and reflections collected out to $2\theta = 50°$ were accepted as statistically above background on the basis that F was greater than $3\sigma(F)$. Lorentz and polarization corrections were made in the usual way.

(B) Solution and Refinement of the Structure. Computations were performed by using standard programs;[9] all computations were carried out on the CDC Cyber 74 system. For structure factor calculations the scattering factors were taken from Cromer and Mann's tabulation.[10] The agreement factors are defined in the usual way as in eq 3 and 4. In all least-squares

$$R = (\sum||F_o| - |F_c||)/(\sum|F_o|) \quad (3)$$

$$R_w = \sum(|F_o| - |F_c|)w^{0.5}/\sum(|F_o|)w^{0.5} \quad (4)$$

refinements, the quantity minimized was $\sum\omega(|F_o| - |F_c|)^2$. A weighting scheme based on counting statistics ($w = A/[\sigma(F)^2 + BF^2]$; see Table I for factors A and B) was employed for calculating R_w and in least-squares refinement.

The structures were solved by using the automatic centrosymmetric direct methods program of SHELX-76. Parameters varied included a scale factor, coordinates of all atoms except hydrogen, anisotropic thermal parameters for all atoms except H atoms and the C atoms and N atoms of the tosylhydrazone unit in structure **15**, and isotropic thermal parameters for all other atoms. The H atom coordinates were determined by using the routine in SHELX-76 that fixes the C-H distances at 1.08 Å and orients the H atom positions to complete the appropriate coordination about each C atom. The full-matrix least-squares refinement converged to give the R and R_w values listed in Table I. The final atomic coordinates, thermal parameters, bond distances, and bond angles are available as supplementary material. The lists of calculated and observed structure factors are available from the authors.

Registry No. **5**, 70562-48-0; **6**, 73274-32-5; **7**, 79135-43-6; **8**, 73274-35-8; **9**, 77188-60-4; **10**, 77188-51-3; **11**, 79199-40-9; **14**, 79135-44-7; **15**, 79135-45-8; 1,3-butadiene, 106-99-0.

Supplementary Material Available: Tables of atomic coordinates and thermal parameters (Tables III, IV, VII, and X) and tables of bond distances and bond angles (Tables II, V, VIII, and XI) (14 pages). Tables VI, IX, XII, and XIII are available from the authors. Ordering information is given on any current masthead page.

(9) Programs utilized were Sheldrick's SHELX-76 program and Johnson's ORTEP program.

(10) "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 72-98.

Selectivity in β-Enamino Ketone Anion Generation and Alkylation

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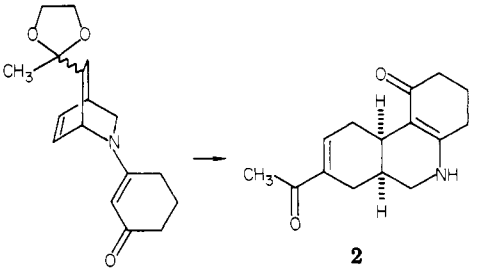
The regioselectivity of anion generation from β-alkoxy- and β-(dialkylamino)-α,β-unsaturated ketones was probed by use of ^{13}C NMR spectroscopy and alkylation techniques. Results indicate that the kinetic anions of these systems can be formed selectively from the parent ketones by using excess lithium diisopropylamide as the base at −78 °C and diethyl ether or tetrahydrofuran as the solvent. The kinetic anion in these systems is the one resulting from deprotonation at the α′-carbon. Alkylation occurs at this center in synthetically useful yields. Equilibration to produce the thermodynamically more stable extended γ-enolate anion occurs when less than 1 equiv of lithium diisopropylamide is present and at elevated temperatures (>−20 °C). The rate of equilibration is sensitive to the solvent employed, occurring much more rapidly in tetrahydrofuran than in diethyl ether. A synthetically more practical method for formation and alkylation of the thermodynamic anions of β-(dialkylamino)-α,β-unsaturated ketones utilizes excess lithium bis(trimethylsilyl)amide as the base in tetrahydrofuran as the solvent at −78 °C followed by quenching with the alkylating agent. Methods for regioselective generation of dianions from β-(alkylamino)-α,β-unsaturated ketones have been explored. Analysis of products produced by methylation suggest that the N,α'- and N,γ-dianions can be produced independently by use of the respective kinetic and thermodynamic anion-producing conditions described above. However, all attempts to identify these dianions by spectroscopic methods failed due to the exceedingly low solubilities of these substances in solvent systems compatible with the technique. Likewise, dialkylation or acylation-alkylation of the N,γ-dianions, in attempts to develop one-step procedures for fused-bicyclic pyrrolidine synthesis, was unsuccessful.

Earlier studies in our laboratory have uncovered an interesting method for the preparation of functionalized hydroisoquinolines and hydrophenanthridines which employs amino-Claisen and related rearrangements of N-vinylisoquinuclidenes in key structural elaboration steps.[2] The utility of this route is exemplified by the six-step sequence for generation of the 1-oxo-decahydrophenanthridine **2** from pyridine via the isoquinuclidine **1**. This methodology appears to be applicable to the synthesis



1 **2**

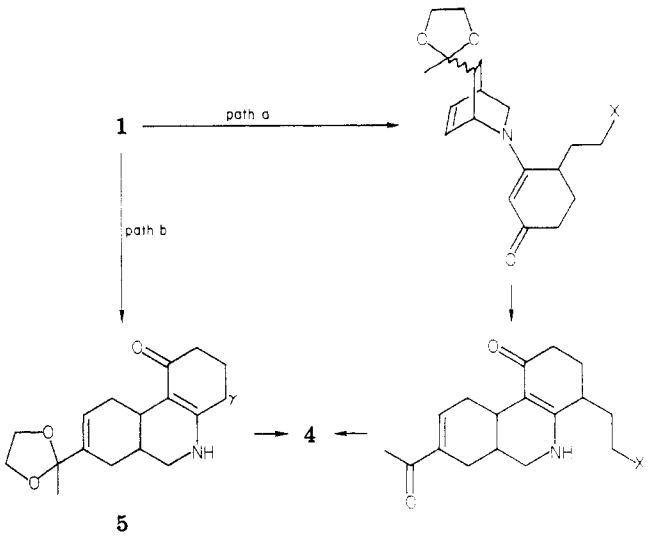
of a variety of naturally occurring materials containing cis-fused hydroisoquinoline and hydrophenanthridine ring systems. One of the targets of our initial efforts to explore

(1) To whom correspondence should be addressed at the University of Maryland.

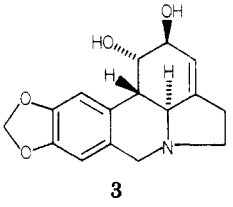
(2) (a) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124-133. (b) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L.; Beamer, R. L. *Tetrahedron Lett.* **1977**, 4299-4302.

0022-3263/81/1946-4643$01.25/0

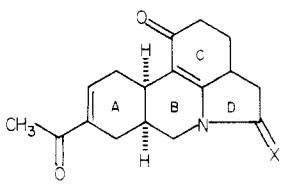
Scheme I



the potential of designs based upon this method is the lycorane skeleton shared by members of the lycorine (3)



3



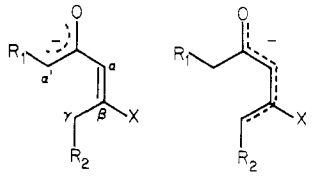
4, X = O or H_2

alkaloid family.[3] At the outset, we anticipated that the tetracyclic enamino or enamido ketones **4** would serve as useful synthons in these routes and that they might be efficiently generated from the known isoquinuclidene **1**. The two-carbon unit serving as a portion of the pyrrolidine D ring of **4** in this plan would be derived by alkylation at the γ-position of the enamino ketone group in **1** (path a in Scheme I). An alternate protocol would involve dialkylation or alkylation–acylation of an *N*,γ-dianion arising from the hydrophenanthridine ketal **5** (path b, Scheme I).

The feasibility of these sequences is contingent upon the availability of procedures for selective alkylation at the γ-position of β-enamino ketone mono- and dianions. As a result, several years ago we initiated studies designed to explore this feature of enamino ketone anion chemistry.[4] Indeed, problems associated with regioselective generation and alkylation of anions arising from carbonyl compounds have long challenged synthetic practitioners. Several general solutions have been proposed.[5] Included among these are techniques for selective blocking or activation, the use of dianion monoalkylations, and employment of selectively prepared, neutral, enol-type derivatives. More recent studies[6] have demonstrated differences between kinetic and thermodynamic acidity and suggested the types of reagents and reaction conditions under which these differences would be manifested.

At the time we initiated our current studies,[4] other groups had employed this technology in methods for regioselective anion generation from α,β-unsaturated ketones[7] and β-alkoxy[8] and β-dialkylamino[9] analogues. These early results had shown that introduction of γ substituents in β-enaminones could be accomplished through alkylation of the extended γ-enolate anions formed by treatment with strong bases such as butyllithium[9c] and lithium diisopropylamide. Despite this, the factors controlling anion regiochemistry, including the nature of reaction conditions, β-heteratom substitution, and base, were not fully understood.[10]

Our desire to utilize this methodology in synthetic routes to the lycorane skeleton stimulated us to undertake a detailed study of this problem. In this report we describe the results of ^{13}C NMR investigations in which anions (**6** and **7**) generated from β-alkoxy and β-dialkylamino α,β-



6 7

unsaturated ketones under a variety of conditions leading to kinetic and thermodynamic control are identified. In addition, this spectroscopic technique has been employed to identify conditions which control the rate of anion equilibration. Finally, the outcome of mono- and dianion alkylation studies, which confirm the spectroscopic results and demonstrate the synthetic versatility of the method, are summarized.

Results and Discussion

^{13}C NMR Studies. ^{13}C NMR spectroscopy was utilized as a probe to determine the site of deprotonation in anion generation from β-alkoxy and β-dialkylamino α,β-unsaturated ketones and as a technique for gaining qualitative information about the rates of anion interconversions. The ketones selected for study were the readily available enol ethers **8** and **9** and the β-enamino ketones **10–12**. NMR spectra were recorded on samples prepared in a fashion analogous to that employed when these anions were regioselectively generated for alkylation studies. Conditions for kinetic anion formation include a slight molar excess of the base lithium diisopropylamide at low temperatures (−78 to 0 °C) and in either tetrahydrofuran or diethyl ether as solvent. Under these conditions, equilibration to the more stable anions should be slow due to the absence of

(3) Wildman, W. C. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: 1967; Vol. VI. Fuganti, C. *Ibid.*, 1975, Vol. XV, Chapter III.

(4) A summary of the initial phases of these studies serving as a basis for this article is found in the dissertation of: Little, G. Texas A&M University, 1978.

(5) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: New York, 1972; Chapter 9–11.

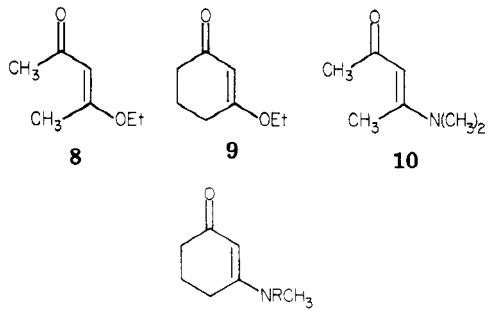
(6) Jones, J. R. *Surv. Prog. Chem.* **1973**, *6*, 83–112. Shatenshtein, A. I. *Adv. Phys. Org. Chem.* **1963**, *1*, 153–201. Bordwell, F. G.; Mathews, W. S.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 442–443.

(7) Malhotra, S. K., Ringlold, H. J. *J. Am. Chem. Soc.* **1964**, *86*, 1997–2003. Nedelec, L.; Gasc, J. C.; Bucort, R. *Tetrahedron* **1974**, *30*, 3263–3268. Lee, R. A.; McAndrews, C.; Patel, K. M., Reusch, W. *Tetrahedron Lett.* **1973**, 965–968. Tanabe, M.; Crowe, D. F. *J. Chem. Soc., Chem. Commun.* **1973**, 564–565.

(8) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776. Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414–3415.

(9) (a) Yoshimoto, M.; Ishida, N.; Hiraoka, T. *Tetrahedron Lett.* **1973**, 39–42. (b) Bryson, T. A.; Gammill, R. B. *Ibid.* **1974**, 3963–3966. (c) Attempts to repeat Yoshimoto's procedure with other enaminones also failed.

(10) (a) Subsequent efforts[10b–d] after initiation of our studies have shown that alternate bases or reaction conditions can be used to selectively generate both the α′ and γ anions from β-enaminones. (b) Gammill, R. B.; Bryson, T. A. *Synthesis* **1976**, 401–403. (c) Telschow, J. E.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 862–865. (d) Koreeda, M.; Chen, Y.; Akagi, H. "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, DC, 1979; American Chemical Society: Washington, DC, 1979; Abstract ORGN 38. Koreeda, M.; Liang, Y.; Akagi, H. *J. Chem. Soc., Chem. Commun.* **1979**, 449–450. Koreeda, M.; Chen, Y. *Tetrahedron Lett.* **1981**, 15–18.



8 9 10

11, R = CH_3
12, R = cyclohexyl

proton sources initially.[11] Indeed, the cyclic enamino ketones 11 and 12 and enol ether 9 undergo clean deprotonation to form α′-enolates exclusively (Table I) when treated in this way. However, ^{13}C NMR analysis of tetrahydrofuran solutions of the acyclic enones 8 and 10 containing excesses of lithium diisopropylamide at −78 °C indicated that mixtures of the α′- and γ-enolates were present and that the γ-anions were being produced at the expense of initially formed α′ regioisomers. It should be mentioned that all attempts to generate the kinetic enolates by use of *n*-butyllithium or (trimethylsilyl)methyllithium failed due to competitive addition reactions. This result is contrasted with the earlier report by Yoshimoto and co-workers[9] which suggested that butyllithium could be used to form the γ-enolate of 4-pyrrolidinopent-3-en-2-one.

The corresponding thermodynamic enolate anions of enones 8 and 10–12 are generated smoothly under a variety of conditions which permit anion equilibration through proton exchange. For example, tetrahydrofuran solutions containing lithium diisopropylamide and excesses of the enones at room temperature yield carbon spectra characteristic of the presence of single anions having the γ-enolate regiochemistry (Table I). The cyclic enol ether 9 stands as an exception in this case. All attempts to prepare the thermodynamic enolate anion of this system were unsuccessful. An approach via initial preparation of the kinetic anion (confirmed spectroscopically) followed by slow additions of the enol ether resulted in formation of a precipitate as soon as the ketone was in excess. Alternative methods for thermodynamic, γ-anion formation involve the use of an excess of the weaker base lithium bis(trimethylsilyl)amide[12] in tetrahydrofuran at −78 °C. Solvent also appears to play a critical role in controlling anion selectivity through its influence on the rate of equilibration. While the γ-enolates of the cyclic β-enamino ketones 11 and 12 are produced nearly instantaneously by treatment with lithium bis(trimethylsilyl)amide in tetrahydrofuran, equilibrations of the α′- to γ-enolates are slow and require approximately 1 week for complete conversion when diethyl ether is solvent (Figure 1). Similarly, anion equilibration which occurs slowly at room temperature when lithium diisopropylamide is used for deprotonation can be made negligibly slow when diethyl ether is employed as solvent (Figure 1).

Regiochemical assignments to the enolate anions described above were made on the basis of characteristic ^{13}C NMR chemical shifts and proton–carbon coupling patterns. The resonances of the carbons at which deprotonation occurs are expected to undergo large downfield shifts due to changes in hybridization from sp^3 to sp^2. Counteracting this effect will be increases in shielding caused by large π-electron densities at the centers of the conjugated enolates where charge is concentrated.[13] The NMR

Table I. ^{13}C NMR Chemical Shifts for β-Substituted α,β-Unsaturated Ketones and Corresponding Kinetic and Thermodynamic Enolates

ketone or ketone enolate	^{13}C NMR chemical shifts[a]				
	α′	C=O	α	β	γ
8	31.6	194.9	99.7	171.3	19.6
8α′	82.1	165.0	104.9	153.7	18.7
8γ	27.7	164.0	91.6	162.2	76.0
9	36.8	199.1	102.6	177.7	29.1
9α′	82.7	159.3	101.2	158.8	29.6
10	31.4	194.2	95.1	163.4	16.0
10γ	27.4	163.0	92.1	158.7	85.0
11	35.5	196.0	98.2	165.9	26.3
11α′[b]	81.4	160.6	105.2	149.3	28.1
11α′[c]	84.1	158.6	102.0	150.2	27.2
11γ[b]	34.7	168.3	92.9	151.8	83.6
11γ[c]	33.7	165.5	95.6	150.0	85.9
12	35.0	196.1	97.9	164.8	26.5
12α′[b]	81.9	159.4	103.2	148.4	27.6
12α′[c]	83.6	158.7	101.9	149.3	27.4
12γ[b]	34.2	166.9	93.1	149.5	85.0
12γ[c]	*d*	165.1	95.8	148.5	86.9

[a] Chemical shifts are reported in parts per million relative to $(CH_3)_4Si$ as an internal standard. The solvent is THF unless otherwise noted. [b] Solvent THF. [c] Solvent Et_2O. [d] Resonance not observed due to its low intensity and solvent interference.

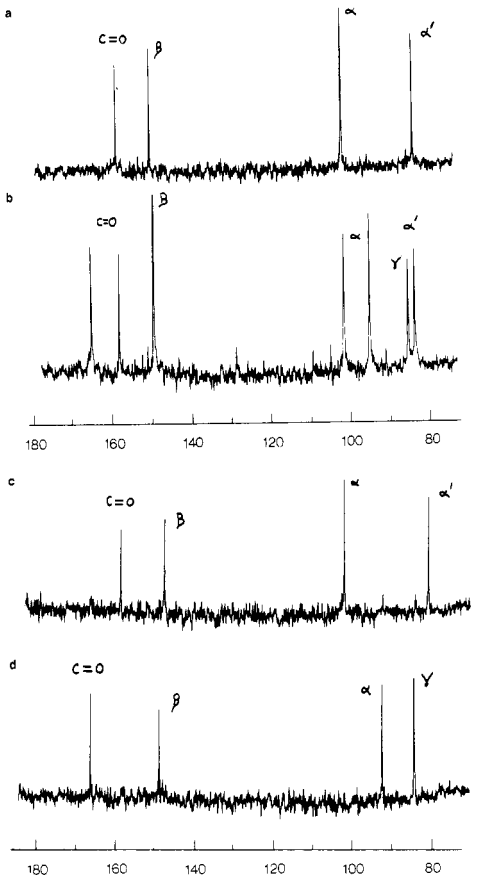


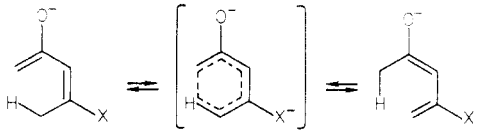
Figure 1. ^{13}C NMR spectra in the 80–180-ppm region for the kinetic and thermodynamic enolates of β-enamino ketones 11 and 12: (a) **11α′** formed in Et_2O at 0 time; (b) **11α′** and **11γ** formed from 11 and excess lithium bis(trimethylsilyl)amide in Et_2O at 60 h; (c) **12α′** formed from 12 and excess lithium diisopropylamide in THF at 0 time; (d) **12γ** formed from 12 and excess lithium diisopropylamide in THF at 12 h.

(11) Proton sources might be generated by side reactions involved in decay of the initially formed anion even when an excess of base is used.
(12) Denniston, A.; Anderson, N. 2nd Chemical Congress of North America, San Francisco, 1980; American Chemical Society: Washington DC, 1980; Abstract ORGN 33.

spectra of the enolate anions possess four downfield resonances, two for quaternary carbons between 145 and 170 ppm and two tertiary carbons between 75 and 106 ppm. The kinetic α'-enolates of 3-(dimethylamino)cyclohex-2-en-1-one (**11**) and its *N*-cyclohexyl analogue **12**, for example, display singlets at 160 ppm and doublets at 83 ppm, attributable to the carbonyl and α'-carbons. These chemical shifts compare favorably to those observed for the carbonyl carbon (159 ppm) and α-carbon (89.6 ppm) of the cyclohexanone enolate.[14] The greater shielding of the α'-carbon in the enaminone kinetic enolates is most probably due to the presence of the enamine moiety linearly conjugated with this center. A comparison of the ^{13}C spectra of the kinetic enolates of the enamino ketones **11** and **12** to those of the parent systems reveals that the α-carbons are more greatly deshielded by 4–7 ppm while the β-carbons are shielded by 13–16 ppm. This difference is consistent with thoughts about shifting of electron density toward the β-amino group upon α'-anion formation. Finally, in going from the kinetic to the thermodynamic enolates, the carbonyl carbons experience increased deshielding corresponding to an ~7-ppm downfield shift, and the α-carbons are shielded by 5–12 ppm. These changes, particularly the increased shielding at the α-carbon, reflect the greater degree of electron delocalization in the extended γ-enolate anions.

Several important conclusions can be drawn from the ^{13}C NMR studies summarized above. The α'-enolate anions of the six-membered-ring cyclic enol ether **9** can be efficiently generated by use of conditions for kinetic deprotonation with excess lithium diisopropylamide. This anion is stable at room temperature in THF for periods of hours. Furthermore, all attempts to bring about equilibration to form the γ-enolate met with failure. Although perplexing, this observation is fully consistent with results presented by Bryson[10b] which show that attempts to generate the γ-anion of **9** with potassium hydride under equilibrating conditions are not successful; methylation under these conditions produces only trace quantities of polyalkylated products of perhaps circuitous origin.

The acyclic enol ether **8** displays totally opposite behavior. In this case, it is impossible to prepare the α'-enolate not contaminated with the thermodynamically more stable γ-enolate. Moreover, equilibration of the anions of **8** gives the γ-anion in high yield and with a rapid rate even at −78 °C in the presence of excess lithium diisopropylamide. Similar results were found with the analogous cyclic β-enamino ketone **10**. In contrast to the cyclic systems, the acyclic kinetic anions appear particularly sensitive to equilibration induced by proton transfer from donors which must be present in exceedingly low concentrations under these conditions. Alternatively, equilibration in the acyclic systems could occur via an intra- rather than an intermolecular pathway (eq 1). The



(1)

transition states (e.g., **13**) for these 1,5 hydrogen shifts appear to be strain free and to correspond to orbital arrays[15] which are aromatic in the ground state since they are homoconjugate with phenolate anions.[16] The conformational flexibility required to permit simultaneous bond rupture and formation might not be present in the cyclic enones, thereby preventing their equilibration by this route. Alternatively, the γ- and α-enolates in the acyclic systems might be both kinetic anions formed in competitive deprotonation processes, as suggested by a thoughtful referee.

Table II. Benzylation of the β-Ethoxy and β-Dialkylamino Enones under Kinetic and Thermodynamic Anion-Forming Conditions

starting enone	conditions (base)[a]	total product yield,[b] %	products (yield, %)[b]
8	kinetic (LDA)	67	**21** (3), **22** (17), **23** (19), **24** (28)
8	thermodynamic (LDA)	45	**21** (3), **22** (18), **23** (24)
9	kinetic (LDA)	100	**14**
10	kinetic (LDA)	39	**25** (29), **26** (10)
10	thermodynamic (LDA)	23	**25**
11	kinetic (LDA)	76	**15**
11	kinetic (LDA)	70	**16**
11	thermodynamic (LHDSA)	21	**18**
11	thermodynamic (LDA)	73	**19**
12	kinetic (LDA)	78	**17**
12	thermodynamic (LHDSA)	80	**20**

[a] Bases used are lithium diisopropylamide (LDA) and lithium bis(trimethylsilyl)amide (LHDSA) under conditions described in the Experimental Section. [b] Yields are for isolated, purified materials.

Studies of anion generation regioselectivity with the cyclic β-enamino ketones **11** and **12** have been given greater emphasis because of our synthetic plans. The spectroscopic results demonstrate clearly that the direction of anion formation in these cases can be controlled by choice of base and solvent as well as by the ratio of base to enaminone employed. The α'-anions are produced by deprotonation with either lithium diisopropylamide or lithium bis(trimethylsilyl)amide. Equilibration occurs rapidly to form the lower energy γ-enolate when proton sources such as the neutral ketone or conjugate acid of the weaker silicon base are present even at low temperature when THF is solvent. In contrast, the α'-anions only slowly convert to the γ-anions in diethyl ether, independent of the base used. This effect might be due to the greater degree of solvation of the lithium cation in THF than in ether.[17b] Importantly, if the degree of association between the metal cation and anion controls the proton-transfer rate, the lifetimes of the kinetic enolates and thus the rates of equilibration should be subject to fine control by choice of the countercation and solvent.[17]

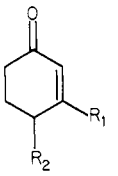
Alkylation Studies. With the results of the spectroscopic studies as background, our efforts then turned to investigations of the regiochemistry of alkylation of β-alkoxy and β-dialkylamino α,β-unsaturated ketones. As

(13) Laterbur, P. C. *Tetrahedron Lett.* **1961**, 274–279. Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954–4962.
(14) House, H. O.; Prabhu, A. U.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209–1214.
(15) (a) Another observation of difficulty in generating γ-enolates from cyclic β-diketone anol ethers even with the equilibrating silicon base is found in the work of de Groot.[15b] (b) de Groot, A.; Jansen, B. J. M. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 81–84.
(16) (a) Zimmerman, H. E. "Pericyclic Reactions"; Marchand, A. P., Lehr, R. E., Eds., Academic Press: New York, 1977, pp 53–106. (b) Staley, S. W. *Ibid.* **1977**, pp 199–260.
(17) (a) The literature contains information on solvent[17b] and metal cation[17c] effects on the ratio of solvent-separated to contact ion pairs in metal enolates. (b) Chan, L. L.; Smid, J. *J. Am. Chem. Soc.* **1968**, *90*, 4654–4661. (c) DePalma, V. M.; Arnett, E. M. *Ibid.* **1978**, *100*, 3514–3525.

expected, the results of these studies show that conditions employed for regioselective enolate anion generation can be incorporated into selective procedures for alkylation of these substituted enones. For example, benzylation and methylation at the α′-positions of the cyclic enol ether **9** and enamino ketones **11** and **12** can be accomplished in high yields to produce the substitution products **14–17** (eq 2) through use of excess lithium diisopropylamide for anion

9, R_1 = OEt
11, R_1 = $N(CH_3)_2$
12, R_1 = $N(CH_3)C_6H_{11}$

14, R_1 = OEt; R_2 = $PhCH_2$
15, R_1 = $N(CH_3)_2$; R_2 = $PhCH_2$
16, R_1 = $N(CH_3)_2$; R_2 = CH_3
17, R_1 = $N(CH_3)C_6H_{11}$; R_2 = CH_3



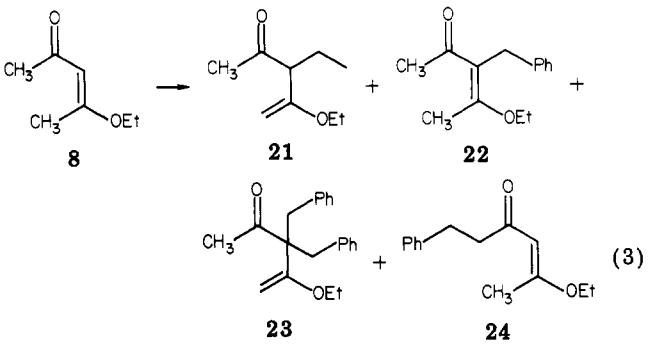
(2)

18, R_1 = $N(CH_3)_2$; R_2 = $PhCH_2$
19, R_1 = $N(CH_3)_2$; R_2 = CH_3
20, R_1 = $N(CH_3)C_6H_{11}$; R_2 = CH_3

generation in tetrahydrofuran at −78 °C, followed by quenching with either benzyl bromide or methyl iodide (Table II). Structural assignments in these cases were based upon characteristic spectroscopic properties, in particular the ^{13}C NMR data. For example, single methine resonances are observed in the carbon spectra of the benzylated enol ether **14** (47 ppm) and enamino ketone **15** (46 ppm), shifted 10 ppm downfield compared to the resonances of the α′-carbons in the starting enones. Also, the chemical shifts of the γ-carbons for the benzylated products are identical with those of the starting enones.

As expected, attempts to prepare the γ-benzylated cyclic enol ether by using thermodynamic anion-forming conditions were unsuccessful. Large quantities of polymeric materials formed when excess enol ether **9** was added to a tetrahydrofuran solution of lithium diisopropylamide. Thus, biomolecular addition processes apparently occur more efficiently than proton transfer in this system. In contrast, γ-alkylations of the cyclic enamino ketones **11** and **12** via corresponding thermodynamic anions are more successful. For example, the γ-benzyl enaminone **18** is produced in a 21% yield (Table II) by treatment of a tetrahydrofuran solution of lithium diisopropylamide and 2 molar equiv of **11**, equilibrated for 18 h at 25 °C. The low efficiency of this reaction is in part due to the need to use large excesses of the starting enone and forcing conditions to ensure complete conversion of the initially formed α′-anion to the γ-enolate. In accord with expectations based upon the ^{13}C NMR results and earlier studies,[10d] use of the weaker base, lithium bis(trimethylsilyl)amide allows anion interconversion to occur rapidly at low temperature and in the abence of excess ketone. Accordingly, treatment of **11** or **12** with 1.1 equiv of this base in tetrahydrofuran for 30 min at −78 °C followed by quenching with methyl iodide leads to production of the γ-methyl derivatives **19** and **20** exclusively in respective yields of 73% and 80%.

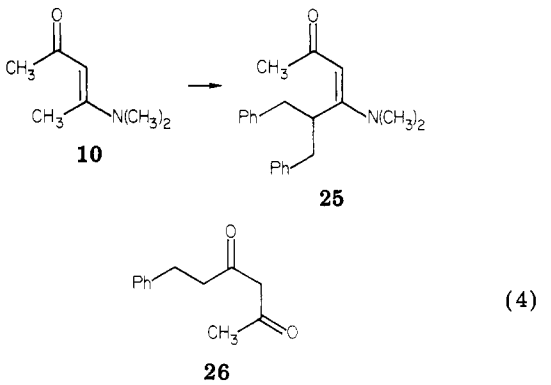
Alkylation reactions of the acyclic enol ether **8** and enamino ketone **10** under either kinetic or thermodynamic anion formation control result in generation of a wide spectrum of products. Benzylation of the anion of the ethoxyenone **8** formed under thermodynamic conditions (LDA) gives a mixture of three ketones resulting from α-monobenzylation (**21** and **22**) and α,α-dibenzylation (**23**; eq 3) in 47% overall yield (75% based upon recovered



8 **21** **22** **23** **24**

(3)

starting material). When this reaction is conducted under conditions which encourage kinetic anion formation, the same α-alkylation products **21–23** are produced along with the α′-benzylated ketone **24**. These observations are consistent with the ^{13}C NMR results which had demonstrated the difficulty in obtaining pure the α′-anion from **8**. This same phenomenon of rapid equilibration impedes benzylation at the α′-position of the acyclic enamino ketone **10**. Under conditions of both thermodynamic and kinetic control, benzylation of the acyclic enamino ketone **10** produces the γ,γ-dibenzyl enone **25** (eq 4). The only



10 **25** **26**

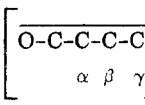
(4)

difference between these reactions is that the product mixture, generated under kinetic enolate anion forming conditions, contains small quantities (10%) of the 6-phenylhexanedione **26**. This material would be produced by hydrolysis of either α′- or γ-benzylated enamino ketone presumably during workup of the crude reaction mixture.

One interesting feature of the alkylation described above and those investigated earlier by Bryson[9b,10b] and Reusch[10c] concerns the regiochemical control exerted by the β substituent. It is well-known[5b] that the thermodynamically more stable γ-enolates of simple α,β-unsaturated ketones undergo reactions with electrophiles at the α-position. The β-alkoxy γ-anions behave similarly as exemplified by benzylation of **8** which leads to α-mono- and α,α-disubstitution products **21–23**.[18] The γ-enolates of β-dialkylamino enones, on the otherhand, add electrophiles at the γ-carbon exclusively. Simple Hückel MO analysis of the γ-anion system yields qualitative information about potential sources for this control. As the data in Table III indicate, both the γ- to α-carbon electron density and the frontier molecular orbital coefficient ratios increase when the β substituent is changed from ethoxy to dimethyl-

(18) γ′-Alkylation products have been observed from thermodynamic enolates of cyclopentane-1,3-dione enol ethers when the α-carbon is alkyl substituted.[10d]

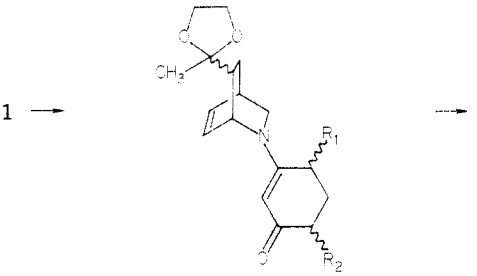
Table III. Data from Hückel MO Calculations for the β-Substituted γ-Enolate Anions



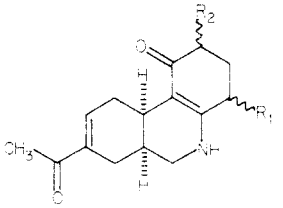
β substituent		electron density	frontier MO coeff
$N(CH_3)_2$	γ	1.30	0.11
	α	1.24	0.51
OEt	γ	1.28	0.08
	α	1.24	0.52

amino. Importantly, both of these factors could play a role in determining the site of alkylation in these multidentate anions.[19] It should be emphasized, however, that the HMO level calculations should only be qualitatively interpreted due to the assumptions made in the derivation of the method. In any event, the trends predicted by using this method appear to be in the correct direction.

Application to the Synthesis of Substituted Hydrophenanthridines. As discussed at the beginning, one of the purposes of the current investigation is to develop general methods for construction of the tetracyclic framework found in members of the lycorine alkaloid family. One approach to this goal involves introduction of a two-carbon or equivalent fragment at the γ-enamino ketone position of the appropriately functionalized isoquinuclidine 1 followed by rearrangement and eventual pyrrolidine D-ring formation. In order to test the application of the methodology developed above to the initial steps of routes based upon this design, we investigated regioselective alkylations of the isoquinuclidine 1. Quenching of the anion of 1, generated under equilibrating conditions (lithium diisopropylamide and excess 1 in THF), with allyl bromide led to formation of a mixture of four diastereomeric C-allylated products in a 58% yield. Assignment of the γ-allyl structures **27** (eq 5) to these



27, $R_1 = CH_2CH{=}CH_2$; $R_2 = H$
28, $R_1 = H$; $R_2 = CH_2CH{=}CH_2$

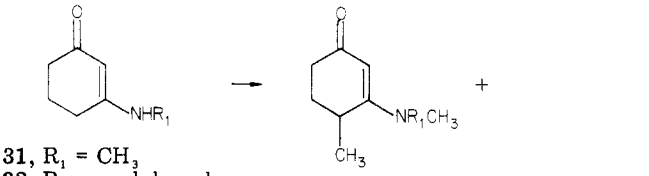


(5)

29, $R_1 = CH_2CH{=}CH_2$; $R_2 = H$
30, $R_1 = H$; $R_2 = CH_2CH{=}CH_2$

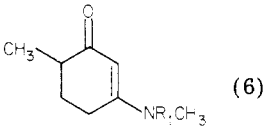
materials was made on the basis of ^{13}C NMR spectroscopic data and comparisons to those obtained for enamino ketones. The mixture of stereoisomeric products is expected since the starting isoquinuclidene 1 is a C-7 epimeric mixture, and approach of allyl bromide to the diastereotopic faces at the γ-carbon of the thermodynamic enolate is expected to be energetically similar. Allylation of the kinetic enolate anion of 1 produces the α′-allyl enamino ketone **28** (62%), thus emphasizing the ease with which alkylation selectivity can be controlled in these systems. As a further demonstration of the utility of this methodology, both the γ- and α′-allylisoquinuclidenes were rearranged to the corresponding hydrophenanthridines **29** and **30** under typical[2] acid-catalyzed amino-Claisen rearrangement conditions (*p*-TSOH, H_2O–C_6H_6, reflux) in respective yields of 40% and 50%. Thus, it appears that this approach would be suitable for synthesis of the tetracyclic framework of the lycorine alkaloids since C–N bond formation should be possible after appropriate cleavage of the allyl moiety of **29** or through alternate γ-alkylation–rearrangement sequences.[21]

β-Monoalkylamino Enone Dianion Production and Alkylation. Alternate approaches to construction of the tetracyclic skeleton of the lycorine alkaloids employ dialkylation or alkylation–acylation processes through dianions arising by deprotonation of appropriately functionalized tricyclic NH enamino ketones such as **5** (vide supra, Scheme I). Importantly, for this method to be useful, the regiochemistry for dianion generation must be subject to experimental control. Also, reaction at both carbon and nitrogen of these dianions would have to occur with equal efficiency and, preferrably, at predictably different rates so that addition of unsymmetric dielectrophiles can be regulated. Since the literature contains little information useful in evaluating these features, we initiated studies in this area. We have examined methods for generation and alkylation of dianions prepared from the simple monocyclic β-enaminones **31** and **32**, and the tricyclic analog **5** by deprotonation with bases including *n*-butyllithium, lithium diisopropylamide, and lithium bis(trimethylsilyl)amide (see eq 6).



31, $R_1 = CH_3$
32, R_1 = cyclohexyl

19, $R_1 = CH_3$
20, R_1 = cyclohexyl



(6)

16, $R_1 = CH_3$
17, R_1 = cyclohexyl

Treatment of the enaminones **31** and **32** with *n*-butyllithium (THF, 0 °C, 1 h) leads to nonselective dianion formation as judged by inspection of the product mixture following quenching with methyl iodide. By this method, both the *N*,γ- and *N*,α′-dimethyl products, synthesized

(19) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976.
(20) (a) Simple HMO calculations have been used to rationalize the α-alkylation selectivity observed for γ anions of nonheteroatom substituted enones.[20b] (b) Rogers, N. A. J.; Sattar, A. *Tetrahedron Lett.* **1965**, 1471–1475.
(21) The details of our synthetic approaches to the lycorine alkaloids based upon this methodology will be reported in the near future.
(22) (a) Ganem[22b] has generated and formylated and *N*,α′-dianion from a phenylamino enone system by using 2 equiv of butyllithium. His system was lacking a β-alkyl substituent and was thus incapable of *N*,γ-dianion production. (b) Ganem, B. *J. Am. Chem. Soc.* **1976**, *98*, 224–226.
(23) Pfeffer, P.; Silbert, L.; Chirinko, J. *J. Org. Chem.* **1972**, *37*, 451–458.

Table IV. Methylation of Dianions Generated from β-Enaminones 31 and 32 by use of Lithium Diisopropyl- and Bis(trimethylsilyl)amide Bases

β-enaminone	amide base	molar ratio of base/enone	temp, °C	time, h	products (ratio)	total yield, %
31	$LiN(SiMe_3)_2$	2.2	0	1	19, 11 (1:7)[a]	
31	$LiN(SiMe_3)_2$	3.7	0	15	19, 11 (1:6.5)[b]	75
32	$LiN(SiMe_3)_2$	2.2	0	2	20, 12 (1:2)[c,d]	96
32	$LiN(SiMe_3)_2$	2.5	0	15	20, 12 (1:2.5)[d]	61
32	$LiN(SiMe_3)_2$	3.8	0	2	20, 12 (1:1.7)[d]	
31	LDA	2.2	−78	1	16, 11 (1:2)[a]	
31	LDA	2.2	0	1	16, 11 (1:1)[a,b]	83
31	LDA	2.2[e]	0	1	16, 11 (1:1)[a]	
31	LDA	2.5[f]	0	1	16, 11 (9:1)[b]	45
31	LDA	3.3	0	2	16, 11 (6:1)[b]	85
32	LDA	2.2	0	0.5	17, 12 (6:1)[b]	
32	LDA	2.8	−25	6	17, 12 (10:1)[b]	69

[a] Product ratio based upon HPLC analysis. [b] Product ratio based upon isolated yields. [c] A trace quantity (ca. 4%) of the kinetic dianion methylation product was detected. [d] Product ratio based upon ^1H NMR analysis. [e] 2.2 equiv of TMEDA was present in the reaction mixture. [f] 2.2 equiv of HMPA was present in the reaction mixture.

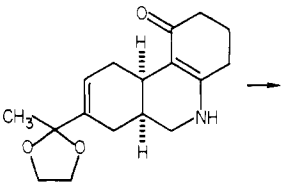
earlier in this study, were produced from 31 in respective isolated yields of 41% and 25%. The product ratio is invariant with the time used for dianion formation, thus indicating perhaps that the lack of selectivity in anion formation is due to nonselective deprotonation rather than rapid equilibration of an initially produced kinetic dianion to a more stable regioisomer. Reactions of the 3-(alkylamino)cyclohexenones with lithium diisopropylamide are discriminant, generating the N,α'-dianion as a result of kinetic deprotonation. However, alkylations employing this base do not give complete conversion to dialkylated products. Accordingly, treatment of anions formed from 31 and 32 under these conditions with methyl iodide yields products of mono-N-methylation (11 and 12) and N,α'-dimethylation (16 and 17) in ratios which vary with the amount of amide base present in excess (see Table IV).

The factors controlling the extent of methylation are uncertain. Both the alkylation and attempted ^{13}C NMR experiments indicate that the dimetalated enamino ketones have low solubilities in tetrahydrofuran and that the resulting mixtures are colloidal in nature. It is known that organolithiums associate to form high molecular weight aggregates and that the degree of aggregation is altered by interactions with polar solvents. This type of behavior could explain in part the observations made. Thus, although formation of monomethyl products might be due to incomplete deprotonation, it also could be the result of aggregation effects which sterically prevent C-alkylation. It seemed that the increased amounts of dimethylation seen when large excesses of lithium diisopropylamide are employed could be rationalized on the basis of either feature. Also, we hypothesized that enhanced deprotonation[12] and decreased aggregation would occur if strongly coordinating substances such as hexamethylphosphoramide or tetramethylethylene diiamine were included in reaction mixtures used for dianion formation. However, no significant effects of these substances on the yields of dimethyl products were noted.

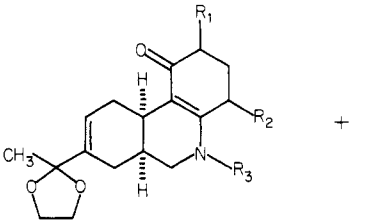
It is important to note that formation of the N,α'-dimethylated products almost certainly occurs by dialkylation of regioselectively generated dianions rather than through sequential N-monoanion alkylation, followed by deprotonation and C-methylation. The times employed for quenching by methyl iodide (as short as minutes) in these cases are too short to allow for further deprotonation. Also, as will be shown below, dimethylations when the silicon base is employed give N,γ-dialkyl products which would not be expected since kinetic deprotonation from the α'-position of the N-methyl products should be followed by rapid alkylation in preference to equilibration.

Methylations of the enamino ketones 31 and 32 conducted by using lithium bis(trimethylsilyl)amide as the base for dianion generation yield both N-methyl (11 and 12) and N,γ-dimethyl (19 and 20) products. The experimental parameters varied in attempting to enhance dimethylation are summarized in Table IV. Even when large excesses of the silicon base are employed, ratios of di- to monomethylated enaminones approach only 1:1.7. The low solubility of the dianions and basicity of this amide base,[12] may here again contribute to inefficient dialkylation. Despite this problem, the results from studies with the monocyclic systems suggest that the regioselectivity of dianion formation can be controlled by choice of base in the same way as was possible for monoanion generation from β-dialkylamino enones.

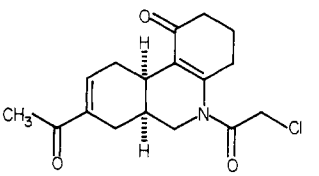
We also tested the synthetic applicability of this method with the tricyclic enamino ketone 5. Alkylation of the thermodynamic N,γ-dianion of 5, produced with a large excess of lithium bis(trimethylsilyl)amide, by excess methyl iodide provides the 4,5-dimethyldecahydrophenanthridine 33 as a mixture of C-4 epimers in a 73% yield (eq 7).



5



33, R_1 = H; R_2 = R_3 = CH_3
34, R_1 = R_3 = CH_3; R_2 = H
35, R_1 = R_2 = H; R_3 = CH_3
36, R_1 = R_2 = H; R_3 = CH_2CO_2Et



(7)

37

Table V. Methylation of Dianions Generated from the Tricyclic β-Enaminone 5 by use of the Lithium Diisopropyl- and Bis(trimethylsilyl)amide Bases

lithium amide base	molar ratio of base/enone	temp, °C	time, h	products (ratio)	total yield, %
$LiN(SiMe_3)_2$	2.1	0	1	**33, 35** (0:1)	
$LiN(SiMe_3)_2$	3.0[a]	0	1	**33, 35** (0:1)	90
$LiN(SiMe_3)_2$	2.1[b]	0	3	**33, 35** (0:1)	
$LiN(SiMe_3)_2$	2.1[c]	0	3	**33, 35** (0:1)	
$LiN(SiMe_3)_2$	4.5	0	13	**33, 35** (1:0)	73
$LiN(SiMe_3)_2$	4.5	0	3.5	**33, 35** (1:0)	
LDA	2.5	0	1	**34, 35** (1:4)	
LDA	2.5	−25	6	**34, 35** (0:1)	65
LDA	4.5	0	2	**34, 35** (1:0)	54

[a] 3 equiv of HMPA was present. [b] 2.1 equiv of TMEDA was present. [c] HMPA was used as solvent.

Alternatively, a large excess of lithium diisopropylamide can be used to form the kinetic dianion which serves as a precursor of the epimeric 2,5-dimethylphenanthridines **34**. Other similarities exist between the mono- and tricyclic systems. Mixtures of the enaminone **5** and amide bases (2–3 equiv) in tetrahydrofuran are heterogeneous and yield the mono-*N*-methyl product **35** exclusively when treated with methyliodide (Table V). Coordinating substances such as hexamethylphosphoramide or tetramethylethylene diamine affect solubilization of the anions but do not have an effect on the extent of alkylation. When large excesses of the amide bases are employed, the reaction mixtures are homogeneous, indicating that either deprotonation is more efficient, producing more soluble dianions, or aggregation is altered. Independent of the nature of the effect, dimethylations of the enamino ketone **5** can be accomplished in a regioselective fashion in reasonably high yields. However, all other attempts to use this methodology for construction of the tetracyclic skeleton of the lycorine alkaloids thus far have been unsuccessful. For example, treatment of the *N*,γ-dianion of **5**, generated by using a large excess of the silicon base, with ethyl bromoacetate, leads to exclusive production of the *N*-alkylated product **36**. This same ester derivative can be conveniently prepared by use of lithium diisopropylamide as the base. Likewise, reaction of the *N*,γ-dianion of **5** with chloroacetyl chloride gives only the *N*-chloroacetyl derivative **37**, arising via N-acylation followed by hydrolysis of the ketal function upon workup. Thus, it appears that other factors might be important in controlling alkylation reactions in this dianion system.

Experimental Section

General Methods. ^1H NMR spectra were taken with Varian T-60, HA-100, and XL-100 spectrometers with tetramethylsilane as an internal standard. Mass spectra were taken by using Du Pont CEC21-1108 high-resolution and 492 low-resolution mass spectrometers. Infrared spectra were recorded on Perkin-Elmer 237B and 298 and Beckman IR 8 spectrophotometers. ^{13}C NMR spectra were obtained by using JEOL PS-100 or Varian XL-100 spectrometers. UV spectra were recorded on a GCA-McPherson EU-700 spectrometer. Melting points were obtained by using a Griffin Mel-Temp 110-V capillary melting point apparatus and are reported uncorrected. Microanalyses were performed by either Galbraith Laboratories, Inc., or by Professor Kasler at the University of Maryland. Preparative TLC chromatographic work was done with either Baker silica gel 7 GF or Baker aluminum oxide 9 F. Column chromatography employed Grace silica gel (Davison grade 923), MCB Type F-2 Q activated alumina, or Merck 230–400-mesh silica gel (for flash chromatography). Molecular distillations were done with a Kugelrohr apparatus. Solvents were redistilled prior to use. Tetrahydrofuran and benzene were distilled from sodium, and diisopropylamine, hexamethylsilazane, hexamethylphosphoric triamide, and tetramethylethylenediamine were distilled from calcium hydride. Drying of the organic layers during the workup of reaction mixtures was accomplished by washing with saturated sodium chloride followed by stirring over anhydrous sodium sulfate. All reactions were conducted under either argon or nitrogen atmospheres.

Carbon-13 Measurements. All carbon-13 anion spectra were obtained with a JEOL PFT-100/Nicolet 1080 Fourier transform spectrometer. An internal capillary containing a deuterium signal was used for locking purposes. All chemical shifts are referenced to tetramethylsilane. For the enolate ions dissolved in THF, about 1000 average transients were required to obtain satisfactory signal to noise ratios. The enolate ions were somewhat less soluble in diethyl ether, and these spectra required accumulation of about 5000 average transients.

Sample Preparation for Carbon-13 Measurements. Tetrahydrofuran solutions of (trimethylsilyl)methyllithium[24] were prepared in the following manner. A suspension of a THF-washed lithium dispersion (2 g, 0.29 mol) and (trimethylsilyl)methyl]-mercury[25] (2.11 g, 11 mmol) in THF in a septum-capped centrifuge tube was agitated for 3 h at 0 °C. The molarity of the lithium reagent in the supernatant liquid was normally ca. 1.5 M. The quantity of this material in solution was determined during measurements by spectroscopic methods. ^{13}C NMR resonances for this anion in THF are 5.7 (q, CH_3) and −7.17 ppm (t, CH_2).

Lithium diisopropylamide was prepared in THF by the reaction of diisopropylamine with (trimethylsilyl)methyllithium or in diethyl ether by the reaction of diisopropylamine with methyllithium. Lithium bis(trimethylsilyl)amide was prepared by the reaction of bis(trimethylsilyl)amine with methyllithium. The kinetic enolate ions were prepared by additions of solutions of the enamino ketones to slight excesses of lithium diisopropylamide in argon-flushed, septum-capped, carbon-13 NMR tubes at 0 °C. The thermodynamic ions in THF were prepared by the addition of lithium diisopropylamide to slight excesses of the ketones. Thermodynamic enolates in THF or diethyl ether were prepared by addition of lithium bis(trimethylsilyl)amide to solutions of the ketones at 0 °C. In all cases except those described below, spectra were recorded at 25 °C after varying time periods. In attempts to generate cleanly the kinetic enolate anions of 4-ethoxy- (**8**) and 4-(dimethylamino)pent-3-en-2-one (**10**), samples were prepared and spectra were recorded at −78 °C, large excesses of lithium diisopropylamide were used, and THF was employed as the solvent.

Benzylation of the Kinetic Anion of 3-Ethoxycyclohex-2-en-1-one (9). Preparation of 14. A solution of lithium diisopropylamide was prepared by the addition of 8.57 mmol of *n*-butyllithium to diisopropylamine (0.866 g, 8.57 mmol) in THF at −15 °C. After being stirred for 4 h, the mixture was cooled to −78 °C. A solution of 3-ethoxycyclohex-2-en-4-one (1.000 g, 7.14 mmol) in THF was added over a 1.5-h period. The resulting mixture was stirred for 45 min, quenched with 3.67 g (21.4 mmol) of benzyl bromide, and stirred for 12 h at 25 °C. The mixture was poured into ice–water and extracted with ether. The combined ethereal fractions were dried and concentrated in vacuo, giving 4.303 g of crude product which was subjected to molecular distillation (55 °C, 3 mm) to remove benzyl alcohol. The residue (2.007 g) was subjected to alumina TLC (50% $CHCl_3$–CCl_4). The band with R_f 0.7–0.9 was further purified by alumina TLC (CCl_4), giving 1.64 g (100%) of 3-ethoxy-6-benzylcyclohex-2-en-1-one (**14**): IR (film) 3031, 3006, 2975, 2940, 1660, 1610, 1200, 760 cm^{-1}; ^{13}C

(24) Connolly, J. W.; Urry, G. *Inorg. Chem.* **1963**, *2*, 645–646.
(25) Kumada, M.; Ishikawa, M. *J. Organomet. Chem.* **1966**, *6*, 451–455.

NMR ($CDCl_3$) 200.3 (s, CO), 177.0 (s, C-3), 140.1 (s, phenyl C-1), 129.1 (d, C_o), 128.3 (d, C_m), 126.0 (d, C_p), 102.2 (d, C-3), 64.2 (t, O–CH_2), 47.1 (d, C-6), 35.7 (t, Bz C), 28.2 (t, C-4), 25.6 (t, C-5), 14.1 ppm (q, CH_3); ^1H NMR (CCl_4) δ 1.30 (t, 3 H, J = 7 Hz, CH_3), 1.78–1.98 (m, 2 H, H-5), 2.21–2.55 (m, 4 H, H-4, Bz H), 3.27 (m, 1 H, H-6), 3.94 (q, 2 H, J = 7 Hz, O–CH_2), 5.22 (s, 1 H, H-2), 7.12 (s, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 230 (89, M^+), 181 (36), 139 (53), 112 (33), 91 (100), 84 (62); high-resolution mass spectrum, m/e 230.1299 ($C_{15}H_{18}O_2$ requires 230.1306).

Benzylation of the Thermodynamic Anion and Attempted Benzylations of the Kinetic Anion of 4-(Dimethylamino)-pent-3-en-2-one (10). Preparation of 25 and 26. Kinetic. A solution of the enaminone **10** (0.984 g, 7.75 mmol) in THF was added at −78 °C to a solution of lithium diisopropylamide (from 9.45 mmol of butyllithium and 9.45 mmol of diisopropylamine), and the resulting mixture was stirred for 45 min at −78 °C. The solution was quenched with 1.75 g (10.3 mmol) of benzyl bromide and stirred at room temperature overnight. The mixture was poured into ice–water and extracted with ether. The combined ethereal fractions were dried (Na_2SO_4) and concentrated in vacuo, giving 2.344 g of crude product which was subjected to alumina TLC (30% $CHCl_3$–70% CCl_4). The band with R_f 0.4–0.6 was shown to contain 0.702 g (29%) of **25**: IR (film) 3080, 3055, 2860, 1725, 1650, 1560 cm^{-1}; ^{13}C NMR ($CDCl_3$) 193.6 (s, CO), 164.9 (s, C-2), 141.6 (s, phenyl C-1), 128.5 (d, C_o), 128.4 (d, C_m), 126.0 (d, C_p), 94.6 (d, C-3), 39.6 (q, NCH_3), 34.4 (t, Bz C), 31.7 (d, C-1), 31.2 ppm (q, C-5); ^1H NMR (CCl_4) δ 1.98 (s, 3 H, CH_3), 2.56–3.24 (m, 5 H, Bz H, H-1), 2.85 (s, 6 H, $N(CH_3)_2$), 4.92 (s, H-3), 6.94–7.36 (m, 10 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 307 (<1, M^+), 217 (28), 202 (36), 190 (44), 112 (25), 105 (21), 91 (100); high-resolution mass spectrum on P − 90, m/e 217.1457 ($C_{14}H_{19}NO$ requires 217.1466).

Preparative GLC (10% OV-101 on a Varaport 30, 12 ft × $^1/_4$ in. column, 200 °C) of a crude reaction mixture obtained by using conditions identical with those described above led to the isolation of what appears to be the hydrolysis product of the monobenzylated kinetic anion, 6-phenylhexane-2,4-dione (**26**): 10% yield; ^1H NMR (CCl_4) δ 1.95 (s, 3 H, H-1), 2.3–3.1 (m, 5 H, H-1, H-2, OH), 5.3 (s, 1 H, H-4), 7.2 (s, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 190 (72, M^+), 105 (20), 104 (32), 91 (78), 85 (100); high-resolution mass spectrum, m/e 190.0998 ($C_{12}H_{14}O_2$ requires 190.0993).

Thermodynamic. A solution of lithium diisopropylamide (from 5.74 mmol of butyllithium and 5.74 mmol of diisopropylamine) and the enaminone **10** (1.00 g, 7.87 mmol) in THF was stirred at −15 °C for 4 h, cooled to −78 °C, and quenched with 1.75 g (10.2 mmol) of benzyl bromide. A workup and purification as described above for alkylation of the kinetic anion gave 0.557 g (23%) of **25**. The dione **26** was not detected in the product mixture by GLC analysis.

Benzylation of the Thermodynamic and Kinetic Anions of 4-Ethoxypent-3-en-2-one (8). Preparation of 21–24. Kinetic. A solution of lithium diisopropylamide (from 9.37 mmol of butyllithium and 9.37 mmol of diisopropylamine) and the enol ether **8** (1.000 g, 7.81 mmol) in THF was stirred at −78 °C for 45 min and quenched with 1.923 g (11.24 mmol) of benzyl bromide. After being stirred for 12 h at 25 °C, the reaction mixture was poured into ice–water and extracted with ether. The combined ethereal fractions were dried and concentrated in vacuo, giving 2.436 g of a crude mixture which was subjected to molecular distillation (30 °C, 0.05 mm) to remove benzyl alcohol and unreacted 4-ethoxypent-3-en-2-one. The remaining 1.380 g of material was subjected to silica gel TLC (25% $CHCl_3$–75% CCl_4). The band with R_f 0.2–0.4 was shown to contain 0.48 g (28%) 6-phenyl-2-ethoxyhex-2-en-4-one (**24**): IR (film) 3055, 3015, 1675, 1580, 1250, 815, 765 cm^{-1}; ^{13}C NMR ($CDCl_3$) 198.3 (s, CO), 172.2 (s, C-2), 141.6 (s, phenyl C-1), 128.4 (d, C_o and C_m), 125.9 (d, C_p), 99.2 (d, C-3), 63.7 (t, O–CH_2), 46.0 (t, C-5), 30.7 (t, C-6), 20.0 (q, C-1), 14.2 ppm (q, C-2′); ^1H NMR (CCl_4) δ 1.28 (t, 3 H, J = 3 Hz, H-2′), 2.23 (s, 3 H, H-1), 2.48–2.96 (m, 4 H, H-5, H-6), 3.72 (q, 2 H, J = 3 Hz, O–CH_2), 5.26 (s, 1 H, H-3), 7.12 (s, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 218 (53, M^+), 113 (93), 91 (38), 85 (100); high-resolution mass spectrum, m/e 218.1298 ($C_{14}H_{18}O_2$ requires 218.1306). Analysis of the crude reaction mixture by GLC (2% OV-101 on GHP Chromosorb, 5 ft × $^1/_8$ in. column) showed it to contain in addition to **24** the products of thermodynamic anion alkylation (see below), 3,3-dibenzyl-2-ethoxypent-1-en-4-one (**23**, 19%), 3-benzyl-2-ethoxypent-2-en-4-one (**22**, 17%), and 3-benzyl-2-ethoxypent-1-en-4-one (**21**, 30%).

Thermodynamic. A solution of lithium diisopropylamide (from 6.25 mmol of butyllithium and 6.25 mmol of diisopropylamine) and 4-ethoxypent-3-en-2-one (1.000 g, 7.81 mmol) in THF was stirred at 0 °C for 4 h, cooled to −78 °C, quenched with 1.389 g (8.13 mmol) of benzyl bromide, and stired for 12 h. The mixture was poured into water and ether extracted. The combined ethereal fractions were dried and concentrated in vacuo, giving 2.141 g of crude reaction mixture, which was subjected to molecular distillation (60 °C, 0.1 mm) to remove benzyl alcohol and unreacted starting material. The residue (0.714 g) was subjected to alumina TLC (50% $CHCl_3$–CCl_4). The band with R_f 0.4–0.6 was isolated and further purified by alumina TLC (CCl_4), giving 0.41 g (24%) of 3,3-dibenzyl-2-ethoxypent-1-en-4-one (**23**): IR (film) 3080, 3055, 2975, 1720, 1650, 1600, 820, 760 cm^{-1}; ^{13}C NMR ($CDCl_3$) 208.3 (s, CO), 162.7 (s, C-2), 137. (s, phenyl C-1), 130.3 (d, C_o), 127.9 (d, C_m), 126.4 (d, C_p), 84.2 (t, C-1), 62.8 (t, O–CH_2), 62.3 (s, C-3), 37.7 (t, Bz C), 26.6 (q, C-5), 14.2 ppm (q, C-2′); ^1H NMR (CCl_4) δ 1.12 (t, 3 H, J = 3 Hz, H-2′), 2.01 (s, 3 H, H-5), 2.95 (dd, 4 H, J = 2 Hz, 7 Hz, Bz H), 3.58 (q, 2 H, J = 3 Hz, 3 Hz, O–CH_2), 4.07 (s, 2 H, H-1), 6.90–7.30 (m, 10 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 308 (1, M^+), 217 (74), 91 (91); high-resolution mass spectrum, m/e 308.1761 ($C_{21}H_{24}O_2$ requires 308.1776).

The crude reaction mixture obtained from benzylation of the thermodynamic anion under conditions identical with those described above was subjected to preparative GLC (10% OV-101 on Varaport 30, 12 ft × $^1/_4$ in. column, 210 °C). Two products were isolated by using this method. 3-Benzyl-2-ethoxypent-1-en-4-one (**21**): 3% yield; IR (film) 3050, 2975, 2925, 1720, 1660, 1610, 770 cm^{-1}; ^{13}C NMR ($CDCl_3$) 206.4 (s, CO), 159.4 (s, C-2), 139.7 (s, phenyl C-1), 128.9 (d, C_o), 128.1 (d, C_m), 126.0 (d, C_p), 84.8 (t, C-1), 63.1 (t, O–CH_2), 61.0 (d, C-3), 34.4 (t, Bz C), 28.3 (q, C-5), 14.2 ppm (q, C-2′); ^1H NMR (CCl_4) δ 1.26 (t, 3 H, J = 3.5 Hz, H-2′), 2.02 (s, 3 H, H-5), 2.62–3.02 (m, 2 H, Bz H), 3.12 (q, 1 H, J = 9 Hz, H-3), 3.66 (q, 2 H, J = 3.5 Hz, O–CH_2), 3.84–3.96 (m, 2 H, H-1), 7.10 (s, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 218 (2 M^+), 175 (68), 131 (63), 91 (63); high-resolution mass spectrum, m/e 218.1296 ($C_{14}H_{18}O_2$ requires 218.1306). 3-Benzyl-2-ethoxypent-2-en-4-one (**22**): 18% yield; IR (film) 3040, 3015, 2965, 2920, 1710, 1600, 1580, 760 cm^{-1}; ^{13}C NMR ($CDCl_3$) 200.9 (s, CO), 164.6 (s, C-2), 141.1 (s, phenyl C-1), 128.2 (d, C_o), 127.9 (d, C_m), 125.6 (d, C_p), 117.9 (s, C-3), 62.9 (t, O–CH_2), 33.0 (q, C-5), 32.5 (t, Bz C), 15.6 (q, C-1), 15.2 ppm (q, C-2′); ^1H NMR (CCl_4) δ 1.17 (t, 3 H, J = 3.5 Hz, H-2′), 1.98 (s, 3 H, H-1), 2.31 (s, 3 H, H-5), 3.71 (s, 2 H, Bz H), 3.92 (q, 2 H, J = 7, 3.5 Hz, O–CH_2), 6.92–7.26 (m, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 218 (3, M^+), 190 (21), 91 (34), 85 (31); high-resolution mass spectrum, m/e 218.1313 ($C_{14}H_{18}O_2$ requires 218.1306).

3-(Methylamino)cyclohex-2-en-1-one (31). The procedure suggested by Greenhill[26] for preparation of β-enamino ketones was employed. Anhydrous methylamine was passed into a refluxing solution of 1,3-cyclcohexanedione (11.2 g, 10 mmol) in anhydrous benzene (50 mL) for 1 h. Water produced was removed continuously by using a Dean–Stark trap. The solution was cooled, and benzene was removed under reduced pressure. The high-viscosity brown oil which was obtained was washed with 100 mL of petroleum ether to give yellow powder. Sublimation (150 °C, 0.005 mm) gave 10.82 g (87%) of **31** as yellow crystals: mp 67–67.5 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.60 (m, 6 H), 2.70 (d, 3 H, J = 4.5 Hz), 5.00 (s, 1 H), 6.35 (br s, 1 H, $W_{1/2}$ = 18 Hz); ^{13}C NMR ($CDCl_3$) 21.818, 28.953, 29.132, 36.195, 94.890, 166.656, 182.873 ppm; IR ($CHCl_3$) 3450, 3300, 2950, 1600, 1520, 1250 cm^{-1}; mass spectrum, m/e 125 (M^+), 97, 82, 69, 54.

Anal. Calcd for $C_7H_{11}NO·0.2H_2O$: C, 65.29; H, 8.93; N, 10.88. Found: C, 65.68; H, 9.08; N, 11.14.

3-(Cyclohexylamino)cyclohex-2-en-1-one (32). A mixture of 1,3-cyclohexanedione (3.36 g, 30 mmol) and cyclohexylamine

(26) Greenhill, J. V. *J. Chem. Soc. C* **1971**, 2699–2703.

(3.78 mL, 33 mmol) in 100 mL of anhydrous benzene was heated to reflux with the use of a Dean–Stark trap for 8 h under N_2. The residue obtained by concentration of the reaction mixture in vacuo was washed with 20 mL of saturated sodium bicarbonate and extracted with 50 mL of methylene chloride. The organic layer was dried and concentrated in vacuo, giving 5.80 g of yellow solid. Recrystallization from ethyl acetate gave 5.02 g (85%) of **32** as yellow needles: mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 1.0–2.05 (m, 12 H), 2.3 (m, 4 H), 3.2 (br s, 1 H, $W_{1/2}$ = 32 Hz), 5.08 (s, 1 H), 5.6 (br s, 1 H, $W_{1/2}$ = 20 Hz); ^{13}C NMR ($CDCl_3$) 22.077, 24.871, 25.519, 29.649, 32.258, 36.478, 51.524, 95.817, 164.061, 183.457 ppm; IR ($CHCl_3$) 3400, 2920, 1570, 1500 cm^{-1}; mass spectrum, m/e 193 (M^+), 165, 150, 136, 110.

Anal. Calcd for $C_{12}H_{19}NO$: C, 67.85; H, 9.01; N, 6.59. Found: C, 67.61; H, 9.09; N, 6.58.

3-(Dimethylamino)cyclohex-2-en-1-one (11). The procedure of Greenhill[26] was followed. Dimethylamine (5 mL) was added to a refluxing solution of 1,3-cyclohexanedione (5.6 g, 5 mmol) in dry benzene (30 mL) with the use of a Dean–Stark trap of 8 h under N_2. Concentration of the reaction mixture in vacuo gave a viscous brown oil which was distilled (143 °C, 0.5 mm) to afford 5.832 g (93%) of **11** as yellow low-melting crystals: ^{1}H NMR ($CDCl_3$) δ 2.0 (m, 2 H, J = 6 Hz), 2.25 (m, 2 H, J = 6 Hz), 2.47 (t, 2 H, J = 6 Hz), 3.0 (s, 6 H), 5.14 (s, 1 H); ^{13}C NMR ($CDCl_3$) 22.040, 26.802, 35.437, 39.566, 98.183, 165.546, 184.186 ppm; IR ($CHCl_3$) 2940, 1600, 1550, 1410, 1260, 1150 cm^{-1}; mass spectrum, m/e 139 (M^+), 111, 96, 68; high-resolution mass spectrum, m/e 139.0994 ($C_8H_{13}NO$ requires 139.0997).

3-(Methylcyclohexylamino)cyclohex-2-en-1-one (12). A solution of 3-(cyclohexylamino)cyclohex-2-en-1-one (0.68 g, 3.55 mmol) in 30 mL of THF was treated with 2.6 mL (3.9 mmol) of 1.5 M n-butyllithium in hexane at −78 °C under N_2. After the mixture was stirred at −78 °C for 1 h, methyl iodide (1 mL) was added, and the mixture was stirred at −78 °C for 30 min and at room temperature for 30 min. The mixture was poured into water and extracted with methylene chloride. The organic extracts were dried and concentrated in vacuo, giving a crude material which was purified by silica gel flash column chromatography with 3% methanol in methylene chloride. This gave 0.71 g (97%) of pure enamino ketone **12** as a yellow solid: mp 78–81 °C; ^{1}H NMR ($CDCl_3$) δ 1.0–2.1 (m, 12 H), 2.1–2.5 (m, 4 H), 2.7 (s, 3 H), 3.5 (br s, 1 H, $W_{1/2}$ = 22 Hz), 5.13 (s, 1 H); ^{13}C NMR ($CDCl_3$) 22.3, 25.3, 25.6, 27.0, 30.3, 31.2, 35.5, 57.4, 98.4, 164.9, 196.4 ppm; IR ($CHCl_3$) 2940, 1600, 1545 cm^{-1}; mass spectrum, m/e 207 (M^+), 125, 97, 82; high-resolution mass spectrum, m/e 207.1629 ($C_{13}H_{21}NO$ requires 207.1623).

Benzylation of the Kinetic Anino of 3-(Dimethylamino)cyclohex-2-en-1-one (11). Preparation of 15. A solution of lithium diisopropylamide (from 8.63 mmol of butyllithium and 8.63 mmol of diisopropylamine) and 1.00 g (7.19 mmol) of **11** in THF was stirred at −78 °C for 45 min, quenched with 1.60 g (9.35 mmol) of benzyl bromide and stirred at room temperature for 12 h. The mixture was poured into ice–water and extracted with ether. The combined ethereal extracts were dried and concentrated in vacuo, giving 1.93 g of the crude product which was subjected to alumina TLC (50% $CHCl_3$–CCl_4). The band with R_f 0.1–0.6 contained 1.24 g (76%) 3-(dimethylamino)-6-benzylcyclohex-2-en-1-one (**15**): IR (film) 3050, 3015, 1630, 1600, 1580, 1560, 1230, 760 cm^{-1}; ^{13}C NMR ($CDCl_3$) 197.3 (s, CO), 164.9 (s, C-3), 140.8 (s, phenyl C-1), 129.2 (d, C_o), 128.3 (d, C_m), 125.8 (d, C_p), 98.2 (d, C-2), 45.6 (d, C-6), 39.5 (q, $N(CH_3)_2$), 36.1 (t, Bz C), 26.0 (t, C-4), 25.8 ppm (t, C-5); ^{1}H NMR (CCl_4) δ 1.40–1.90 (m, 2 H, H-5), 2.14–2.54 (m, 4 H, H-4, Bz H), 2.87 (s, 6 H, $N(CH_3)_2$), 3.25 (d, 1 H, H-6, J = 13, 3 Hz), 4.94 (s, 1 H, H-2), 7.12 (s, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intenstiy) 229 (7, M^+) 58 (24), 43 (100); high-resolution mass spectrum, m/e 229.1455 ($C_{15}H_{19}NO$ requires 229.1466).

Methylation of the Kinetic Anion of 3-(Dimethylamino)cyclohex-2-en-1-one (11). Preparation of 16. A solution of 3-(dimethylamino)cyclohex-2-en-1-one (0.139 g, 1.0 mmol) and lithium diisopropylamide (1.1 mmol from butyllithium and diisopropylamine) in 6 mL of THF was stirred for 30 min at −78 °C and quenched with methyl iodide (0.3 mL). The mixture was stirred for an additional 30 min at 0 °C, treated with saturated sodium chloride, and extracted with methylene chloride. The organic layer was dried and concentrated in vacuo, giving a white solid, shown by HPLC (Partisil 10-ODS-2, 1:1 MeOH–H_2O) to contain one product (t_R = 9.35 min). Purification by TLC on silica gel (8% MeOH–CH_2Cl_2) gave (R_f 0.5) 0.097 g (70%) of crystalline **16**: mp 41–43 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (d, 3 H, J = 6.7 Hz), 1.2–2.4 (m, 5 H), 2.97 (s, 6 H), 5.14 (s, 1 H); ^{13}C NMR ($CDCl_3$) 15.8, 25.9, 29.9, 38.4, 39.5, 97.7, 164.6, 198.9 ppm; IR ($CDCl_3$) 2970, 2930, 1600, 1555 cm^{-1}; mass spectrum, m/e 153 (M^+), 138, 111.

Anal. Calcd for $C_9H_{15}NO{\cdot}0.9H_2O$: C, 63.79; H, 9.45; H, 8.27. Found: C, 64.23; H, 9.45; N, 8.12.

Methylation of the Kinetic Anion of 3-(Methylcyclohexylamino)cyclohex-2-en-1-one (12). Preparation of 17. The β-enaminone **12** (0.102 g, 0.5 mmol) was treated with 0.55 mmol of lithium diisopropylamide followed by CH_3I and worked up in the manner described above for the analogous kinetic anion generation. TLC on silica gel (8% MeOH–CH_2Cl_2) gave 0.086 g (78%) of **17** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 6 Hz), 1.2–2.65 (m, 15 H), 2.78 (s, 3 H), 3.5 (br s, 1 H, $W_{1/2}$ = 24 Hz), 5.7 (s, 1 H); ^{13}C NMR ($CDCl_3$) 15.7, 25.1, 25.4, 25.8, 29.9, 30.1, 30.9, 38.3, 57.0, 97.4, 164.0, 199.0 ppm; IR (neat) 2930, 2850, 1610, 1545 cm^{-1}; mass spectrum, m/e 221 (M^+), 206, 179, 151, 138, 124; high-resolution mass spectrum, m/e 221.1779 ($C_{14}H_{23}NO$ requires 221.1780).

Benzylation of the Thermodynamic Anion of 3-(Dimethylamino)cyclohex-2-en-1-one (11). Preparation of 18. A solution of lithium diisopropylamide (from 4.16 mmol of butyllithium and 4.16 mmol of diisopropylamide) and 3-(dimethylamino)cyclohex-2-en-1-one (1.20 g, 8.68 mmol) in THF was stirred at room temperature for 18 h, quenched with benzyl bromide (0.924 g, 5.40 mmol), and stirred at room temperature for 12 h. The mixture was poured into ice–water and extracted with ether. The combined ethereal fractions were dried and concentrated in vacuo, giving 2.106 g of crude product which was subjected to alumina TLC ($CHCl_3$). The band with R_f 0.2–0.6 was shown to contain 0.415 g (21%) of 3-(dimethylamino)-4-benzylcyclohex-2-en-1-one (**18**): IR (film) 3055, 3020, 2870, 1600, 1550, 1270, 1160, 755, 710 cm^{-1}; ^{13}C NMR ($CDCl_3$) 195.6 (s, CO), 168.7 (s, C-3), 139.1 (s, phenyl C-1), 128.7 (d, C_o and C_p), 126.7 (d, C_p), 98.4 (d, C-2), 39.7 (q, $N(CH_3)_2$), 37.1 (t, Bz C), 36.4 (d, C-4), 30.7 (t, C-6), 24.7 ppm (t, C-5); ^{1}H NMR (CCl_4) δ 1.62–1.86 (m, 2 H, H-5), 2.00–2.30 (m, 2 H, H-6), 2.66–3.04 (m, 1 H, H-4), 2.80 (d, 2 H, J = 2 Hz, H-4), 2.93 (s, 6 H, $N(CH_3)_2$), 4.89 (s, 1 H, H-2), 7.17 (s, 5 H, aromatic); mass spectrum (70 eV), m/e (relative intensity) 229 (57, M^+), 138 (36), 91 (29), 58 (25), 43 (100); high-resolution mass spectrum, m/e 229.1457 ($C_{15}H_{19}NO$ requires 229.1466).

Methylation of Thermodynamic Anion of 3-(Dimethylamino)cyclohex-2-en-1-one (11). Preparation of 19. A solution of 3-(dimethylamino)cyclohex-2-en-1-one (**11**; 0.14 g, 1.0 mmol) and lithium bis(trimethylsilyl)amide is 15 mL of THF was stirred at −78 °C for 1 h, quenched with methyl iodide (0.2 mL), and stirred for 30 min at −78 °C and for 30 min at room temperature. The mixture was treated with saturated sodium chloride and extracted with methylene chloride. The organic layer was dried and concentrated in vacuo, giving a yellow oil which was analyzed by HPLC (Partisil 10-ODS-2, 1:1 MeOH–H_2O) and showed a single product, t_R 6.9 min. The product was purified by TLC on silica gel (8% MeOH–CH_2Cl_2) giving (R_f 0.45) 0.11 g (73%) of **19**: ^{1}H NMR ($CDCl_3$) δ 1.221 (d, 3 H, J = 7.1 Hz), 1.6–2.9 (m, 5 H), 2.988 (s, 6 H), 5.013 (s, 1 H); ^{13}C NMR ($CDCl_3$) 16.973, 28.860, 29.130, 30.676, 39.484, 97.405, 169.882, 195.746 ppm; IR ($CHCl_3$) 2940, 1620, 1550 cm^{-1}; mass spectrum, m/e 153 (M^+), 138, 125, 110, 97, 82; high-resolution mass spectrum, m/e 153.1150 ($C_9H_{15}NO$ requires 153.1154).

Methylation of Thermodynamic Anion of 3-(Methylcyclohexylamino)cyclohex-2-en-1-one (12). Preparation of 20. A solution of 3-(methylcyclohexylamino)cyclohex-2-en-1-one (**12**; 0.207 g, 1.0 mmol) was treated with lithium bis(trimethylsilyl)amide (1.1 mmol) in THF, quenched with methyl iodide, and worked up by using the procedure described above for the analogous thermodynamic anion. The crude product was purified by TLC on silica gel (8% MeOH–CH_2Cl_2) giving (R_f 0.5) 0.177 g (80%) of **20**: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3 H, J = 6 Hz), 1.35–2.6 (m, 15 H), 2.8 (s, 3 H), 4.6 (br s, 1 H, $W_{1/2}$ = 24 Hz), 5.1 (s, 1 H); ^{13}C NMR ($CDCl_3$) 17.1, 17.3, 25.0, 25.3, 25.5, 28.9, 30.3, 30.6, 30.9, 57.1, 96.9, 169.3, 195.6 ppm; IR (neat) 2935, 2860, 1620, 1550 cm^{-1}; mass spectrum, m/e 221 (M^+) 193, 178, 150, 138; high-resolution

mass spectrum, m/e 221.1773 ($C_{14}H_{23}NO$ requires 221.1780).

Anal. Calcd for $C_{14}H_{23}NO \cdot 1.03H_2O$: C, 70.09; H, 10.53; N, 5.84. Found: C, 70.00; H, 10.11; N, 5.88.

2-(4-Allyl-1-oxocyclohex-2-en-3-yl)-*endo*- and -*exo*-7-[1,1-(ethylenedioxy)eth-1-yl]-2-azabicyclo[2.2.2]oct-5-ene (27). A solution of 1.56 g (5.39 mmol) of the *N*-(oxocyclohexenyl)isoquinuclidene **1** and 4.9 mmol of lithium diisopropylamide in THF was made at 0 °C and stirred at 25 °C for 17 h. The reaction was cooled to 0 °C and mixed with 0.50 mL (5.9 mmol) of allyl bromide, warmed to 25 °C, stirred for 58 h, poured into ice–water, and extracted with chloroform. The organic fractions were dried and concentrated in vacuo, yielding 1.85 g of material which was purified by TLC on silica gel (1:9 methanol–ether) to yield 504 mg (53% based on 722 mg of recovered starting material) of a pink oil from a band with R_f 0.3. This was characterized as a diastereomeric mixture of (oxocyclohexenyl)isoquinuclidenes **27**: IR ($HCCl_3$) 2930, 1590, 1530 cm^{-1}; UV (EtOH) max 308 nm (ϵ 29400); ^1H NMR ($DCCl_3$) δ .12, 1.14, 1.20, 1.24 (s, 3 H, O_2CCH_3), 1.40 (m, 1 H, endo H-8), 1.62 (m, 1 H, exo H-8), 1.74–2.58 (m, 7 H, H-7, oxocyclohexenyl methylenes, and $=CHCH_2$), 2.58–3.36 (m, 4 H, H-3, H-4 and $=CHCH_2CH$), 3.94 (m, 4 H, $=OCH_2CH_2O$), 4.66 (m, 1 H, H-1), 4.90 (s, 1 H, $COCH=$), 5.0–5.34 (m, 2 H, $=CH_2$), 5.86 (m, 1 H, $CH=CH_2$), 6.18–6.60 (m, 2 H, H-5 and H-6); ^{13}C NMR ($DCCl_3$) characteristic resonances δ 22.0 and 22.3 (q, O_2CCH_3), 45.8 (d, C-7), 47.4 and 47.6 (d, C-1), 48.0, 48.2, and 49.9 (t, C-3), 63.9 and 64.4 (t, OCH_2CH_2O), 96.8 (d, $COCH=$), 109.6 and 109.8 (s, OCO), 117.1 and 117.4 (t, $=CH_2$), 129.7, 130.1, 132.6, 133.4, 134.7 (d, C-5 and C-6), 135.5 and 135.7 (d, $CH=CH_2$), 164.8, 165.1, 166.0 and 168.2 (s, $NC=CHCO$), 195.5 (s, $COCH=$); mass spectrum, m/e (relative intensity) 329 (P, 33), 286 (46), 214 (28), 172 (100), 87 (71); high-resolution mass spectrum, m/e 329.1988 ($C_{20}H_{27}NO_5$ requires 329.1990).

2-(6-Allyl-1-oxocyclohex-2-en-3-yl)-*endo*- and -*exo*-1-[1,1-(ethylenedioxy)eth-1-yl]-2-azabicyclo[2.2.2]oct-5-ene (28). A solution of 923 mg (3.19 mmol) of the *N*-(oxocyclohexenyl)-isoquinuclidene **1** and 3.8 mmol of lithium diisopropylamide in THF was made at 0 °C and stirred at 25 °C for 0.75 h and quenched at 0 °C by the addition of 0.32 mL (93.7 mmol) of allyl bromide. The reaction was warmed to 25 °C, stirred for 17 h, poured into ice–water, and extracted with chloroform. The organic fractions were dried and concentrated in vacuo, yielding 1.07 g of material which was purified by TLC on silica gel (1:9 methanol–ether) to yield 646 mg (62%) of a pink oil from a band with R_f 0.4. This material was characterized as a diastereomeric mixture of (oxocyclohexenyl)isoquinuclidenes **28**: IR ($HCCl_3$) 1600, 1540 cm^{-1}; UV (EtOH) max 306 nm (ϵ 31400); ^1H NMR ($DCCl_3$) δ 1.12 and 1.20 (s, 3 H, O_2CCH_3), 1.24–3.22 (m, 13 H, H-3, H-4, H-7, H-8, cyclohexenoyl methylenes, and $=CHCH_2$), 3.82 (m, 4 H, OCH_2CH_2O), 4.66 (m, 1 H, H-1), 4.86–5.16 (m, 3 H, $=CH_2$ and $COCH=$), 5.82 (m, 1 H, $CH=CH_2$), 6.16–6.60 (m, 2 H, H-5 and H-6); ^{13}C NMR ($DCCl_3$) characteristic resonances δ 21.6 and 22.3 (q, O_2CCH_3), 43.3 (d, COCH), 45.9 (d, C-7), 47.4 and 47.8 (d, C-1), 48.7 and 50.1 (t, C-3), 64.4 and 64.6 (t, OCH_2CH_2O), 97.1 (d, $COCH=$), 109.7 and 110.0 (s, OCO), 116.1 (t, $=CH_2$), 129.9, 132.8, and 134.4 (d, C-5 and C-6), 137.2 (d, $CH=CH_2$), 161.2 and 162.3 (s, $NC=CHCO$), 197.0 and 197.3 (s, $COCH=$); mass spectrum, m/e (relative intensity) 329 (P, 34), 286 (36), 215 (68), 214 (100), 87 (46); high-resolution mass spectrum, m/e 329.1988 ($C_{20}H_{27}NO_3$ requires 329.1990).

$\Delta^{4a,10b}$,Δ^{8}-8-Acetyl-4-allyl-1-oxodecahydrophenanthridine (29). A solution of 504 mg (1.53 mmol) of 2-(4-allyl-1-oxocyclohex-2-en-3-yl)-*endo*- and -*exo*-7-[1,1-(ethylenedioxy)eth-1-yl]-2-azabicyclo[2.2.2]oct-5-ene, 1 mL of H_2O, and 291 mg (1.53 mmol) of *p*-toluenesulfonic acid in 20 mL of benzene was refluxed for 9 h under an Ar atmosphere. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo. This gave 375.3 mg of crude product, which was subjected to preparative TLC on silica gel (1:9 methanol–ether) to yield 174 mg (40%) of a white powder from a band with R_f 0.3. This material was characterized as the 4-allylhydrophenanthridine **29**: mp 183–186 °C; IR ($HCCl_3$) 3400, 3260, 1660, 1560, 1510 cm^{-1}; UV (EtOH) max 232 nm (ϵ 15800), 304 (23300); ^1H NMR ($DCCl_3$) δ 1.60–2.20 (m, 5 H, H-3, H-6a, and H-7), 2.27 (s, 3 H, $COCH_3$), 2.20–2.44 (m, 5 H, H-4, H-10, and $=CHCH_2$), 2.44–2.80 (m, 2 H, H-2), 2.80–3.19 (m, 3 H, H-6, and H-10a), 4.92–5.22 (m, 2 H, $=CH_2$), 5.75 (m, 1 H, NH), 5.55–6.02 (m, 1 H, $CH=CH_2$), 6.77 (m, 1 H, H-9); ^{13}C NMR ($DCCl_3$) δ 25.2 (q, $COCH_3$), 25.4 and 25.7 (t, C-3), 26.0 (d, C-6a), 27.9 (d, C-10a), 28.4 (t, C-7), 29.1 and 29.3 (t, C-10), 32.3 (t, $=CHCH_2$), 36.8 (t, C-2), 37.4 and 37.5 (d, C-4), 42.1 (t, C-6), 108.3 (s, C-10b), 117.3 (t, $=CH_2$), 135.9 (d, $CH=CH_2$), 136.4 (s, C-8), 138.5 and 138.8 (d, C-9), 162.2 and 162.3 (s, C-4a), 192.2 (C-1), 199.2 (s, $COCH_3$); mass spectrum, m/e (relative intensity) 285 (P, 70), 189 (51), 188 (100); high-resolution mass spectrum, m/e 285.1741 ($C_{18}H_{23}NO_2$ requires 285.1728).

$\Delta^{4a,10b}$,Δ^{8}-8-Acetyl-2-allyl-1-oxodecahydrophenanthridine (30). A solution of 642 mg (1.96 mmol) of 2-(6-allyl-1-oxocyclohex-2-en-3-yl)-*endo*- and -*exo*-7-[1,1-(ethylenedioxy)eth-1-yl]-2-azabicyclo[2.2.2]oct-5-ene, 1 mL of H_2O, and 373 mg (1.96 mmol) of *p*-toluenesulfonic acid in 20 mL of benzene was refluxed for 10 h under an Ar atmosphere. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo. This gave 276.9 mg (50%) of a white crystalline material characterized as the 2-allylhydrophenanthridine **30**: mp 181–183 °C (C_6H_6); IR ($HCCl_3$) 3410, 3260, 1660, 1570, 1510 cm^{-1}; UV (EtOH) max 233 nm (ϵ 13800), 300 (23400); ^1H NMR ($DCCl_3$) δ 1.52–2.26 (m, 5 H, H-3, H-6a, and H-7), 2.29 (s, 3 H, $COCH_3$), 2.26–2.52 (m, 4 H, H-10 and $=CHCH_2$), 2.52–3.22 (m, 6 H, H-2, H-4, H-6, and H-10a), 4.90–5.18 (m, 2 H, $=CH_2$), 5.80 (m, 1 H, $CH=CH_2$), 6.20 (m, 1 H, NH), 6.80 (m, 1 H, H-9); ^{13}C NMR ($DCCl_3$) δ 25.2 (q, $COCH_3$), 25.4 (t, C-3), 26.1 (t, C-4), 26.3 (d, C-6a), 27.4 (t, C-7), 28.3 (d, C-10a), 29.0 and 29.3 (t, C-10), 34.9 and 35.1 (t, $=CHCH_2$), 42.2 (t, C-6), 43.9 (d, C-2), 108.6 (s, C-10b), 116.1 (t, $=CH_2$), 136.4 (s, C-8), 137.2 (d, $CH=CH_2$), 138.6 (d, C-9), 158.0 (s, C-4a), 194.4 (s, C-1), 199.2 (s, $COCH_3$); mass spectrum, m/e (relative intensity) 285 (P, 100), 244 (79), 189 (71), 188 (100); high-resolution mass spectrum, m/e 285.1738 ($C_{18}H_{23}NO_2$ requires 285.1728).

***n*-Butyllithium Generation and Methylation of Dianions from 3-(Cyclohexylamino)cyclohex-2-en-1-one (32).** A solution of 3-(cyclohexylamino)cyclohex-2-en-1-one (0.193 g, 1.0 mmol) and *n*-butyllithium in hexane (1.46 mL of 1.5 M solution, 2.2 mmol) was stirred at 0 °C for 1 h and quenched at 0 °C with 0.5 mL of methyl iodide. Water was added, and the resulting mixture was extracted with methylene chloride. The organic layer was concentrated to give an oil which was purified by preparative TLC on silica gel (8% MeOH–CH_2Cl_2), yielding the kinetic dianion dimethylated product **17** (90 mg, 41%) from the faster moving band and the thermodynamic dianion dimethylated product **20** (55 mg, 25%) from slower band. The NMR spectra of the two products were identical with those of authentic samples prepared by monomethylation of monoanions.

Lithium Diisopropylamide and Lithium Bis(trimethylsilyl)amide Generation and Methylation of Dianions from 3-(Methylamino)- (31) and 3-(Cyclohexylamino)cyclohex-2-en-1-one (32). General Methods. Solutions of the 3-(alkylamino)cyclohex-2-en-1-ones **31** and **32** (1 mmol) in THF (10 mL) were treated with THF solutions of the lithium diisopropyl- and bis(trimethylsilyl)amide bases in molar ratios, at the temperatures, and for the time period listed in Table IV. Methyl iodide (0.5 mL) was added to these milky solutions at 0 °C, the resulting mixtures stirred at 0 °C for 30 min, and saturated NaCl added. The CH_2Cl_2 extracts of these solutions were dried and concentrated in vacuo, yielding mixtures of the mono and dimethylated products in ratios recorded in Table IV. Product yields were determined by either HPLC or ^1H NMR analysis or by isolation from preparative TLC.

Lithium Diisopropylamide and Lithium Bis(trimethylsilyl)amide Generation and Methylation of Dianions from $\Delta^{4a,10b}$,Δ^{8}-8-[1,1-(ethylenedioxy)eth-1-yl]-1-oxodecahydrophenanthridine (5). General Methods. Solutions of the tricyclic β-enaminone **5** (1 mmol) in THF (10 mL) were treated with THF solutions of the lithium diisopropyl- and bis(trimethylsilyl)amide bases in molar ratios, at the temperatures, and for the time periods listed in Table V. Methyl iodide (0.5 mL) was added at 0 °C, the resulting mixture stirred at 0 °C for 30 min, and saturated NaCl added. The CH_2Cl_2 extracts of these solutions were dried and concentrated in vacuo, yielding product mixtures which were separated by preparative TLC on silica gel (8% CH_3OH–CH_2Cl_2). The following methylated products were isolated in the ratios and yields recorded in Table V.

$\Delta^{4a,10b}$,Δ^{8}-2,5-Dimethyl-8-[1,1-(ethylenedioxy)eth-1-yl]-1-oxodecahydrophenanthridine (**34**): yellow solid; mp 112–115 °C; ^1H

NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 6.5 Hz), 1.42 (s, 3 H), 1.55–2.8 (m, 11 H), 3.05 (d, 3 H, J = 2 Hz), 2.8–3.4 (m, 2 H), 3.85 (m, 4 H), 5.75 (br s, 1 H, $W_{1/2}$ = 7 Hz); ^{13}C NMR ($CDCl_3$) 16.3, 23.8, 24.9, 25.9, 26.2, 27.5, 28.0, 28.6, 29.1, 38.3, 38.5, 51.8, 52.0, 64.1, 64.2, 109.1, 110.5, 120.0, 133.8, 162.3, 195.5 ppm; IR ($CHCl_3$) 3000, 2930, 1600, 1550 cm^{-1}; mass spectrum, m/e 317 (M^+), 272, 257, 243, 175.

Anal. Cacld for $C_{17}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 70.88; H, 8.60, N, 4.72.

$\Delta^{4a,10b}$,Δ^8-4,5-Dimethyl-8-[1,1-(ethylenedioxy)eth-1-yl]-1-oxodecahydrophenanthridine (**33**): pale yellow solid; mp 154–156 °C; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6.5 Hz), 1.42 (s, 3 H), 1.6–2.6 (m, 11 H), 3.05 (s, 3 H), 2.7–3.35 (m, 2 H), 3.80 (m, 2 H), 3.90 (m, 2 H), 5.70 (m, 1 H); ^{13}C NMR ($CDCl_3$) 16.9, 17.1, 23.7, 25.6, 26.1, 26.0, 26.6, 27.6, 27.4, 27.5, 27.9, 28.2, 28.5, 30.6, 30.8, 37.9, 38.2, 51.9, 52.2, 63.9, 64.0, 108.9, 110.2, 119.8, 133.6, 133.7, 163.0, 191.2, 191.8 ppm; IR ($CHCl_3$) 2990, 2940, 1580, 1532, 1400, 1185 cm^{-1}; mass spectrum, m/e 317 (M^+), 271, 257, 175, 161; high-resolution mass spectrum, m/e 317.1984, ($C_{19}H_{27}NO_3$ requires 317.1990).

Anal. Cacld for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.26; H, 8.74; N, 4.22.

$\Delta^{4a,10b}$,Δ^8-5-Methyl-8-[1,1-(ethylenedioxy)eth-1-yl]-1-oxodecahydrophenanthridine (**35**): white solid; mp 163.5–165 °C; ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 1.6–2.6 (m, 12 H), 2.95 (s, 3 H), 2.7–3.05 (m, 2 H), 3.75 (m, 4 H), 5.65 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 21.6, 23.7, 26.0, 26.1, 26.6, 27.5, 28.5, 35.4, 38.5, 51.9, 55.0, 63.9, 64.1, 108.8, 119.7, 133.7, 159.0, 192.0 ppm; IR ($CHCl_3$) 2980, 2940, 2880, 1595, 1545, 1395 cm^{-1}; mass spectrum, m/e 303 (M^+), 271, 257, 175, 161; high-resolution mass spectrum, m/e 303.1827 ($C_{18}H_{25}NO_3$ requires 303.1834).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.79; H, 8.51; N, 4.75.

Attempted Acylation–Alkylation of the Thermodynamic Dianion of 5. Preparation of $\Delta^{4a,10b}$,Δ^8-5-(Chloroacetyl)-8-acetyl-1-oxodecahydrophenanthridine (37). A solution of 87 mg (0.3 mmol) of the tricyclic β-enaminone **5** and 1.5 mmol of lithium bis(trimethylsilyl)amide in 10 mL of THF was stirred at −78 °C for 0.5 h and at 0 °C for 5 h and quenched with 0.2 mL of chloroacetyl chloride at 0 °C. The resulting mixture was stirred for 12 h at room temperature, quenched with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo, giving an oil which was purified by silica gel flash chromatography (gradual increase in polarity from CH_2Cl_2 to 2% CH_3OH–CH_2Cl_2) to yield 61 mg (51%) of the 5-(chloroacetyl)-hydrophenanthridine **37** as a white solid: mp 154–156 °C; ^1H NMR ($CDCl_3$) δ 1.65–2.8 (m, 8 H), 2.3 (s, 3 H), 2.8–4.0 (m, 5 H), 4.2 (s, 2 H), 6.9 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 23.3, 25.2, 26.3, 27.8, 29.3, 30.2, 37.0, 43.3, 47.0, 126.0, 135.9, 138.1, 153.8, 166.9, 196.9, 197.0, 198.4 ppm; IR ($CHCl_3$) 3005, 2945, 1690, 1658, 1645, 1595 cm^{-1}; mass spectrum, m/e (relative intensity) 323 (M^+ + 2), 321 (M^+), 286 (M^+ − Cl), 244, 190, 148 (100); high-resolution mass spectrum, m/e 321.1138 ($C_{17}H_{20}NO_3{}^{35}Cl$ requires 321.1131), 286.1449 ($C_{17}H_{20}NO_3$ requires 286.1443).

The yield of this process was raised to 83% when anion generation employed 1.1 equiv of the lithium amide base at −78 °C for 2 h and at 0 °C for 0.5 h and when chloroacetylation was conducted at −78 °C for 1 h and at 0 °C for 0.5 h.

$\Delta^{4a,10b}$,Δ^8-5-[(Carboethoxy)methyl]-8-[1,1-(ethylenedioxy)eth-1-yl]-1-oxodecahydrophenanthridine (36). To a solution of 145 mg (0.5 mmol) of $\Delta^{4a,10b}$,Δ^8-[1,1-(ethylenedioxy)-eth-1-yl]-1-oxodecahydrophenanthridine in 20 mL of THF was added 1.5 mmol of lithium bis(trimethylsilyl)amide at −78 °C. The resulting solution was stirred at −78 °C for 30 min and then at 0 °C for 6 h. The mixture was cooled to −78 °C, quenched with 0.17 mL (1.5 mmol) of ethyl bromoacetate, warmed to 25 °C, stirred for 3 h, diluted with water, and extracted with methylene chloride. The organic extracts were dried and concentrated in vacuo, yielding 222.5 mg of material which was purified by preparative TLC on silica gel (8% MeOH in CH_2Cl_2) to give 172.5 mg (92%) of the ester **36** as a yellow oil: IR ($HCCl_3$) 2960, 1740, 1610, 1550 cm^{-1}; UV (EtOH) max 309 nm (ϵ 24 700); ^1H NMR ($DCCl_3$) δ 1.29 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.42 (s, 3 H, O_2CCH_3), 1.60–2.69 (m, 11 H, H-2, H-3, H-4, H-6a, H-7, and H-10), 2.79–3.17 (m, 2 H, H-6α, and H-10a), 3.34 (t, 1 H, J = 12 Hz), 3.85 (m, 4 H, OCH_2CH_2O), 4.05 (AB q, 2 H, J = 18 Hz, CH_2CO_2), 4.25 (q, 2 H, J = 7 Hz, CH_2CH_3), 5.74 (m, 1 H, H-9); ^{13}C NMR ($DCCl_3$) 14.2 (q, CH_2CH_3), 21.7 (t, C-3), 23.8 (q, O_2CCH_3) 26.2 (d, C-4), 26.2 (t, C-6a), 27.5 (t, C-7), 28.6 (d, C-10a), 28.7 (t, C-10), 35.8 (t, C-2), 51.4 (t, $=CH_2CO_2$), 52.4 (t, C-6), 61.6 (t, OCH_2CH_3), 64.1 and 64.2 (t, OCH_2CH_2O), 109.1 (s, OCO), 113.2 (s, C-10b), 120.0 (d, C-9), 133.9 (s, C-8), 157.9 (s, C-4a), 169.2 (s, CO_2), 193.7 (s, COC); mass spectrum, m/e (relative intensity) 375 (P, 31), 330 (74), 234 (22), 148 (100), 87 (19); high-resolution mass spectrum, m/e 375.2031 ($C_{21}H_{29}NO_5$ requires 375.2045).

This mono-N-alkylation product could also be generated by quenching the N-monoanion, formed from the hydrophenanthridine (804 mg, 2.78 mmol) and lithium diisopropylamide (3.36 mmol) in THF with ethyl bromoacetate (3.61 mmol). Purification by preparative TLC gave 901 mg (86%) of the ester **36**.

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Registry No. **5**, 78890-72-9; **8**, 1540-24-5; **8** α', 78919-40-1; **8** τ, 78919-41-2; **9**, 5323-87-5; **9** α, 78890-73-0; **10**, 3433-62-3; **10** τ, 78890-74-1; **11**, 6135-22-4; **11** α', 78890-75-2; **11** τ, 78890-76-3; **12**, 16195-95-2; **12** α', 78890-77-4; **12** τ, 78890-78-5; **14**, 78890-79-6; **15**, 78890-80-9; **16**, 78890-81-0; **17**, 78890-82-1; **18**, 78890-83-2; **19**, 78890-84-3; **20**, 78890-85-4; **21**, 78890-86-5; **22**, 78890-87-6; **23**, 78890-88-7; **24**, 78890-89-8; **25**, 78890-90-1; **26**, 52393-50-7; **27**, 78890-91-2; *endo*-**28**, 78890-92-3; *exo*-**28**, 78962-87-5; **29**, 78890-93-4; **30**, 78890-94-5; **31**, 55998-74-8; **32**, 16179-64-9; **33**, 78919-42-3; **34**, 78919-43-4; **35**, 78919-44-5; **36**, 78890-95-6; **37**, 78890-96-7; 1,3-cyclohexanedione, 504-02-9.