of *n*-butyllithium (6.9 mL, 11.0 mmol) with diisopropylamine (0.98 mL, 12.0 mmol) in 30 mL of anhydrous tetrahydrofuran, the resultant lithium diisopropylamide with ethyl (methylthio)acetate (1.35 g, 10.1 mmol), and the thus-formed carbanion with salt **2c** (2.80 g 7.76 mmol). Chromatography of the crude product on silica gel gave 2.05 g (64%) of an amorphous, ca. 1:1 diastereomer mixture of esters **13**, whose chromatography on Florisil and elution with 9:1 hexane–ethyl acetate separated the two isomers.

First isomer: mp 169–172 °C (MeOH); UV λ_{max} 220 nm (log ϵ 4.40), 287 (4.43); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1720 (s), 1665 (s), 1610 (s), [C=C] 1590 (s), 1540 (m) cm^{-1}; ^1H NMR δ 1.28 (t, 3, J = 7 Hz, Me), 1.3–3.8 (m, 8, methylenes, methines), 2.20 (s, 3, SMe), 3.72 (s, 3, OMe), 4.21 (q, 2, J = 7 Hz, OCH_2), 4.61 (dd, 1, J = 11, 2 Hz, H-3), 7.15 (t, 1, J = 7 Hz, H-10), 7.19 (t, 1, J = 7 Hz, H-11), 7.34 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12), 7.61 (s, 1, olefinic NCH); ^{13}C NMR δ 53.8 (SCH), 146.5 (NCH), 168.6 (urethane C=O), 171.9 (ester C=O).

Second isomer: mp 170–172 °C (MeOH); UV λ_{max} 220 nm (log ϵ 4.40), 289 (4.43); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1715 (s), 1665 (s), 1610 (s), 1590 (s), [C=C] 1550 (m) cm^{-1}; ^1H NMR δ 1.32 (t, 3, J = 7 Hz, Me), 1.3–3.8 (m, 8, methylenes, methines), 2.19 (s, 3, SMe), 3.68 (s, 3, OMe), 4.22 (q, 2, J = 7 Hz, OCH_2), 4.82 (dd, 1, J = 12, 3 Hz, H-3), 7.11 (t, 1, J = 7 Hz, H-10), 7.15 (t, 1, J = 7 Hz, H-11), 7.34 (d, 1, J = 7 Hz, H-9), 7.49 (d, 1, J = 7 Hz, H-12), 7.66 (s, 1, NCH); ^{13}C NMR δ 53.1 (SCH), 147.0 (NCH), 168.0 (urethane C=O), 172.3 (ester C=O); exact mass m/e 414.1613 (calcd for $C_{22}H_{26}O_4N_2S$ m/e 414.1611).

A mixture of 576 mg (1.40 mmol) of the first isomer (**13**) and excess Raney nickel (from Aldrich Chemical Co) in 30 mL of absolute ethanol was stirred and refluxed for 2 h. It then was passed through a short column of Celite and the latter washed with ethanol. The combined eluate and washings were evaporated, and the residue was triturated with ether, leading to 461 mg (90%) of crystalline ester **14a**, mp 188–190 °C (Et_2O); ^1H and ^{13}C NMR spectra were identical with those reported earlier.[12]

Ester 15. A solution of 2.40 g (20.0 mmol) of methyl (methylthio)acetate in 10 mL of anhydrous tetrahydrofuran was added over a 0.5-h period to a stirring lithium diisopropylamide solution, prepared from 2.00 g (19.8 mmol) of diisopropylamine in 15 mL of dry tetrahydrofuran and 12.8 mL (20.0 mmol) of a 1.6 M hexane solution of *n*-butyllithium, under nitrogen at −78 °C and the solution stirred at this temperature for 1 h. There were added 2.00 g (5.2 mmol) of salt **1** in one portion and immediately thereafter 80 mL of dry tetrahydrofuran. The red suspension was stirred at −78 °C for 2 h, the temperature permitted to rise to −40 °C, and the mixture stirred at this temperature for 1 h. Hydrogen bromide gas, enough to bring the pH down to 5, was bubbled through the (by now) nearly clear solution and the mixture allowed to reach room temperature. It was stirred for 0.5 h and neutralized with saturated sodium bicarbonate solution. It then was extracted exhaustively with methylene chloride, dried, and evaporated. The residue was chromatographed and eluted with 2:1 hexane–ethyl acetate, yielding 616 mg (28%) of one crystalline isomer of the two diastereomers of ester **15**: mp 243–244 °C (MeOH); UV λ_{max} 222 nm (log ϵ 4.32), 270 (3.77), 290 (3.64), 356 (4.42); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1720 (s), 1675 (s), [C=C] 1575 (s) cm^{-1}; ^1H NMR δ 1.5–3.8 (m, 8, 2 CH, 2 CH_2), 2.13 (s, 3, SMe), 3.63, 3.70 (s, 3 each, 2 OMe), 4.57 (dm, 1, J = 8 Hz, H-3), 5.37 (d, 1, J = 15 Hz, acrylic ester α-H), 6.67 (s, 1, olefinic NCH), 6.9–7.6 (m, 4, indole Hs), 7.28 (d, 1, J = 15 Hz, acrylic ester β-H); ^{13}C NMR (Me_2SO-d_6) δ on formula **15**; exact mass m/e 426.1613 (calcd for $C_{23}H_{26}O_4N_2S$ m/e 426.1613).

Ester 14b. A 50% Raney nickel slurry in water (pH 10, Aldrich Chemical Co.) was washed with water and then ethanol. An ethanol suspension (2 mL) of excess Raney nickel (ca. 250 mg) was added to a suspension of 156 mg (0.37 mmol) of ester **15** in 4 mL of ethanol and the mixture refluxed with stirring under nitrogen for 4 h. It then was filtered and the filtrate evaporated to dryness. Water (5 mL) was added to the residue and the mixture extracted exhaustively with methylene chloride. The extract was dried and evaporated. Thick-layer chromatography of the residue on silica gel gave 93 mg (66%) of crystalline ester **14b**, mp 209–210 °C (MeOH) (lit.[1b] mp 209–211 °C), spectrally identical with an authentic sample.

Ester 16. A solution of 56 mg (0.42 mmol) of *N*-chlorosuccinimide in 2 mL of methylene chloride was added slowly to a suspension of 170 mg (0.40 mmol) of ester **15** in 10 mL of methylene chloride under nitrogen at 0 °C and the mixture stirred for 2 h. It was washed with water, dried, and evaporated. Thick-layer chromatography of the residue on silica gel led to 120 mg (70%) of crystalline ester **16**: mp 189–190 °C; UV λ_{max} 222 nm (log ϵ 4.33), 266 (3.83), 290 (3.69), 374 (4.24); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1720 (s), 1690 (s), [C=C] 1605 (s), 1590 (s) cm^{-1}; ^1H NMR δ 1.74 (dt, 1, J = 10, 9 Hz, H of CH_2), 2.19 (s, 3, SMe), 2.6–3.1 (m, 3, H of CH, other H of CH_2, H-6), 3.6–3.8 (m, 3, H-6, 2 H-5), 3.76, 3.79 (s, 3 each, 2 OMe), 4.80 (dd, 1, J = 11, 9 Hz, H-3), 7.12 (t, 1, J = 7 Hz, H-10), 7.19 (t, 1, J = 7 Hz, H-11), 7.35 (s, 1, olefinic NCH), 7.36 (d, 1, J = 7 Hz, H-12), 7.50 (d, 1, J = 7 Hz, H-9), 7.64 (s, 1, acrylic ester β-H); ^{13}C NMR ($CDCl_3$) δ on formula **16**; exact mass (M − CH_3SH − CH_3OH) m/e 344.0915 (calcd for $C_{21}H_{16}O_3N_2$ m/e 344.1161).

Vinylogous Amide 17. A solution of 75 mg (4.3 mmol) of 80% *m*-chloroperbenzoic acid in 3 mL of methylene chloride was added dropwise over a 10-min period to a stirring suspension of 135 mg (3.2 mmol) of ester **15** (the crystalline stereoisomer above) at −78 °C and the mixture permitted to reach slowly room temperature. Water (5 mL) was added and the mixture treated first with 5 mL of 10% sodium sulfite solution and then 10% sodium bicarbonate solution. The methylene chloride solution was dried and evaporated. A suspension of the residue (150 mg) and 10 mg of calcium carbonate in 20 mL of dry benzene was refluxed for 14 h and then evaporated under vacuum. Water (10 mL) was added to the residue and the mixture extracted exhaustively with methylene chloride. The extract was evaporated and the residue purified by thick-layer chromatography on silica gel, leading to 64 mg (54%) of crystalline vinylogous amide **17**: mp 192–193 °C (MeOH); UV λ_{max} 222 nm (log ϵ 4.07), 283 (3.35), 291 (3.28), 360 (3.93); IR ($CHCl_3$) [NH] 3460 (m), [C=O] 1686 (s), 1677 (s), [C=C] 1570 (s) cm^{-1}; ^1H NMR δ 2.69 (dt, 1, J = 15, 1 Hz, H of CH_2), 2.9–3.2 (m, 2, 2 H-6), 3.5–3.7 (m, 2, 2 H-5), 3.73, 3.74 (s, 3 each, 2 OMe), 4.47 (dd, 1, J = 15, 11 Hz, other H of CH_2), 4.66 (dd, 1, J = 11, 1 Hz, H-3), 5.90 (s, 1, α-keto H), 5.90 (d, 1, J = 16 Hz, acrylate α-H), 7.05 (s, 1, olefinic NCH), 7.12 (t, 1, J = 7 Hz, H-10), 7.19 (t, 1, J = 7 Hz, H-11), 7.33 (d, 1, J = 7 Hz, H-12), 7.43 (d, 1, J = 16 Hz, acrylate β-H), 7.49 (d, 1, J = 7 Hz, H-9); ^{13}C NMR (Me_2SO-d_6) δ on formula **17**; exact mass m/e 378.1580 (calcd for $C_{22}H_{22}O_4N_2$ m/e 378.1579).

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