°C; IR (KBr) 2220 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.68 (3 H, s, OMe), 4.29 (2 H, br s, CH_2), 4.53 (2 H, br s, CH_2), 6.54, 6.86 (each 2 H, d, Ph), 7.80 (2 H, br s, NH_2). Anal. Calcd for $C_{15}H_{13}ClN_4O \cdot {}^1/_2H_2O$: C, 58.16; H, 4.56; Cl, 11.45; N, 18.09. Found: C, 58.03; H, 4.49; Cl, 11.43; N, 18.11.

4-Amino-7-cyano-1-(4-methoxyphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyridine (14). A mixture of **13** (902 mg, 3 mmol), Et_3N (0.8 mL), and 10% Pd/C (500 mg) in a mixture of dioxane (150 mL) and EtOH (200 mL) was hydrogenated in a Parr apparatus with an initial pressure of 50 psi for 5 days. The catalyst was removed by filtration through a Celite pad. The filtrate was concentrated in vacuo, and the residue was recrystallized from $CHCl_3$–EtOH to give **14** (184 mg, 23%): mp 253–254 °C; IR (KBr) 2210 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.69 (3 H, s, OMe), 4.34 (2 H, br s, 3-CH_2), 4.58 (2 H, br s, 1-CH_2), 6.58, 6.90 (each 2 H, d, Ph), 7.12 (2 H, s, NH_2), 8.31 (1 H, s, H-6). Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.74; H, 5.26; N, 21.10.

1-(4-Methoxyphenyl)pyrrolidin-3-one (18). A mixture of **17** (10.53 g, 0.04 mol) in 6 N HCl (120 mL) was heated at 100 °C (bath temperature) until evolution of CO_2 ceased (about 1 h). The mixture was cooled in an ice bath, neutralized with 10 N NaOH, and extracted with Et_2O (4 × 200 mL). The combined extracts were washed (H_2O), dried (Na_2SO_4), and concentrated, and the residue was crystallized from Et_2O–hexane to give **18** (5.68 g, 67%): mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 2.68 (2 H, t, 5-CH_2), 3.61 (2 H, t, 4-CH_2), 3.63 (2 H, s, 2-CH_2), 3.77 (3 H, s, OMe), 6.63, 6.89 (each 2 H, d, Ph). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.95; H, 6.77; N, 7.31.

3-(Dicyanomethylene)-1-(4-methoxyphenyl)pyrrolidine (19). A mixture of **18** (17.41 g, 0.084 mol), malononitrile (6.66 g, 0.1 mol), and DBU (1 mL) in dry C_6H_6 (200 mL) was stirred below 10 °C for 2 h and then concentrated in vacuo below 20 °C. The dark residue was triturated with EtOH (200 mL), and the dark green solid was collected by filtration to give **19** (10.5 g, 48%): mp 144–145 °C; IR (KBr) 2250 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 3.22 (2 H, dt, 5-CH_2, J = 7.0 and 1.4 Hz), 3.56 (2 H, dt, 4-CH_2, J = 7.0 and 1.4 Hz), 3.77 (3 H, s, OMe), 4.32 (2 H, t, 2-CH_2, J = 1.4 Hz), 6.64, 6.69 (each 2 H, d, Ph). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.37; H, 5.40; N, 17.69.

3-(Dicyanomethylene)-4-[(*N*,*N*-dimethylamino)methylene]-1-(4-methoxyphenyl)pyrrolidine (20). Lithium diisopropylamide mono(tetrahydrofuran) (7.1 mL, 10.5 mmol, 1.5 M in cyclohexane) was added dropwise to a suspension of **19** (2.10 g, 8.8 mmol) in THF (150 mL, freshly distilled over $CaCl_2$) in an dry ice–Me_2CO bath. After the mixture was stirred for 1 h, (dimethylamino)methylene chloride (prepared from 1.64 mL of $POCl_3$ and 1.36 mL of DMF in 10 mL of THF) was added dropwise, and the stirring was continued at −65 °C for 18 h. The solid was collected by filtration and triturated with boiling EtOH (50 mL) to give **20** (1.02 g, 40%): mp 218–219 °C dec; IR (KBr) 2210 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.31 (6 H, s, NMe_2), 3.68 (3 H, s, OMe), 4.23 (2 H, br s, CH_2), 4.44 (2 H, br s, CH_2), 6.60, 6.85 (each 2 H, d, Ph), 8.24 (1 H, s, NCH=). Anal. Calcd for $C_{17}H_{18}N_4O \cdot {}^1/_4H_2O$: C, 68.32; H, 6.24; N, 18.75. Found: C, 68.41; H, 6.31; N, 18.74.

6-Amino-7-cyano-2-(4-methoxyphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyridine (21). A mixture of **20** (2.94 g, 10 mmol) in saturated NH_3/MeOH (60 mL) was heated in a sealed steel vessel at 150 °C for 3 h. After cooling, yellow needles separated and were collected by filtration and washed with MeOH to give **21** (2.17 g, 81%): mp 242–243 °C; IR (KBr) 2210 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.68 (3 H, s, OMe), 4.42 (2 H, br s, 3-CH_2), 4.55 (2 H, br s, 1-CH_2), 6.61, 6.87 (each 2 H, d, Ph), 6.89 (2 H, br s, NH_2), 8.21 (1 H, s, H-4). Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.60; H, 5.31; N, 21.13.

2,4-Diamino-6-(4-methoxyphenyl)-6,7-dihydropyrrolo-[3,4-*c*]pyrido[2,3-*d*]pyrimidine (3b). To a solution of *t*-BuOK (94 mg, 0.84 mmol) in DMF (8 mL) was added *N*,*N*-dimethylguanidine sulfate (204 mg, 0.75 mmol) with stirring. After 15 min, **21** (133 mg, 0.5 mmol) was added. The mixture was heated at 120 °C (bath temperature) under N_2 for 3 days and then cooled to room temperature. The yellow solid was collected by filtration, washed (DMF), and triturated with boiling water to give **3b** (126 mg, 82%): mp 327–328 °C; ^1H NMR (Me_2SO-d_6) δ 3.70 (3 H, s, OMe), 4.56 (2 H, br s, CH_2), 4.94 (2 H, br s, CH_2), 6.71 (2 H, br s, NH_2), 6.81, 6.86 (each 2 H, d, Ph), 8.65 (1 H, s, H-8). Anal. Calcd for $C_{16}H_{16}N_6O \cdot {}^1/_4H_2O$: C, 61.43; H, 5.32; N, 26.86. Found: C, 61.26; H, 5.28; N, 26.84.

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Registry No. **3a**, 117652-33-2; **3b**, 117652-32-1; **4**, 101348-30-5; **5**, 117652-34-3; **6**, 117652-35-4; **9**, 33141-33-2; **10**, 117652-36-5; **11**, 117652-37-6; **12**, 117678-51-0; **13**, 117652-38-7; **14**, 117652-39-8; **15**, 63767-58-8; **16**, 117652-40-1; **17**, 117652-41-2; **18**, 117652-42-3; **19**, 117652-43-4; **20**, 117652-44-5; **21**, 117652-45-6; *p*-anisidine, 104-94-9; acrylonitrile, 107-13-1; 2,5-dimethoxyaniline, 102-56-7; ethyl acrylate, 140-88-5; malononitrile, 109-77-3; *N*,*N*-dimethylguanidine sulfate, 598-65-2.

Preparation of Highly Substituted 2-Pyridones by Reaction of Vinyl Isocyanates and Enamines

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A method for the synthesis of highly substituted 2(1*H*)-pyridones is reported. Vinyl isocyanates, prepared from the corresponding α,β-unsaturated carboxylic acids, undergo cyclization with various enamines to furnish six-membered heterocycles. The methodology is exemplified by numerous examples. Application of this strategy is further illustrated by the synthesis of several aza steroid analogues.

The 2(1*H*)-pyridone moiety is a prominent structural feature in a variety of natural products as well as in other species of medicinal interest.[1] Classical approaches to these systems have generally relied on a variety of condensation reactions to effect the ring closure of appropriate precursors.[2] More recently, Overman has reported the preparation of alkyl-substituted 2-pyridones from propargylic pyrrolidine pseudoureas,[3] and Ghosez has de-

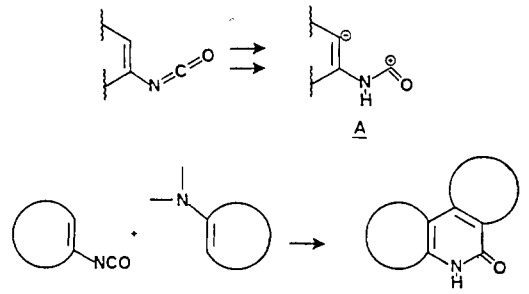
(1) (a) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1977; Vol. 1; 1980, Vol. 2. (b) Girundon, M. F. *The Alkaloids*, The Chemical Society: London, 1977; Vol. 7. (c) Niromiya, I.; Naito T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. XXII, p 189. (d) Snieckus, V. in *Survey of Progress in Chemistry*; Scott, A. F., Ed.; Academic Press: New York, 1980; Vol. 9, pp 121–267.

(2) Tieckelmann, H. In *Pyridine and its Derivatives*; Abramovitch, R. A., Ed.; Wiley: New York, 1975; supplement, Part 3, Chapter 12, pp 599–728.

(3) Overman, L. E.; Tsuboi, S.; roos, J. P.; Taylor, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 747.

0022-3263/89/1954-0224$01.50/0

Scheme I



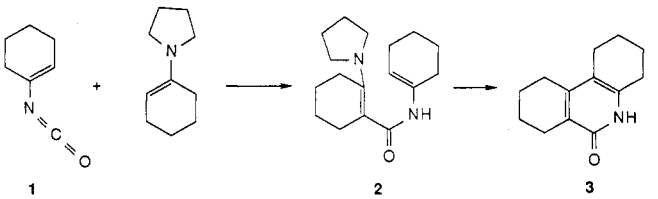
scribed a Diels–Alder route into these heterocycles.[4] An elegant cobalt-mediated synthesis of 2-pyridones has been applied to the total synthesis of camptothecin.[5] Other approaches to these important pyridine derivatives have also appeared in the current literature.[6]

Recently, we disclosed the concept of employing the vinyl isocyanate functional group as an equivalent for the useful 1,4-dipolar species A as depicted in Scheme I and demonstrated its utility for the construction of highly substituted 2-pyridone species.[7] Prior to our present work only sporadic reports of vinyl isocyanate reactivity had appeared.[8]

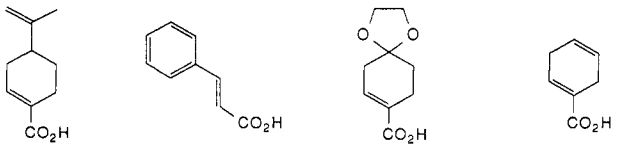
We were particularly intrigued by the possibility of using our methodology for achieving a highly convergent construction of polycyclic 2-pyridone systems. In this paper we detail the results of the vinyl isocyanate enamine cyclocondensation protocol as applied to the synthesis of a number of complex polycyclic 2-pyridones.

General Reaction Characteristics. Vinyl isocyanate 1 was selected as a prototype system from which to develop the basic methodology. All of the isocyanate species employed in this study were prepared directly from the corresponding α,β-unsaturated acids by using one of several modified Curtius procedures.[9] Typically the resultant isocyanates were used without further purification, and the formation of the isocyanates was conveniently monitored by IR spectroscopy or by measuring the quantity of N_2 evolved during thermal decomposition of the intermediate acyl azides involved.

Exposure of isocyanate 1 to 1-pyrrolidino-1-cyclohexene at room temperature in acetonitrile provided the moderately labile adduct 2 in high yield.[10] This substrate could then be smoothly transformed into the pyridone 3 on heating neat or in refluxing benzene or toluene. The nature of the enamine and the solvent polarity appear to play significant roles in the initial bond-forming process. For the most part pyrrolidine enamines tended to be more reactive and gave higher yields of products than the corresponding piperidine and morpholine series. Consequently, the majority of transformations described in this paper employ the corresponding pyrrolidine enamine as the "dienophilic" reaction partner. Although the entire sequence can be performed in benzene or toluene as solvent, improved yields of pyridone product can often be obtained if the initial carbon–carbon bond formation is performed in acetonitrile followed by solvent exchange to benzene or toluene and subsequent heating.



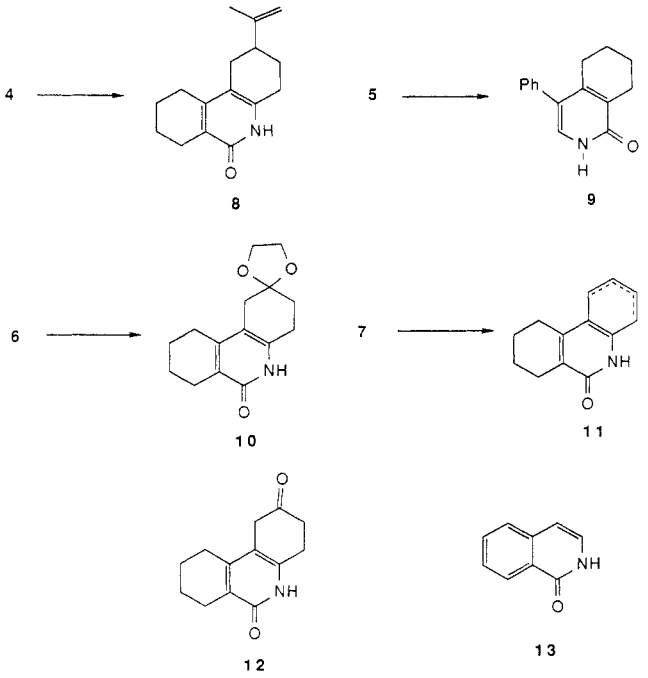
Pyridones Derived from Functionalized Isocyanates. To examine the functional group compatibility of our cyclocondensation process and to define the scope of the method, we investigated the reactions of several functionalized isocyanates. Commercially available (–)-perillic acid (4) and cinnamic acid (5) were examined in this context as were the readily available acids 6 and 7. Ketal acid 6 was conveniently prepared from Danishefsky's diene[11] in 57% yield, and 7 was available from the cycloaddition of butadiene and propiolic acid in 97% yield. The requisite isocyanates were generated directly from the corresponding acids under mild conditions with diphenyl phosphorazidate (DPPA),[9c,d] and the resultant acyl azides could be isolated or immediately converted into the isocyanates by heating in benzene or toluene at reflux. In the majority of cases examined, the entire sequence from α,β-unsaturated carboxylic acid to pyridone could be conveniently done in one pot with no isolation or purification of intermediates. In some instances the final yield of pyridone could be improved somewhat if the acyl azide was first isolated and the solvent changed prior to the cyclocondensation step (see the Experimental Section).



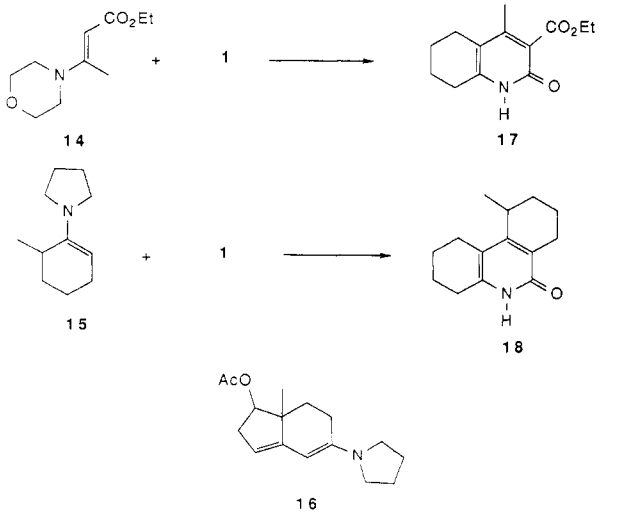
The various functional groups present in acids 4–6 survived the overall cyclocondensation process intact. On the other hand, a modest amount of double-bond isomerization was detected in the pyridone product derived from diene acid 7. The ketal in pyridone 10 could be easily removed under mildly acidic conditions to furnish ketone 12,[12] thus demonstrating that further manipulation of functionality present in the A or C ring of the hydrophenanthridine system was possible.[13] In contrast to the cyclic vinyl isocyanate results, more reliable access to cinnamic acid derived isocyanates was realized by employing a mixed anhydride approach into the intermediate acyl azides.[9a] The low yield of pyridone 9 (30%) also reflects an apparent propensity for the cinnamic acid isocyanate to polymerize in competition with acylation in the presence of enamines. Furthermore, additional material was lost in this example via partial equilibration to

(4) Sainte, F.; Serckx-Ponci, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428.
(5) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991.
(6) For other pyridone syntheses, see: (a) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1173. (b) Winters, G.; Sala, A.; DePaoli, A.; Ferri, V. *Synthesis* **1984**, 1052.
(7) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1984**, *49*, 4569.
(8) (a) Fuks, R. *Tetrahedron* **1970**, *26*, 2161. (b) Takaki, K.; Okamura, A.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1978**, *43*, 402. (c) Dondoni, A.; Kniezo, L.; Medici, A. *J. Org. Chem.* **1982**, *47*, 3994.
(9) (a) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511. (b) Kricheldorf, H. R. *Synthesis* **1972**, 551. (c) Saikachi, H.; Kitagawa, T. *Chem. Pharm. Bull.* **1977**, *25*, 1651. (d) Shioitri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(10) IR (KBr) ν 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–2.2 (m, 12 H), 2.6–3.0 (m, 8 H), 3.3–3.8 (m, 4 H), 5.3 (br s, 1 H), 8.7 (br s, 1 H); MS, *m/e* (relative intensity) M^+ 274 (9), 179 (11), 179 (100), 150 (12).
(11) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(12) IR ($CDCl_3$) ν max 3380, 3260, 3145, 3010, 2955, 1715, 1635, 1460, 1370 cm^{-1}; ^1H NMR δ 1.8–2.6 (m, 6 H), 2.8–3.2 (m, 6 H), 3.3 (br s, 2 H); MS, *m/e* (relative intensity) M^+ 217 (5), 215 (100), 200 (64), 186 (12), 77 (13).
(13) For examples of the amaryllidaceae alkaloids, see: Wildmen, W. C. *Alkaloids* **1968** *11*, 307. For the chelidonine alkaloids, see: Takao, N.; Bessho, N.; Kamigauchi, M.; Iwasa, K.; Tomita, K.; Fujiwara, T.; Fujii, S. *Tetrahedron Lett.* **1979**, 495.

the *Z* double bond isomer, which rapidly underwent an electrocyclic closure to give compound **13**.[14,15]

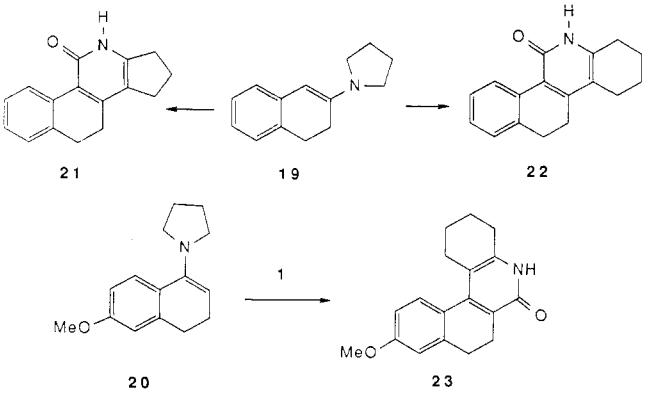


Pyridones Derived from Functionalized Enamines. The reaction of more functionally elaborate enamines with various vinyl isocyanates has also been investigated. At the onset of our study, we were concerned about the utility of all but the most nucleophilic enamine partners in the cyclocondensation process with vinyl isocyanates. We were gratified when relatively electron deficient enamine species such as compound **14** provided reasonable yields of the corresponding pyridone products. For example, enamide **14** reacted smoothly with isocyanate **1** to provide pyridone **17** in 43% yield. This demonstrates the efficacy of the

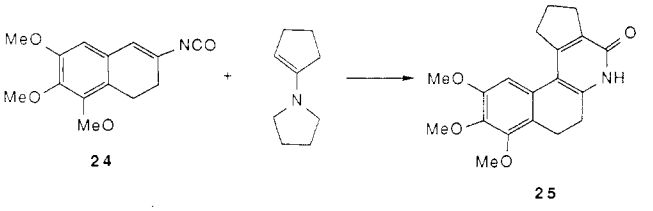


process for the construction of more highly functionalized tetrahydroquinolones. The alkyl substitution on this enamine appears to have little effect on the outcome of the process. In contrast, the dienamine **16**[16] immediately darkened when exposed to isocyanate **1**, and no identifiable products were isolated from this particular reaction. It appears that this result may be reflective of the relative instability of the dienamine rather than any intrinsic limitation of the cyclization. Finally, substituted enamine **15** provided the corresponding pyridone **18** regioselectively without incident. Clearly, the ability to use a variety of functionalized enamines with functionally elaborate isocyanates greatly expands the potential utility of this methodology.

Synthesis of Polycyclic Pyridones. The cyclocondensation of vinyl isocyanates with enamines as described above is particularly suitable for the convergent construction of tetracyclic aza analogues of steroids and related molecules. There has been considerable interest in the preparation and biological activity of these types of heterocyclic species in recent years.[17]



The highly crystalline 12-aza steroid species **21** and **22** were prepared in a *single step* from the commercially available enamine **19** and the corresponding isocyanates that were derived from cyclopentenecarboxylic acid and cyclohexenecarboxylic acid, respectively. Angularly fused systems are also readily available via this protocol. Tetracycle **23** was prepared from enamine **20**[18] in 50% yield. Complex isocyanates can also participate as the "diene" partner in the assembly of tetracyclic 2-pyridone derivatives as illustrated in the conversion of **24** into **25**.



These results clearly illustrate the experimental ease with which this technology can be employed for preparing relatively complex polycyclic systems in a highly convergent fashion.

Experimental Section

General Experimental Procedures. Tetrahydrofuran (THF) was distilled from sodium benzophenone; benzene and toluene were freshly distilled from sodium ribbon prior to use. Pyrrolidine was used without prior purification. Unless stated otherwise, all reactions were performed under an atmosphere of dry nitrogen. ^{1}H NMR and ^{13}C NMR spectra were obtained on a QE-300 spectrometer, and all chemical shifts are reported in parts per million relative to tetramethylsilane. Abbreviations for signal multiplicities are: s, singlet; d, doublet; t, triplet; m, multiplet;

(14) Mickol, G. J.; Boyer, J. H. *J. Org. Chem.* **1972**, *37*, 724.
(15) MacMillan, J. H.; Washburne, S. S. *J. Org. Chem.* **1973**, *38*, 2982.
(16) Pandit, U. K.; DeJonge, K.; Erhart, K.; Huisman, H. O. *Tetrahedron Lett.* **1969**, 1207.
(17) (a) Huisman, H. O. In *MTP International Review of Science, Organic Chemistry Series One*; Johns, W. F., Ed.; University Park Press: Baltimore, 1973; Vol. 8, pp 235–267. (b) Huisman, H. O.; Speckamp, W. N. In *MTP International Review of Science, Organic Chemistry Series Two*; Johns, W. F., Ed.; Butterworths: London, 1976; Vol. 8, pp 207–236. (c) Lakhvich, F. A.; Lis, L. G.; Akhrem, A. A. *Russ. Chem. Rev.* **1984**, *53*, 582.
(18) White, W. A.; Weingarten, J. *J. Org. Chem.* **1967**, *32*, 213.

br s, broad singlet. Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Midwest Microlabs.

Preparation of Enamines. Enamine **19** was purchased from Aldrich and used without further purification. Enamines **14–16**[16] were prepared by the method of Stork,[19] and enamine **20** was prepared as follows.[18] To a 200-mL three-necked flask fitted with mechanical stirrer, condenser, and dropping funnel was added 6-methoxytetralone (1.76 g, 0.01 mol) in 50 mL of ethyl ether and a solution of pyrrolidine (2.85 g, 0.04 mol) in 10 mL of ether. To the resulting solution was added $TiCl_4$ (0.95 g, 5 mmol) in 10 mL of ether over a 20–30-min period. During this time the reaction temperature was maintained between 0 °C and 10 °C. After the addition of $TiCl_4$ was complete, the mixture was allowed to stir for 15 h at room temperature. On filtration and concentration, the enamine crystallized and was used immediately without further purification.

Preparation of α,β-Unsaturated Acids. 1-Cyclohexene-1-carboxylic acid and 1-cyclopentene-1-carboxylic acid were prepared from the corresponding ketones via the cyanohydrins.[20] Acids **4**, **5**, and 3,4-dihydro-5,6,7-trimethoxynaphthalene-2-carboxylic acid were obtained from Aldrich and used without further purification. Acid **6** was prepared by the procedure outlined by Danishefsky.[11] Acid **7** was synthesized by heating propiolic acid and excess 1,3-butadiene at 110 °C in a pressure bottle for 12 h.

General Preparation of Vinyl Isocyanates. Procedure A. To an ice-cooled solution of 10 mmol of carboxylic acid in 10 mL of dry benzene or DMF was added 10 mmol of triethylamine and 10 mmol of diphenyl phosphorazidate (DPPA). The resultant solution was stirred at room temperature for 3 h. The acyl azide product was isolated by diluting the solution with cold water and extracting with ether. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to provide crude product. The acyl azide was dissolved in 20 mL of dry benzene and heated at reflux until azide decomposition was complete as monitored by IR spectroscopy or nitrogen evolution. The resultant isocyanate was used directly in the pyridone formation step.

Procedure B. Cinnamic acid (10 mmol) was suspended in 10 mL of water, and enough acetone was added to make the mixture homogeneous. This solution was cooled to 0 °C, and triethylamine (12.5 mmol) and ethyl chloroformate (13 mmol) were slowly added. The resultant mixture was stirred at 0 °C for 30 min, and a solution of sodium azide (14.7 mmol) in 25 mL of water was introduced. Stirring was continued at this temperature for an additional 60 min at which time the reaction was poured into ice–water. The solid that separated was taken into ether and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give the acyl azide. This material was dissolved in toluene (30 mL) and heated at reflux for 40 min.

General Procedure for the Preparation of 2(1*H*)-Pyridones. To a cooled solution of the vinyl isocyanate (10 mmol) in 10 mL of acetonitrile was added a solution of the enamine (10 mmol) in 2 mL of acetonitrile at a rate such that the reaction temperature was maintained between 0 °C and 10 °C. The reaction mixture was then stirred at room temperature for an additional 6–8 h. In most cases a precipitate appeared during the first few hours. After the requisite time had elapsed, the solvent was evaporated and the intermediate was isolated. In most cases this material was taken directly to the pyridone product without further purification. This transformation was accomplished by dissolving the initial adduct in dry benzene or toluene (20 mL) and heating at reflux for approximately 48 h. During this time product began to precipitate out of solution. After the reaction mixture was allowed to cool, the solvent was evaporated, and the crude pyridone residue was recrystallized from 95% ethanol.

1,2,3,4,5,6,7,8,9,10-Decahydro-6-oxophenanthridine (3). Reaction of vinyl isocyanate **1** (1.26 g, 10 mmol) (via procedure A) and enamine **2** (1.51 g, 10 mmol) gave 1.48 g (73%) of pyridone **3** (95% EtOH): mp 295–297 °C (lit.[21] mp 296–98 °C); IR ($CHCl_3$) ν 3400, 3280, 3120, 3020, 2460, 2880, 1645, 1550, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–1.7 (m, 8 H), 2.2–2.5 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.3, 22.7, 23.4, 25.6, 26.3, 26.9, 119.4, 123.9, 138.1, 148.8, 163.6; UV (EtOH) λ_{max} 233 (ε 5227), 305 nm (ε 9541); mass spectrum, *m/e* (relative intensity) 203 (21), 202 (18), 199 (16), 114 (57), 86 (32), 43 (100); high resolution, *m/e* calcd 203.1310, found 203.1310. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43; N, 6.90. Found: C, 76.81; H, 8.43; N, 6.84.

(−)-2-(1-Methylethenyl)-1,2,3,4,5,6,7,8,9,10-decahydro-6-oxophenanthridine (8). Reaction of the vinyl isocyanate derived (via procedure A) from (*S*)-(−)-perillic acid (1.66 g, 10 mmol) and 1-pyrrolidino-1-cyclohexene (1.51 g, 10 mmol) yielded 1.58 g (65%) of pyridone **8** (1:1 EtOH/Et_2O): mp 231–33 °C; $[\alpha]^{25}_D$ −88.2° (*c* = 0.5, $CHCl_3$); IR ($CHCl_3$) ν 3400, 3300, 3120, 2450, 2860, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–2.0 (m, 6 H), 1.95 (s, 3), 2.00 (m, 1 H), 2.20–2.45 (m, 8 H), 4.79 (s, 1 H), 4.83 (s, 1 H), 10.5 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.8, 22.2, 23.5, 26.4, 27.2, 28.8, 41.3, 109.6, 113.1, 118.2, 124.4, 137.0, 145.9, 163.3; UV (EtOH) λ_{max} 233 (ε 14 800), 305 nm (ε 1820); mass spectrum, *m/e* (relative intensity) 243 (60), 242 (15), 288 (10), 200 (30), 175 (60), 87 (100), 86 (98); high resolution, *m/e* calcd 243.1623, found 243.1620. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.69; N, 5.76. Found: C, 78.95; H, 8.69; N, 5.75.

4-Phenyl-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (9). Reaction of *trans*-cinnamyl isocyanate 1.48 g (10 mmol) (via procedure B) with 1-pyrrolidino-1-cyclohexene 1.51 g (10 mmol) yielded 0.67 g (30%) of pyrridone **9** as pale yellow needles (EtOH): mp 244–45 °C; IR ($CHCl_3$) ν 3380, 3230, 3100, 2900, 2820, 1640, 1620, 1600, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69–1.90 (m, 4 H), 2.40–2.80 (m, 4 H), 7.23–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.1, 23.8, 28.7, 123.0, 127.1, 127.3, 128.3, 129.3, 129.7, 137.1, 148.2, 164.1; UV (EtOH) λ_{max} 260 (ε 12 525), 305 nm (ε 10 350); mass spectrum, *m/e* (relative intensity) 225 (90), 224 (60), 210 (50), 145 (13), 111 (30), 97 (60), 83 (65), 57 (100); high resolution, *m/e* calcd 225.1153, found 225.1157. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.21. Found: C, 80.02; H, 6.55; N, 6.46.

1,2,3,4,5,6,7,8,9,10-Decahydro-2,6-phenanthridinedione 2,2-(Ethanediyl acetal) (10). Reaction of the isocyanate derived via procedure A from 1.84 g (10 mmol) of acid **6**, with 1.51 g (10 mmol) of 1-pyrrolidino-1-cyclohexene yielded 1.675 g (64%) of pyridone (**10**) as yellow needles: mp 290–292 °C dec; IR ($CHCl_3$) ν 3400, 1645, 1615, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (m, 4 H), 1.91 (t, *J* = 6 Hz, 2 H), 2.41 (m, 2 H), 2.56 (m, 2 H), 2.60 (s, 2 H), 2.87 (t, *J* = 6 Hz, 2 H), 4.04 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 22.1, 23.3, 25.6, 26.4, 30.1, 34.1, 64.6, 107.8, 111.1, 124.6, 136.7, 148.4, 163.7; mass spectrum, *m/e* (relative intensity) 261 (100), 218 (41), 189 (46), 188 (65), 176 (12), 175 (83); high resolution, *m/e* calcd 261.1364, found 261.1362. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.35. Found: C, 68.61; H, 7.27; N, 5.36.

Mixture of Isomeric Hexahydro-6(5*H*)-phenanthridinones (11). Reaction of the isocyanate derived via procedure A from 0.124 g (1 mmol) of acid **7** with 0.151 g (1 mmol) of 1-pyrolidino-1-cyclohexene gave 96 mg (48%) of pyridone **11** (EtOH/Et_2O): mp 276–77 °C; IR (Nujol) ν 3280, 3120, 3020, 1645, 1630, 1550, 1460, 1380, 960, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (br s, 4 H), 2.20 (m, 4 H), 3.05 (m, 2 H), 3.32 (m, 2 H), 5.80–6.35 (m, 2 H); mass spectrum, *m/e* (relative intensity) 201 (100), 200 (80), 199 (11), 186 (54), 173 (11); high resolution, *m/e* calcd for $C_{13}H_{15}NO$ 201.1153, found 201.1157.

Ethyl 4-Methyl-2-oxo-5,6,7,8-tetrahydroquinoline-3-(1*H*)-carboxylate (17). To a chilled solution of 0.126 g (1 mmol) of cyclohexene carboxylic acid in 2 mL of benzene was added 0.101 g (1 mmol) of triethylamine and 0.151 g (1 mmol) of DPPA. This solution was stirred at room temperature for 3 h and then heated to reflux. Formation of isocyanate was monitored by IR spectroscopy (disappearance of 2140-cm^{-1} absorbance). When all of the azide had been consumed the solution was cooled to room temperature. The heating mantle was removed and replaced with an ice bath, and 0.199 g (1 mmol) of enamine **14** was added. The mixture was allowed to warm to room temperature and stirred at that temperature for 3 h. Finally, the resulting solution was

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heating at reflux for 48 h. The mixture was cooled, and the solvent was evaporated. The residue was suspended in water and extracted with chloroform (3 × 100 mL). Removal of solvent furnished 0.102 g of pyridone **17** (43%) recrystallized from 95% EtOH: mp 228 °C; IR ($CHCl_3$) ν 3280, 3180, 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 1.71 (m, 4 H), 2.11 (s, 3 H), 2.44 (m, 2 H), 2.63 (m, 2 H), 4.41 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 16.7, 21.4, 22.7, 24.1, 27.3, 61.2, 114.1, 144.1, 150.6, 161.1, 167.3; UV (EtOH) λ_{max} 230 (ϵ 5506), 316 nm (ϵ 9471); mass spectrum, m/e (relative intensity) 235 (46), 190 (59), 189 (36), 163 (100), 162 (22), 161 (60), 134 (16), 133 (59); high resolution, m/e calcd for $C_{13}H_{17}NO_3$ 235.1208, found, 235.1202.

10-Methyl-1,2,3,4,7,8,9,10-octahydro-6(5*H*)-phenanthridinone (18). Condensation of vinyl isocyanate **1** from 0.126 g (1 mmol) of cyclohexenecarboxylic acid (via procedure A) and 0.155 g (1 mmol) of enamine **15** produced 52% of pyridone **10** as a white solid after recrystallization from 95% EtOH: mp 248–250 °C; UV (CH_3OH) λ_{max} 234 (ϵ 3326), 305 nm (ϵ 5090); IR ($CDCl_3$) ν 3300, 2900, 2850, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6 Hz, 3 H), 1.60–1.86 (m, 8 H), 2.30–2.90 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 16.3, 20.2, 21.8, 22.9, 23.9, 27.2, 28.5, 29.1, 112.9, 123.2, 138.0, 153.5, 163.5; mass spectrum, m/e (relative intensity) 217 (100), 216 (40), 203 (15), 202 (80), 192 (18), 97 (50), 96 (15), 83 (20), 81 (16), 69 (30), 57 (40), 55 (55), 43 (50), 41 (55), 39 (15), 29 (15), 27 (15); high resolution, m/e calcd for $C_{14}H_{19}NO$ 217.1466, found 217.1467.

6,7,8,9,10,11-Hexahydro-5*H*-benzo[*h*]cyclopent[*c*]isoquinolin-5-one (21). Condensation of the isocyanate derived via procedure A from 1.12 g (10 mmol) of cyclopentenecarboxylic acid with 1.99 g (10 mmol) of enamine **19** gave 1.35 g (57%) of pyridone **21** (95% EtOH): mp 289–292 °C; IR ($CHCl_3$) ν 3240, 3130, 3010, 2410, 2860, 1635, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (m, 2 H), 2.70 (m, 2 H), 2.81 (m, 4 H), 3.07 (t, J = 6 Hz, 2 H), 7.34 (m, 4 H), 8.82 (d, J = 9 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 21.7, 25.7, 27.1, 27.9, 30.7, 116.7, 125.7, 125.9, 126.8, 132.5, 135.3, 147.6, 161.1; UV (EtOH) λ_{max} 262 (ϵ 5275), 268 (ϵ 5038), 350 nm (ϵ 11 499); mass spectrum, m/e (relative intensity) 237 (100), 236 (28), 218 (4), 208 (9). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.74; H, 6.34; N, 6.05.

7,8,9,10,11,12-Hexahydrobenzo[*i*]phenanthridin-5(6*H*)-one (22). Reaction of isocyanate **1** derived from 1.26 g (10 mmol) of cyclohexenecarboxylic acid via procedure A with 1.99 g (10 mmol) of enamine **19** gave 1.53 g (61%) of pyridone **22** (95% EtOH): mp >300 °C; IR ($CHCl_3$) 3370, 3250, 3130, 2920, 1640, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–2.00 (m, 4 H), 2.50–2.88 (m, 8 H), 7.10–7.22 (m, 4 H); ^{13}C NMR (CD_3OD) δ 20.9, 22.2, 23.4, 23.9, 26.5, 27.1, 110.9, 119.2, 125.6, 126.1, 126.5, 132.3, 135.5, 141.5, 150.1, 160.0; UV (EtOH) λ_{max} 240 (ϵ 9414), 248 (ϵ 8577), 344 nm (ϵ 2071); mass spectrum, m/e (relative intensity) 251 (100), 250 (22), 223 (13), 22 (14). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.81; N, 5.57. Found: C, 80.91; H, 6.60; N, 5.60.

10-Methoxy-1,2,3,4,7,8-hexahydrobenzo[*k*]phenanthridin-6(5*H*)-one (23). Reaction of the vinyl isocyanate prepared from 0.25 g (2 mmol) of cyclohexenecarboxylic acid (via procedure A) and 0.455 g (2 mmol) of enamine **20** gave 0.25 g (46%) of pyridone **23** (95% EtOH): mp 292–93 °C; IR (KBr) ν 3400, 1635, 1440, 1320, 1250, 1225, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (m, 2 H), 1.71 (m, 2 H), 2.73–2.81 (m, 8 H), 3.87 (s, 3 H), 6.79–6.86 (m, 2 H), 7.62 (d, J = 9 Hz, 1 H), 12.20 (m, 1 H); ^{13}C NMR ($DCCl_3$) δ 21.6, 21.7, 23.7, 27.3, 28.6, 29.6, 45.8, 55.2, 110.7, 112.3, 113.5, 124.2, 125.6, 129.6, 140.5, 142.9, 146.3, 159.6, 162.9; UV (EtOH) λ_{max} 234 nm (ϵ 19 865); mass spectrum, m/e (relative intensity) 298 (78), 280 (100), 279 (8), 266 (9). Anal. Calcd or $C_{18}H_{19}NO_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.53; H, 6.71; N, 4.50.

8,9,10-Trimethoxy-2,3,6,7-tetrahydro-1*H*-benzo[*f*]cyclopenta[*c*]quinolin-4(5*H*)-one (25). Reaction of the vinyl isocyanate derived from 0.422 g (1.6 mmol) of 3,4-dihydro-5,6,7-trimethoxy-2-naphthoic acid via procedure A and 1 equiv of 1-pyrrolidino-1-cyclopentene yielded 0.177 g (34%) of pyridone **25** (95% EtOH): mp 279–281 °C; IR (Nujol) ν 3200–2800, 1655, 1600, 1472, 1417, 1368, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (m, 2 H), 2.95 (m, 6 H), 3.25 (t, J = 7 Hz, 2 H), 2.89 (s, 3 H), 3.91 (s, 3 H), 3.93 (s, 3 H), 6.96 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.4, 24.5, 26.3, 29.6, 36.0, 56.4, 60.9, 61.0, 105.8, 111.3, 120.90, 129.2, 130.8, 140.4, 144.5, 150.5, 151.8, 152.6, 160.5; mass spectrum, m/e (relative intensity) 327 (24), 312 (24), 183 (18), 165 (18), 156 (16), 155 (37), 153 (12). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.27. Found: C, 69.66; H, 6.60; N, 4.08.

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Organometallic Ring-Opening Reactions of *N*-Acyl and *N*-Alkoxycarbonyl Lactams. Synthesis of Cyclic Imines

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The reactions of hexyl- and phenylmagnesium bromides with *N*-acyl and *N*-alkoxycarbonyl lactams in tetrahydrofuran at −78 °C have been performed to determine the factors affecting the regioselectivity. *N*-Pivaloyl γ- and δ-lactams undergo the ring-opening reactions with both Grignard reagents, whereas on the *N*-benzoyl γ-lactam a complete selectivity is achieved only with phenylmagnesium bromide. The *N*-Cbz γ- and δ-lactams preferentially react at the exocyclic carbonyl group, especially with hexylmagnesium bromide. The *N*-Boc five- to eight-membered lactams undergo the ring-opening reaction to give *N*-Boc-ω-amino ketones, although the efficiency slightly decreases by increasing the ring size. The deprotection of the *N*-Boc-ω-amino ketones with trifluoroacetic acid easily affords the corresponding five- to seven-membered cyclic imines. Pyridine alkaloids containing the cyclic imine moiety have been prepared by a modified route, exploiting the more easily available pyridyllithium reagents, instead of the corresponding Grignard reagents.

The selective ring-opening reaction of *N*-methyl lactams **1** ($n \geq 1$; R′ = CH_3) to give ω-methylamino ketones **2** by means of organometallic reagents cannot be generally accomplished. In fact, forcing experimental conditions are required owing to the low reactivity of the carbonyl group, so that mixtures of several products are obtained, depending on the ring size of the lactam and the nature of the organometallic reagent.[1-3] Only when aryl organo-

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