identical and characteristic; they are consistent with those given in the literature for cephalosporins or 7-methoxycephalosporins.[1,3a,22] Note, in particular, loss of the lactam CO and fission along paths a and b in Scheme III.

Registry No. 1, 61934-81-4; 2, 119788-90-8; 3, 119788-91-9; 4, 119788-92-0; 5, 34644-30-9; 6, 119788-93-1; 7, 119788-94-2; 11, 119788-95-3; 13, 119788-96-4; 14, 119788-97-5; 15, 119788-98-6; 16, 119788-99-7; 17, 119789-00-3; acrolein, 107-02-8.

Model Studies Probing the Amino-Claisen Rearrangement Approach to Hydroisoquinoline Synthesis. Development of Methods for Stereocontrolled Introduction of Reserpine E Ring Type Functionality

Ellen W. Baxter, David Labaree, Shouchung Chao, and Patrick S. Mariano*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

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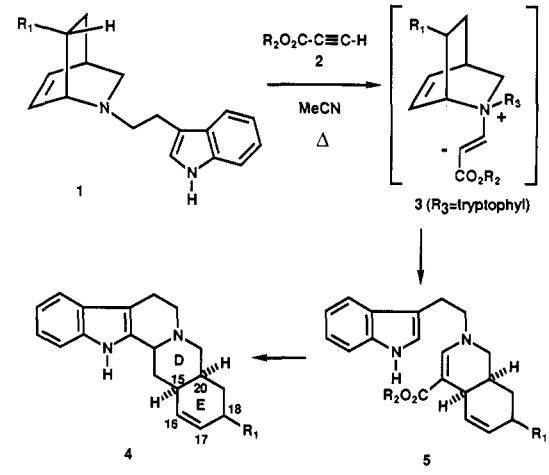
Studies probing several aspects of a proposed yohimbane alkaloid synthetic strategy based upon the zwitterionic amino-Claisen rearrangement reactions of isoquinuclidenes have been conducted. As part of these efforts, methods have been developed to prepare 7-ketoisoquinuclidenes and their derivatives. An approach to these substances utilizing an oxidative cleavage sequence starting with 7-acetylisoquinuclidenes has been shown to be limited to C-6 electron withdrawing group substituted systems owing to an interesting rearrangement reaction which occurs upon attempts to α-oxidize enolate anions derived from these substrates. A more successful approach has been developed which employs Diels–Alder cycloaddition of the ketene equivalent, α-acetoxyacrylonitrile to *N*-carbethoxy-1,2-dihydropyridine followed by deprotection to liberate the 7-ketone function. Zwitterionic amino-Claisen rearrangements occurring in reactions of a series of isoquinuclidenes with alkyl propiolates have been probed, and limitations of this process have been uncovered. However, the diethoxy ketal of a 7-ketoisoquinuclidene has been shown to be efficiently converted to an enone-containing, cis-fused hydroisoquinoline upon treatment with methyl propiolate. Finally, methods for stereoselective introduction of the reserpine E ring functionality have been modeled. The strategy involves cyanosilylation of the enone function followed by hydroboration–oxidation of the regioselectively formed silyl enol ether, alcohol methylation, silyl ether deprotection, and esterification. The stereochemical aspects of these processes are discussed.

In previous reports[1] we have described an efficient approach for yohimbane ring construction based upon a combination of zwitterionic amino-Claisen rearrangement and Wenkert cyclization methodologies. The strategy, outlined in Scheme I, utilizes rearrangement of the zwitterion **3** generated by conjugate addition of isoquinuclidenes **1** to propiolate esters **2**, to produce *N*-tryptophyl-*cis*-hydroisoquinolines **5**. (In this paper, tryptophyl is 2-indol-3-ylethyl.) These substances then undergo decarboxylative cyclization[2] to form the pentacyclic cis-D,E yohimbanes **4**. Since the isoquinuclidenes can be conveniently accessed by 1,2-dihydropyridine Diels–Alder routes, the overall process represents an efficient strategy for preparation of the structurally complex yohimbane members.

Application of this strategy to the synthesis of interesting members of the yohimbane family requires the development of methods for stereocontrolled introduction of E-ring functionality that is commonly found in these substances. Reserpine (**10**) with its differentially functionalized *trans*-diol groups at C-17 and C-18 and β-methoxycarbonyl group at C-16 of the DE-cis-fused pentacyclic skeleton represents the perhaps most challenging of the targets in this area from the viewpoint of functionality and stereochemistry complexity. As a result of this, we have further probed our strategy for yohimbane

Scheme I



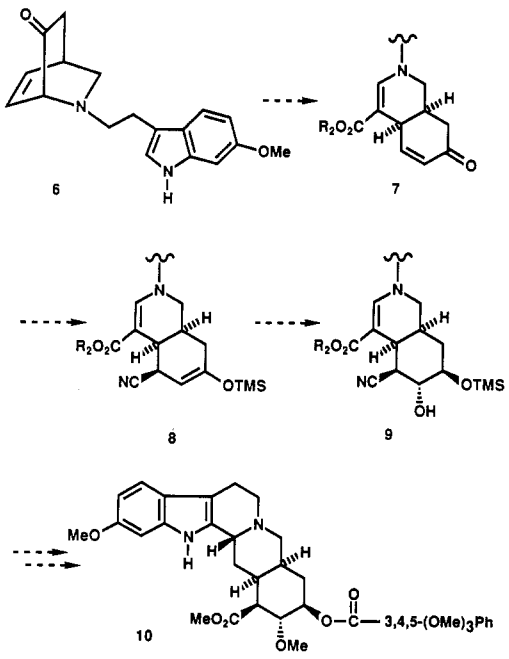
synthesis with the intent of demonstrating its compatibility with procedures for stereoselective introduction of the reserpine E ring functionality. Our plan, outlined in Scheme II, was to utilize the enone-containing cis-fused hydroisoquinoline **7** as a key intermediate. The ester function at C-16 would be introduced in the form of a cyano group by silyl-cyanation chemistry. Hydroboration of the resulting silyl enol ether **8** would then furnish the regioselectively blocked, vicinal diol **9**, which we felt would serve as a useful precursor of the target alkaloid. Conformational considerations (see below) suggested that the chiral centers introduced by these operations would be delivered with the desired relative stereochemistry. In

(1) (a) Kunng, F. A.; Gu, J. M.; Chao, S.; Chen, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262. (b) Chao, S.; Kunng, F. A.; Gu, J. M.; Mariano, P. S. *Ibid.* **1984**, *49*, 2708.

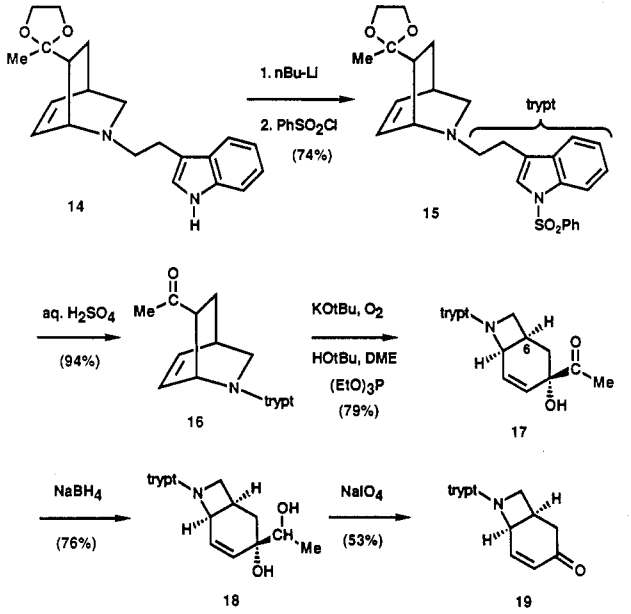
(2) (a) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461. (b) Wenkert, E.; Spague, P. W.; Webb, R. L. *J. Org. Chem.* **1973**, *38*, 4305.

0022-3263/89/1954-2893$01.50/0

Scheme II



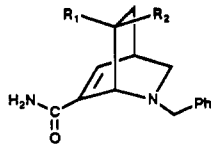
Scheme III



addition, we anticipated that the intermediate enones **7** would be derivable by amino-Claisen rearrangement of appropriate isoquinucliden-7-ones **6** or their blocked ketone analogues.

In this report we describe a preliminary investigation of the key features of the design outlined in Scheme II. Specifically, we have developed general methods for synthesis of hydroisoquinoline enones related to **7** and their further transformation to functionalized hydroisoquinolines related to **9**. In the course of these studies, an interesting isoquinuclidene rearrangement reaction has been uncovered and interesting conformational preferences for substances related to **9** have been observed.

Isoquinucliden-7-ones by Oxidative Cleavage. A number of different methods can be envisaged for preparation of isoquinucliden-7-ones, related to **6**, which would serve as key intermediates in the sequence proposed above for reserpine and related yohimbane synthesis. The first route explored was based upon procedures developed previously by Buchi and his co-workers[3] as part of their work on the preparation of velbanamine and catharanthine. In that work the 7-isoquinuclidenecarboxamide **11** was transformed by an enolate oxygenation–oxidative cleavage sequence via the α-hydroxy ketone **12** to the corresponding 7-ketone **13**. In order to test the utility of

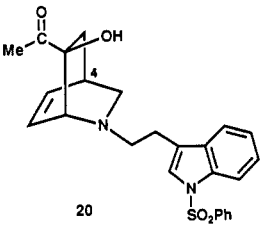


11 (R_1=MeCO, R_2=H)

12 (R_1=MeCO, R_2=OH)

13 (R_1,R_2= =O)

this process as a general method for generation of isoquinucliden-7-ones related to **6**, we have prepared the blocked-tryptophyl-substituted isoquinuclidene **16** from the known[1] ketal **14** by the route shown in Scheme III. In contrast to the Buchi example, exposure of **16** to KOtBU in oxygen-saturated HOtBu/DME solutions containing $(EtO)_3P$ led to production of the azabicyclo[4.2.0] hydroxy ketone **17** rather than the isoquinuclidine **20**. This substance was furnished as a single diastereomer, to which we have assigned the α-hydroxy stereochemistry on the basis of mechanistic considerations.

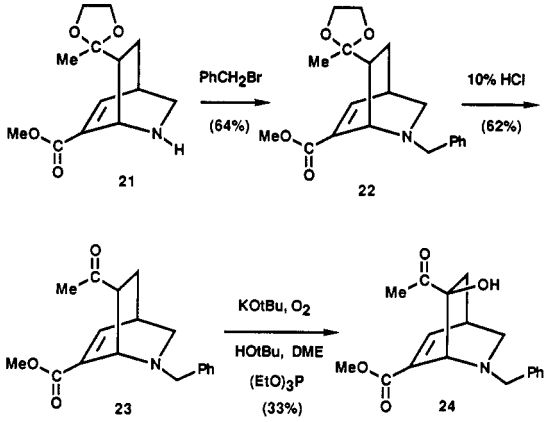


The spectroscopic data accumulated for **17** do not allow unambiguous assignment of the azabicyclo[4.2.0] structure. However, the presence of a methine carbon resonance at 24 ppm in the ^{13}C NMR spectrum was significant since it appeared to be attributable to the C-6 azetidine ring carbon of **17** rather than C-4 of the expected isoquinuclidene **20**. Thus, the normally upfield positions of azetidine ring β-carbons in ^{13}C NMR spectra coupled with the expectation that the chemical shift of the C-4 resonance of **16** at 52.7 ppm would not change dramatically upon introduction of the C-7 hydroxyl function served to rationalize the bicyclic azetidine structure assignment. Firm support for assignment derived from the results of further chemical transformations of this substance. Reduction ($NaBH_4$) of **17** provided the diastereomeric diols **18**, which were transformed to the conjugated enone **19** by oxidative cleavage ($NaIO_4$). Since this reaction sequence could not have transformed the 7-hydroxy-7-acetylisoquinuclidine **20** to a conjugated enone, it supports assignment of the bicyclic azetidine **17** as the product of α-oxygenation of **16**.

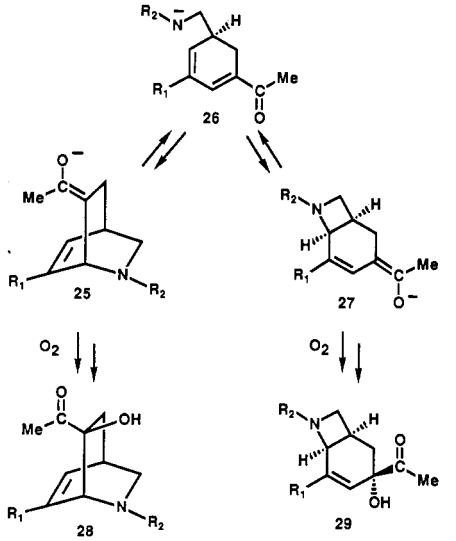
Further information about the factors controlling the differences noted in the enolate-oxygenation reactions of 7-acetylisoquinuclidenes **11** and **16** has come from studies with the 6-carbomethoxy analogue **23**. This material was prepared from the known[1] secondary amine **21** by the route shown in Scheme IV. Importantly, oxygenation of **23** by using the Buchi conditions[3] gave the hydroxyisoquinuclidine **24** as the only detectable product albeit in low yield.

(3) Buchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999.

Scheme IV



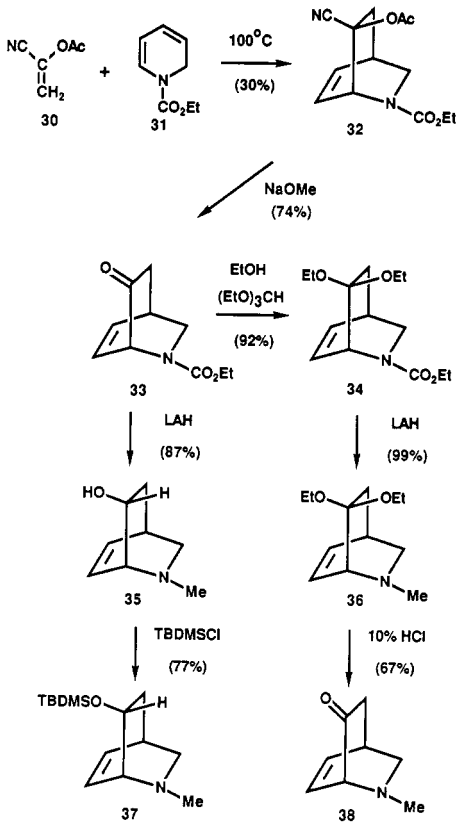
Scheme V



The mechanistic pathway involved in the conversion of isoquinuclidene **16** to the bicyclic azetidine **17** and the dissimilar behavior of the isoquinuclidenes **13**, **23**, and **16** under the Buchi oxygenation conditions require discussion. The results suggest that the thermodynamic enolates **25** formed by H-7 deprotonation of the 7-acetylisoquinuclidenes can exist in equilibrium with the corresponding dienolate anions **27**. Interconversion of these enolate anions can occur via the amide anions **26** (Scheme V). α-Oxygenation of dienolates **27** followed by $P(OEt)_3$ reduction would serve to produce the azetidines **24** while oxygenation of **25** gives isoquinuclidenes **28**. The differences in behavior noted above can be attributed to the presence of an amide or ester function at C-6 in the dienolate anion **27** which could influence the reactivity of these species with oxygen. Thus, selective oxygenation of the enolate anions **25** in the amide- and ester-substituted systems might be due to the reduced reactivity of the electron withdrawing group stabilized, dienolate anion intermediates. In the absence of these substituents, oxygenation of the dienoate appears to be preferred. In the latter case, electronic[4] and steric effects combine to control the respective regiochemical (α-position) and stereochemical (exo-face) outcome of the oxygenation process. It is important to note that the differences in the reactivity of isoquinuclidenes **13**, **23**, and **16** do not appear to be due to substituent effects upon the equilibrium between anions

(4) For an example of an α-oxygenation of a dienolate anion with MOOPH, see: Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398.

Scheme VI



25 and **27** since when the isoquinuclidene **16** is subjected to the reaction conditions in the absence of oxygen and $P(OEt)_3$, a mixture (1:1) of C-7 epimeric unrearranged ketones is formed in near quantitative yield. The complete absence of a bicyclo[4.2.0] product in this mixture suggests that, unlike oxygenation, protonation of the anion mixture occurs exclusively on the enolate **25** when R_1 = H.

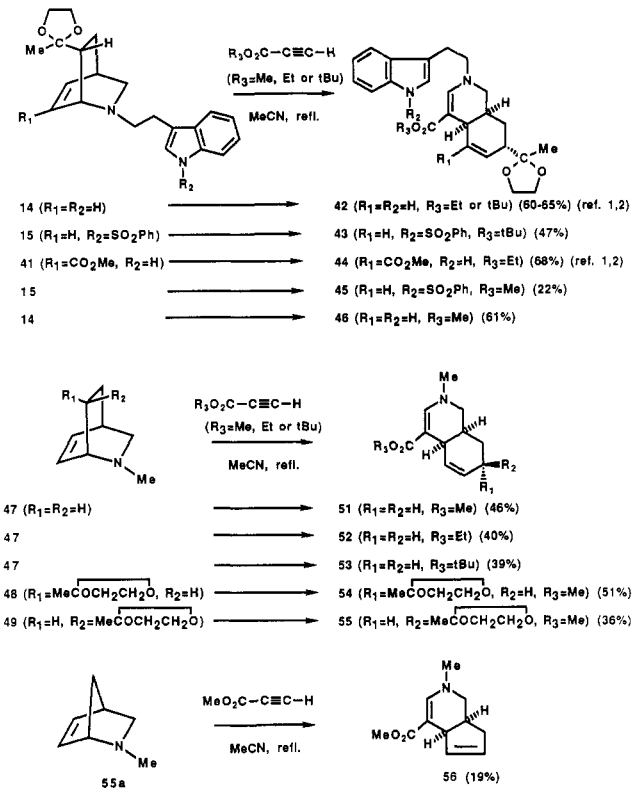
Isoquinucliden-7-ones by Ketene Equivalent Cycloadditions. An alternate strategy for synthesis of 7-ketoisoquinuclidenes related to **6** (Scheme II) employs cycloaddition reactions of appropriately blocked 1,2-dihydropyridines with ketene equivalents. Routes based upon this methodology would be more direct and should not suffer from the same limitations noted above for sequences based upon the oxidative cleavage procedure. Investigations of this strategy have uncovered a useful sequence for production of 7-ketoisoquinuclidenes and their derivatives. The best method for accomplishing this goal involves Diels–Alder additions of α-acetoxyacrylonitrile (**30**)[5] to *N*-carbalkoxy-1,2-dihydropyridines.[6] Accordingly, addition of **30** to the *N*-(ethoxycarbonyl)dihydropyridine **31** (neat, 100 °C) provides the 7-cyano-7-acetoxyisoquinuclidene **32**, which can be transformed to the corresponding 7-ketone **33** by treatment with NaOMe (Scheme VI).[5,7] For the purposes of these model studies, **33** was transformed to the *N*-methyl 7-ketal **36**, 7-ketone

(5) (a) The use of ketene equivalents in cycloadditions with 1,2-dihydropyridines has been suggested in Wender et al.: Wender, P. A.; Schaus, J. M.; Torney, D. C. *Tetrahedron Lett.* **1970**, 999. (b) For use of α-cyano vinyl acetate (ref 5c) as a ketene equivalent, see: Ranganathan, S.; Ranganathan, D.; Mehrohta, A. *Synthesis* **1977**, 289. Kotsuki, H.; Nishizawa, H. *Heterocycles* **1981**, *16*, 1287. (c) Oku, A.; Arita, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3337.

(6) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.

(7) (a) Attempts to use nitroethylene as a ketene equivalent (ref 7b) in cycloadditions with N-blocked dihydropyridines have not been successful. (b) Ranganathan, S.; Ranganathan, D.; Mehrohta, A. *J. Am. Chem. Soc.* **1974**, *96*, 5261.

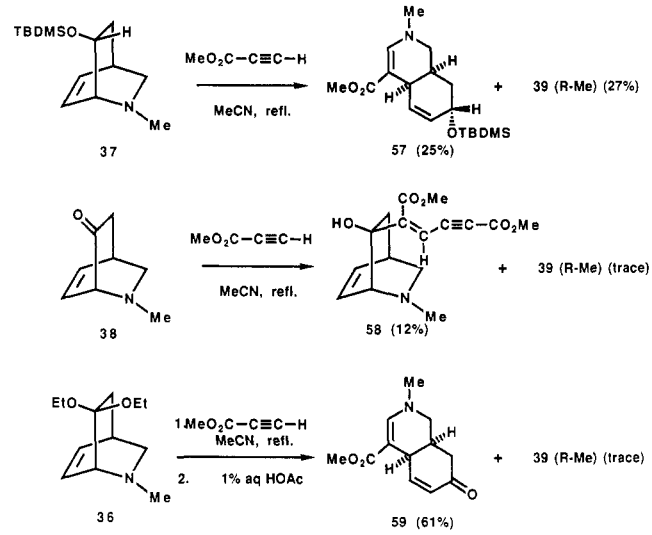
Scheme VII



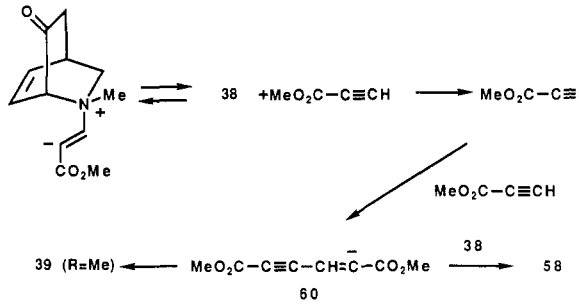
38, and 7-blocked alcohol **37** by the procedures outlined in Scheme VI.[8]

Scope and Limitations of the Zwitterionic Amino-Claisen Rearrangement. With routes for preparation of 7-ketoisoquinuclidenes in hand, our attention next turned to transformation of these systems into functionalized, cis-fused hydroisoquinolines. As stated above, we had uncovered earlier an interesting addition–rearrangement reaction occuring between isoquinuclidenes and propiolate esters which leads to efficient production of *cis*-hydroisoquinolines.[1,10] The design of this process was based upon previous observations which have shown that conjugate additions of tertiary amines to propiolate esters occur to generate zwitterionic intermediates[9] and that ammonium salts of *N*-vinylisoquinuclidenes undergo facile amino-Claisen rearrangement.[10] Accordingly, we have shown that a variety of tertiary amine containing isoquinuclidenes react with propiolate esters by pathways involving amino-Claisen rearrangement of intermediate zwitterions (e.g., **3** in Scheme I) to furnish cis-fused hydroisoquinolines. Examples of these processes taken from our earlier work[1] and the current investigations are shown in Scheme VII.[11] Clearly, the efficiencies of these reactions range from low to moderate. Competitive formation of the

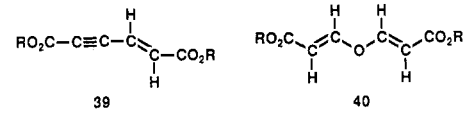
Scheme VIII



Scheme IX



propiolate dimers **39** and bisvinyl ethers **40**[12] (see Experimental Section) under the reaction conditions employed for the zwitterionic amino-Claisen rearrangements accounts in part for the low yields of these processes.



In order to test a key element in the reserpine synthesis plan outlined in Scheme II, zwitterionic amino-Claisen rearrangement reactions of the model isoquinuclidenes **36–38** were probed. Each of these substances contains functionality at C-7 which could be either directly or indirectly transformed into the conjugated enone moiety found in the hydroisoquinoline **7**, an important intermediate in this strategy. Thus, the amino-Claisen rearrangement and subsequent chemistry developed with these types of substances would be directly applicable to a reserpine synthetic approach.

Reaction of the TBDMS-blocked 7-ketoisoquinuclidene **37** with methyl propiolate provided as expected the hydroisoquinoline **57** in a low yield along with the propiolate dimer **39** (R = Me) (Scheme VIII). Although this substance can be converted into the bicyclic enone **59**, the low efficiency of the zwitterionic amino-Claisen rearrangement step made this route less practical.

7-Ketoisoquinuclidenes would serve as direct precursors to hydroisoquinolines containing the conjugated enone function. However, reaction of **38**, a model iso-

(8) The use of the *N*-trichloroethoxycarbonyl analogue of **31** allows preparation of a ketal related to **34** which can be easily N-deblocked to produce a secondary amine containing, isoquinuclidene 7-ketal. This substance can be N-alkylated to produce a number of tertiary amine derivatives related to **36** (unpublished results: Mariano, P. S.; Baxter, E.; Labaree, D.)

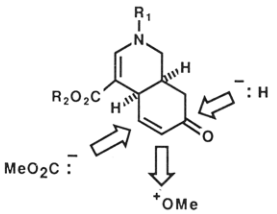
(9) (a) McCulloch, A. W.; McInnes, A. G. *Can. J. Chem.* **1974**, *52*, 3569. (b) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952.

(10) (a) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L.; Beamer, R. *Tetrahedron Lett.* **1977**, 4299. (b) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124. (c) Chen, Y.; Mariano, P. S.; Little, G. M.; O'Brien, D.; Huesmann, P. L. *J. Org. Chem.* **1981**, *46*, 4643. (d) Chen, Y.; Huesmann, P. L.; Mariano, P. S. *Tetrahedron Lett.* **1983**, 1021.

(11) Other allylic amines including *N,N*-dimethyl-*N*-allylamine and 1-benzyl-1,2,3,6-tetrahydropyridine fail to undergo zwitterionic amino-Claisen rearrangement when reacted with propiolate esters.

(12) (a) The mechanisms for formation of **39** and **40** have been discussed (ref 9 and 12b). (b) Wenkert, E.; Adams, K. A. H.; Leicht, C. L. *Can. J. Chem.* **1963**, *41*, 1844.

Scheme X



quinucliden-7-one, with methyl propiolate failed to provide the corresponding enone **59**. Instead, the isoquinuclidene **58** and dimer **39** (R = Me) were the only detectable products produced in this process. These substances appear to form by a common mechanism involving the intermediacy of the enyne anion **60** (Scheme IX). Thus, it appears that when amino-Claisen rearrangement of the reversibly formed zwitterionic intermediate is slow, other reaction pathways become competitive. In the case of **38** and other isoquinuclidenes shown in Scheme VII, one competitive process involves deprotonation of the propiolate ester followed by precedented[12] addition of the resulting acetylide anion to another prpiolate to provide the enyne anion **60**. Protonation of this material gives the dimer **39** (R = Me), and addition to the ketone grouping in **38** gives the isoquinuclidene **58**.

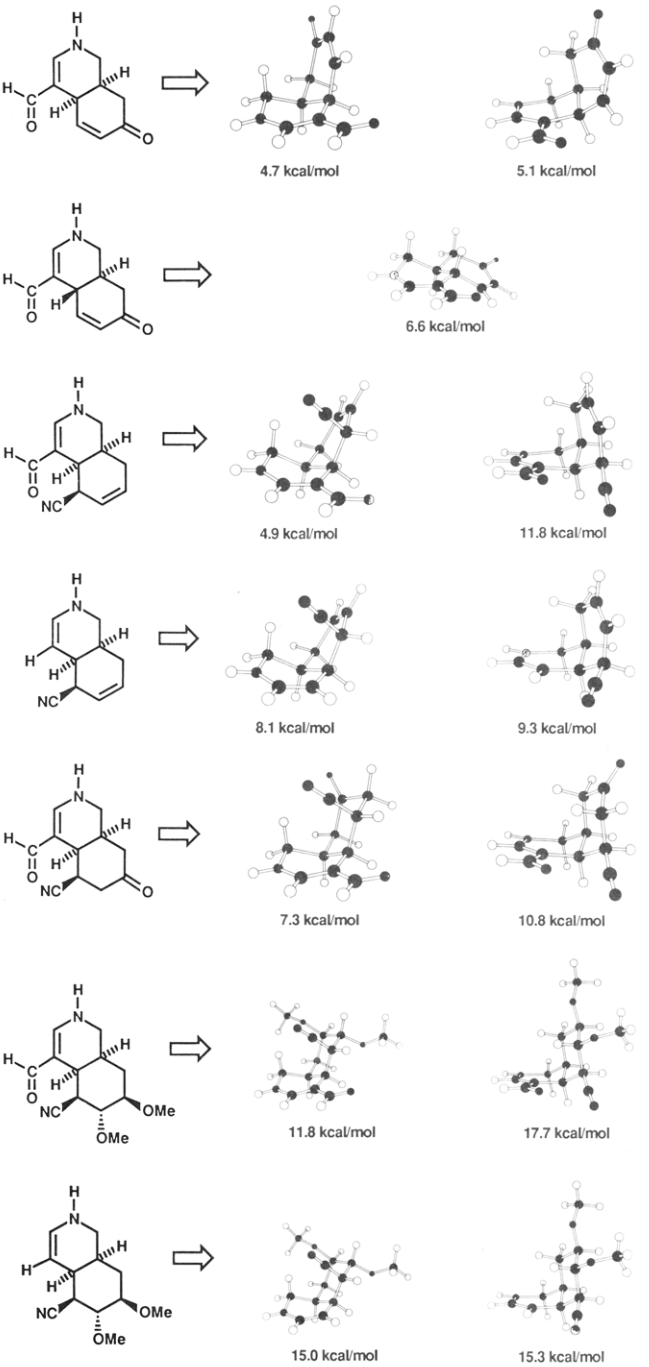
Zwitterionic amino-Claisen rearrangement of the isoquinuclidene 7-ketal **36** is a much more favorable process. Accordingly, reaction of **36** with methyl propiolate followed by allylic ketal deblocking with aqueous HOAc leads to production of the hydroisoquinoline enone **59** in a 63% yield. While it is difficult to rationalize the variable efficiencies of these amino-Claisen rearrangement reactions as well as those listed in Scheme VII, the transformation of **36** to **59** models an efficient method for generation of potentially useful intermediates in a reserpine synthetic sequence following the strategy outlined in Scheme II.

Strategy for Reserpine E Ring Functionality Introduction. The final feature addressed in these preliminary studies involves the development of methods for the stereocontrolled introduction of E-ring functionality. Our plan for this purpose (Scheme X) was to use conjugate addition reactions of alkoxycarbonyl anion equivalents to cis-fused enones related to **7** followed by trapping in a formal sense of the enolate anion generated in this way by an alkoxy cation equivalent. Reduction of the resulting ketone function either simultaneous with or subsequent to this chemistry would then introduce the last of the three adjacent functionalized centers at C-16, C-17, and C-18 of reserpine.

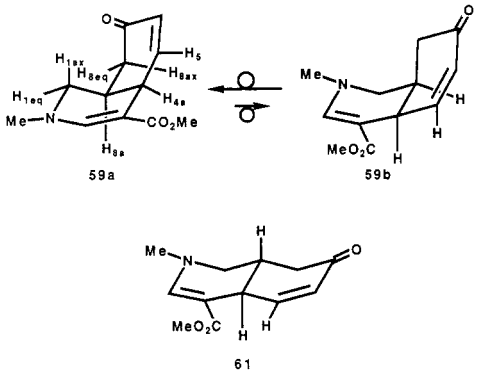
Although several procedures for execution of this strategy were considered initially, the route involving enone cyano-silylation followed by hydroboration–oxidation of a regioselectively formed silyl enol ether appeared to be the most attractive.[13] Implementation of this chemistry is dependent upon the ability to control the relative stereochemistry at the five contiguous centers in the nonheterocyclic ring of the resulting functionalized hydroisoquinoline. With this issue in mind and driven by the desire to test this methodology, we have conducted model studies with the hydroisoquinoline enone **59**.

The presence of cis-ring fusion stereochemistry in **59** is a consequence of its mode of formation, by the zwitterionic amino-Claisen rearrangement process.[1] However, unlike in the examples previously investigated, **59** contains a potentially acidic γ-enone proton at C-4a (hydroisoquinoline numbering). Thus, it was first necessary to show that epimerization at this center to produce the trans-fused hydroisoquinoline **61** had not occurred under the rearrangement conditions. The ^{1}H NMR spectroscopic data for **59** are sufficient for this purpose. The coupling patterns and magnitudes for H_8, H_5, and H_1 (e.g., J(8eq–8a), J(8ax–8a), J(5–4a), and J(1eq–8a) of 2.1–5.6 Hz and J(1ax–8a) of 11.8 Hz) are consistent with the existence of **59** as a cis-fused hydroisoquinoline possessing a conformation (**59a**) in which the C-4a–C-5 bond is axial with respect to the tetrahydronicotinate ring. The preference for conformer **59a** over **59b** of the cis-fused system is confirmed by molecular mechanics calculations (Macromodel, MM2) on simple model enones (Table I). The

Table I. Energies (Macromodel) and Drawings (Chem-3D) of Minimized Conformations of Model Hydroisoquinolines



(13) (a) Hydroboration–oxidation of a silyl enol ether (ref 13b) has been used seriously in a relatively distant model study for reserpine synthesis (ref 13c). (b) Larsen, G. L.; Hernandez, D.; Hernandez, A. *J. Organomet. Chem.* **1974**, *76*, 9. Larsen, G. L.; Prieto, J. A. *Tetrahedron* **1983**, *39*, 855. (c) Jung, M. E.; Light, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7614.



59a 59b

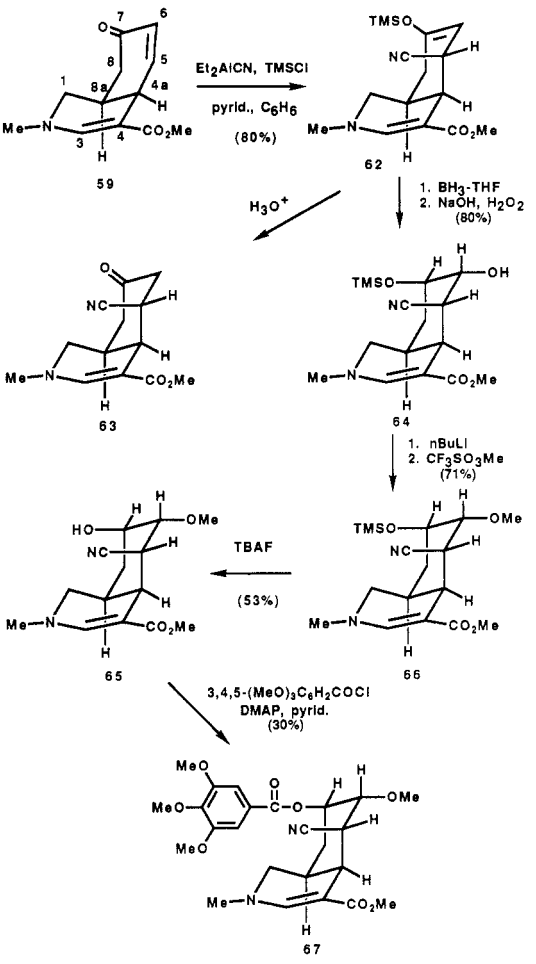
61

calculations also show that the *trans*-hydroisoquinoline stereoisomer **61** would be of higher energy than **59**, thus making epimerization at C-4a in **59a** a thermodynamically unfavorable process. These configurational and conformational preferences were predicted on the basis of our earlier studies in this area,[10] which had shown that conformers such as **59b** and isomers such as **61** suffer from severe $A^{1,2}$ strain[14] existing between the tetrahydronicotinate methoxcarbonyl and equatorial carbocyclic C-5 appendages.

Conjugate addition of cyanide to the cyclohexenone moiety of **59** under conditions of kinetic control should display a stereoelectronic preference for axial addition. Although this requires attack of cyanide from the concave face of conformer **59a**, this direction of approach is not greatly hindered since the C-3 and C-4 carbons are sp^2-hybridized. This evaluation appears to be correct, since in the event silyl-cyanation of **59** conducted under kinetically controlled conditions[15,16] (Et_2AlCN, TMSCl) gives the cyano enol ether **62** as a mixture of C-5 isomers in a ratio of 6:1 favoring the β-cyano epimer (Scheme XI). Stereochemical analysis of the major adduct is more readily performed with the derived ketone **63** formed upon alumina chromatography or aqueous HOAc treatment of **62**. The ^1H NMR data clearly show that **63** and thus **62** are cis-fused hydroisoquinolines having the conformations depicted with angular CN groups. Central to this analysis are the vicinal proton coupling constants, which are large for the pair H_{1ax}/H_{8a} (13.3 Hz) and small for the pair H_{6ax}/H_{5eq} (7.2 Hz). An interesting feature of this stereochemical analysis is the preference in **65** (and **64**) for a conformation having the axial CN function, a feature that is predicted by molecular mechanics methods (Table I). Here, as in the case of enone **61** and other hydroisoquinolines in this series, the severe $A^{1,2}$ strain existing between the tetrahydronicotinate methoxycarbonyl and carbocyclic C-5 substituent prevents adoption of the alternative equatorial CN conformation.

An interesting aspect of the silyl-cyanation process is that it provides the silyl enol ether function in a highly regioselective fashion. This is capitalized upon in the next step, which involves a regio- and stereocontrolled hydroboration–oxidation sequence. Accordingly, treatment of **62** with BH_3/THF followed by reaction with $NaOH/H_2O_2$ provides the selectively TMS protected cyano diol **64**, a product arising by borane delivery from the convex (anti to cyano) face of the bicyclic olefin structure.

Scheme XI



In order to complete this model sequence, the cyano silyl ether **64** was transformed consecutively into the C-6 methyl ether **66**, deblocked alcohol **65**, and C-7 ester **67** (Scheme XI). The chemistry employed in these as well as in the preceding steps appears fully compatible with its proposed applications to a complex yohimbane synthesis route.

Stereochemical Considerations. An intriguing feature of the chemistry outlined above concerns the conformational preferences displayed by hydroisoquinolines **62–67**. As ^1H NMR analyses clearly demonstrate, all of these substances appear to exist in conformations in which the C-5 carbon appended to the tetrahydronicotinate ring is axial. This is exemplified by the spectrum of benzoate **67** where the coupling constants for the proton pairs H_{8ax}/H_7, H_7/H_6, H_6/H_5, and H_5/H_{4a} fall in the region of 1.8–5.2 Hz, indicating that H_5, H_6, and H_7 are all equatorial. This is true despite the obvious large repulsive interactions that exist between the carbocyclic ring axial substituents in these materials. Macromodel energy calculations (MM2) on model systems closely related to these hydroisoquinolines show that the observed conformational preferences are reasonable. As shown in Table I, simplified hydroisoquinolines containing the structurally less complex s-trans enamino aldehyde function along with other group replacements that minimize the number of acyclic units were used for these calculations. In each case, the results indicate a preference for a conformation with the C-5 carbon axial to the hydronicotinate ring. This matches the preferences observed by ^1H NMR methods. While in a number cases twist-boat conformers were also found to be lower in energy than the C-5 equatorial conformers, none

(14) Johnson, F. L. *Chem. Rev.* **1968**, *68*, 375.

(15) (a) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, 3389. (b) Utimoto, K.; Wakabayashi, Y.; Inoue, M.; Horiie, T.; Shishiyama, Y.; Obayashi, M.; Nozaki, M. *Tetrahedron* **1983**, *39*, 967. (c) Samson, M.; Vandewalle, M. *Synth. Commun.* **1978**, *8*, 231.

(16) Attempts to bring about cyano-silylation of this enone under alternate conditions (such as with the use of TMSCN (ref 15a,b) led to mixtures of 1,4- and 1,2-adducts which favored the latter for longer time reactions.

of them were more stable than the C-5 axial conformers.

It is perhaps easy to rationalize the conformational preferences in the hydroisoquinolines **59**, **62**, and **63** where arrays of sp^2-hybridized centers and a linear cyano group should minimize the energetic consequences of 1,3-diaxial interactions. All of these features are not present in **64–67**, yet the calculations and NMR measurements still demonstrate a large preference for conformers in which the three B-ring substituents are axial. It appears that the major factor contributing to this is $A^{1,2}$ strain since the energetic preferences between conformers decrease upon replacement of the C-4 aldehyde function by a hydrogen (see Table I).

Summary. The studies outlined above have demonstrated the potential application of the zwitterionic amino-Claisen rearrangement process for generation of intermediates which find utility in synthetic approaches to members of the yohimbane alkaloid families. Specifically, methods for generation of 7-ketoisoquinuclidenes have been developed. Along the way a novel rearrangement reaction of a 7-acetylisoquinuclidene lacking electron withdrawing group substitution at C-6 has been uncovered. In addition, a probe of the zwitterionic amino-Claisen rearrangement reactions of a series of substituted isoquinuclidenes has pointed out the limitations of this process and has disclosed its application in a route for preparation of a cis-fused hydroisoquinoline containing an enone moiety in the carbocyclic ring. This functionality serves as a useful handle for stereoselective introduction of the type of functionality found in the reserpine E ring. As such these exploratory studies have served to model a novel and potentially efficient approach for synthesis of the alkaloid. Finally, interesting conformational preferences have been observed for the substituted hydroisoquinolines **64–67**.

Experimental Section

General. ^1H NMR spectra were recorded in $CDCl_3$ solutions at 200 or 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 50 MHz. Resonances are assigned on the basis of INEPT results. Column chromatography was performed with Florisil (100–200 mesh), Alcoa type F-20 alumina (80–200 mesh), (flash) Woelm N 32-63 alumina (170–230 mesh), or silica gel 60 (230–400 mesh). Preparative thin-layer chromatography was performed by using silica gel (type 60 GF 254) plates. All reactions were carried out under a N_2 atmosphere. The purities of all new compounds prepared in this study were judged to be >90% by ^1H and ^{13}C NMR and chromatographic methods.

2-[*N*-(Phenylsulfonyl)tryptophyl]-7-*endo*-[1,1-(ethylenedioxy)ethyl]isoquinuclidene (15). To a solution of the *N*-tryptophylisoquinuclidene **14**[1] (1.33 g, 3.93 mmol) in THF (13 mL) at −78 °C was slowly added *n*-BuLi (2.1 mL of 1.6 M in hexane). When addition was complete, the reaction mixture was allowed to warm to 0 °C for 0.5 h and then cooled to −78 °C. Benzenesulfonyl chloride (2.78 g, 15.7 mmol) was added, and the reaction mixture was stirred at 25 °C for 12 h, poured into brine, and extracted with $CHCl_3$. The organic extracts were combined, washed twice with water, dried, and concentrated in vacuo to give a residue, which was subjected to chromatography on Florisil ($CHCl_3$ to 2% MeOH/$CHCl_3$) to yield 1.39 g (74%) of the blocked *N*-tryptophylisoquinuclidene **15** as a yellow oil: ^1H NMR 1.13 (s, 3 H, CH_3), 1.13–1.24 (m, 1 H, H-8 endo), 1.92–1.98 (m, 1 H, H-8 exo), 2.25–2.37 (m, 1 H, H-3 endo), 2.79–3.45 (m, 7 H, H-3 exo, H-7, H-4, CH_2CH_2N), 3.92 (br s, 4 H, OCH_2CH_2O), 4.12 (br s, 1 H, H-1), 6.19 (t, J = 6.8 Hz, 1 H, H-6), 6.57 (t, J = 7.4 Hz, 1 H, H-5), 7.22–7.99 (m, 10 H, aromatic); ^{13}C NMR 22.4 (CH_3), 27.3 (C-8), 31.1 (C-4), 23.8, 56.8 (β-indolyl-CH_2CH_2N), 46.0 (C-7), 53.3 (C-3), 53.6 (C-1), 64.3, 64.5 (OCH_2CH_2O), 110.6 (OCO), 131.0, 132.1 (C-5, C-6), 113.6, 119.5, 121.2, 122.9, 123.0, 124.6, 126.6, 129.0, 131.0, 133.5, 135.1, 138.2 (indole ring and aromatic); IR ($CHCl_3$) 1580 cm^{-1} (w); mass spectrum, m/e (relative intensity) 223 (7), 209 (13), 208 (100), 87 (92); high-resolution mass spectrum, m/e 478.1926 ($C_{27}H_{30}O_4N_2S$ requires 478.1926).

2-[*N*-(Phenylsulfonyl)tryptophyl]-7-*endo*-acetylisoquinuclidene (16). To a suspension of silica gel (7.67 g, silica gel 60, Merck, 230–400 mesh) in CH_2Cl_2 (20 mL) was added 10% H_2SO_4 (0.77 g). After 5 min, the isoquinuclidene ketal **15** (639 mg) was added and the resulting mixture was stirred at 25 °C for 40 h, diluted with 10% MeOH/$CHCl_3$, neutralized with saturated $NaHCO_3$ solution, and filtered. The filtrate was dried and concentrated in vacuo to give 7-acetylisoquinuclidene **16** (574 mg, 94%) as an oil: ^1H NMR 1.66–1.77 (m, 2 H, H-8), 2.00–2.13 (m, 1 H, H-3 endo), 2.09 (s, 3 H, CH_3), 2.46–2.70 (m, 2 H, CH_2CH_2N), 2.73–2.95 (m, 3 H, CH_2CH_2N, H-4), 3.02 (d, J = 6.7 Hz, 1 H, H-3 exo), 3.07–3.20 (m, 1 H, H-7), 3.73–3.83 (m, 1 H, H-1), 6.13 (t, J = 5.3 Hz, 1 H, H-6), 6.37 (t, J = 6.7 Hz, H-5), 7.17–8.00 (m, 10 H, aromatic); ^{13}C NMR 24.1, 57.3 (β-indolyl-CH_2CH_2N), 25.2 (C-8), 28.2 (CH_3), 30.8 (C-4), 52.7 (C-7), 54.2 (C-3), 54.5 (C-1), 129.3 (C-6), 134.3 (C-5), 113.6 119.4, 121.4, 122.8, 123.0, 124.6, 126.5, 129.0, 131.0, 133.5, 135.1, 138.2 (indole ring and aromatic), 207.9 (C=O); IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 434 (P), 373, 361, 311, 282, 276, 223, 171, 144; high-resolution mass spectrum, m/e 434.1763 ($C_{25}H_{26}N_2O_3S$ requires 434.1625).

8-[*N*-(Phenylsulfonyl)tryptophyl]-8-aza-4-acetyl-4-hydroxybicyclo[4.2.0]oct-2-ene (17). A solution of potassium *tert*-butoxide (310 mg, 2.77 mmol) in *tert*-butyl alcohol (1.85 mL) was mixed with triethyl phosphite (74 mg, 0.44 mmol) in monoglyme (0.6 mL) and cooled to −20 °C (dry ice/CCl_4 bath). The 7-acetylisoquinuclidene **16** (120 mg, 0.28 mmol) in CH_2Cl_2 (0.9 mL) was added, and dry O_2 was bubbled through the stirred reaction mixture for 3 h at −20 °C. Acetic acid (0.18 mL) was added to the reaction mixture, and the resulting solution was concentrated in vacuo. The pale yellow concentrate was suspended in cold 6 N sulfuric acid and then washed with benzene. The aqueous acid layer was made alkaline with saturated Na_2CO_3 solution and extracted with $CHCl_3$. The $CHCl_3$ layers were washed with brine, dried, and concentrated in vacuo to give the bicyclic azetidine **17** (99 mg, 79%) as a yellow oil: ^1H NMR 1.15–1.38 (m, 2 H, H-5), 1.91 (dt, J = 9.2, 2.3 Hz, 1 H, H-7 ax or H-7 eq) 2.22 (s, 3 H, CH_3), 2.31–2.92 (m, 6 H, indolyl-CH_2CH_2N, H-6, OH), 3.06 (dd, J = 9.2, 2.2 Hz, 1 H, H-7 ax or H-7 eq), 3.43 (dd, J = 5.3, 1.2 Hz, 1 H, H-1), 6.27 (ddd, J = 8.0, 5.3, 1.3 Hz, 1 H, H-3 or H-2), 6.61 (t, J = 6.9 Hz, 1 H, H-3 or H-2), 7.2–7.9 (m, 10 H, aromatic); ^{13}C NMR 24.6 (C-6), 23.7, 56.6 (indolyl-CH_2CH_2N), 31.6 (CH_3), 35.2 (C-7), 52.1 (C-5), 60.4 (C-1), 81.4 (C-4), 128.4 (C-2), 134.9 (C-3), 113.4, 119.2, 121.1, 122.7, 122.9, 124.5, 126.4, 126.5, 129.0, 130.8, 133.5, 135.4, 138.1 (indole ring and aromatic), 210.8 (C=O); IR ($CHCl_3$) 3420 (br), 1715, 1690 cm^{-1}; mass spectrum, m/e 450 (P), 432, 406, 377, 363, 340, 312, 309, 283, 282, 269, 223; high-resolution mass spectrum, m/e 450.1585 ($C_{25}H_{26}O_4N_2S$ requires 450.1613).

8-[*N*-(Phenylsulfonyl)tryptophyl]-8-aza-4-(1′-hydroxyethyl)-4-hydroxybicyclo[4.2.0]oct-2-ene (18). To a solution of hydroxy ketone **17** (95 mg, 0.21 mmol) in methanol (3.8 mL) at 0 °C was added $NaBH_4$ (23.9 mg, 0.63 mmol). After stirring at 0 °C for 1 h, the reaction mixture was poured into brine and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo to give a residue, which was subjected to chromatography on Florisil ($CHCl_3$) to give 73 mg (76%) of a diastereomeric mixture of diols **18**: ^1H NMR 1.15 (d, J = 6.2 Hz, 3 H, CH_3), 1.25–1.37 (m, 2 H, H-5), 1.47 (br s, 1 H, OH), 1.87 (br d, J = 7.1 Hz, 1 H, H-7 ax or eq), 2.16 (dd, J = 13.7, 1.9 Hz, 1 H, H-6), 2.51–2.93 (m, 5 H, indolyl-CH_2CH_2N, OH), 3.07 (dd, J = 9.2, 2.3 Hz, 1 H, H-7 ax or eq), 3.54 (d, J = 5.2 Hz, 1 H, H-1), 3.95 (q, J = 6.2 Hz, 1 H, $HC(OH)CH_3$), 6.25 (dd, J = 8.0, 5.3 Hz, 1 H, H-2), 6.69 (t, J = 7.2 Hz, 1 H, H-3), 7.19–7.97 (m, 10 H, aromatic); ^{13}C NMR 17.3 (CCH_3), 23.7, 56.6 (β-indolyl-CH_2CH_2N), 31.7 (C-6), 32.9 (C-7), 53.2 (C-5), 64.1 (C-1), 74.0 ($HC(OH)CH_3$), 75.2 (C-4), 128.2 (C-2), 137.1 (C-3), 118.5, 119.1, 120.2, 122.7, 123.0, 124.6, 126.6, 129.0, 130.5, 133.6, 135.0, 138.0 (indole ring and aromatic); IR ($CHCl_3$) 3580 (s), 3340–3460 (s) cm^{-1}; mass spectrum, m/e 452 (P), 313, 284, 270, 223; high-resolution mass spectrum, m/e 452.1752 ($C_{25}H_{28}N_2O_4S$ requires 452.1769).

8-[*N*-(Phenylsulfonyl)tryptophyl]-8-azabicyclo[4.2.0]oct-2-en-4-one (19). A solution of diol **18** (78 mg, 0.17 mmol) in 1.2 mL of methanol at 0 °C was treated with a 0 °C solution of 56 mg of sodium periodate in 0.3 mL of water. A white precipitate formed immediately. After 5 min, 0.66 mL of ice water

was added. After stirring for 15 min at 0 °C and for 24 h at 25 °C, the reaction mixture was diluted with saturated aqueous Na_2CO_3 and extracted with chloroform. The $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated in vacuo, giving 70 mg of a residue, which was subjected to preparative TLC (1% MeOH/$CHCl_3$), yielding 37 mg (53%) of enone **19** as a yellow oil: ^{1}H NMR 2.54–3.42 (m, 9 H, H-6, H-7, β-indolyl-CH_2CH_2N, H-5), 4.78 (d, J = 4.4 Hz, 1 H, H-1), 6.10 (d, J = 10.3 Hz, 1 H, H-3), 6.78 (dd, J = 10.4, 3.2 Hz, 1 H, H-2), 7.20–8.00 (m, 10 H, aromatic); ^{13}C NMR 23.7, 59.0 (β-indolyl-CH_2CH_2N), 37.4 (C-7), 39.6 (C-6), 60.5 (C-5), 71.7 (C-1), 130.8, (C-3), 145.8 (C-2), 113.7, 119.4, 120.6, 123.1, 124.7, 126.6, 129.2, 130.9, 133.7, 135.2, 138.3 (indole ring and aromatic), 196.9 (C=O); IR ($CHCl_3$) 1685 cm^{-1}; mass spectrum, m/e (relative intensity) 283 (6), 271 (2), 270 (4), 141 (3), 94 (61), and recovered starting material 22.9 mg (30%).

2-Benzyl-6-carbomethoxy-7-*endo*- and -*exo*-[1,1-(ethylenedioxy)ethyl]isoquinuclidene (22). A solution of 437 mg (2.55 mmol) of benzyl bromide in 1.0 mL of dry acetonitrile was added to 642 mg (2.54 mmol) of 6-carbomethoxy-7-*exo*- and -*endo*-[1,1-(ethylenedioxy)ethyl]isoquinuclidene (**21**)[1] and 642 mg (7.60 mmol) of sodium bicarbonate in 1.7 mL of dry acetonitrile and stirred at 60 °C for 2 h. The mixture was poured into water and extracted with chloroform. The combined extracts were washed with water, dried, and concentrated in vacuo, giving a brown oil, which was purified by silica gel chromatography (8:1 hexanes/ethyl acetate), yielding 559 mg (64%) of the *N*-benzylisoquinuclidene **22** as a yellow oil.

Endo epimer: ^{1}H NMR 1.10–1.26 (m, 1 H, H-8 endo), 1.76 (dd, J = 9.7, 3.0 Hz, 1 H, H-8 exo), 1.88 (dt, J = 10.7, 2.6 Hz, 1 H, H-3 endo), 2.59–2.68 (m, 2 H, H-4, H-7), 2.88 (dd; J = 10.5, 1.5 Hz, 1 H, H-3 exo), 3.48 (AB quartet, 2 H, benzylic), 3.76 (s, 3 H, OCH_3), 3.80–3.94 (m, 4 H, OCH_2CH_2O), 4.18 (t, J = 1.8 Hz, 1 H, H-1), 7.16–7.30 (br s, 5 H, aromatic), 7.36 (dd, J = 7.0, 1.4 Hz, 1 H, H-5); ^{13}C NMR 22.1 (CH_3), 26.8 (C-8), 32.1 (C-4), 47.2 (C-7), 51.4 (OCH_3), 52.4 (C-3), 53.2 (C-1), 61.2 (benzylic), 64.2, 64.7 (OCH_2CH_2O), 110.2 (OCO), 126.7, 128.1, 128.7, 135.0 (aromatic), 139.5 (C-6), 141.6 (C-5), 165.6 (C-O); IR ($CHCl_3$) 1700, 1620, 1250, 1080 cm^{-1}; mass spectrum, m/e (relative intensity) 343 (P, 2), 229 (69), 228 (63), 138 (34), 92 (23), 91 (100); high-resolution mass spectrum, m/e 343.1793 ($C_{20}H_{25}NO_4$ requires 343.1783).

Exo epimer: ^{1}H NMR 1.44 (m, 2 H, H-8), 1.52 (s, 3 H, CH_3), 1.68 (td, J = 5.5, 1.8 Hz, 1 H, H-7), 1.77 (d, J = 9.9 Hz, 1 H, H-3 endo), 2.69 (m, 1 H, H-4), 2.98 (dd, J = 10.0, 2.1 Hz, 1 H, H-3 exo), 3.44 (AB quartet, 2 H, benzylic), 3.79 (s, 3 H, OCH_3), 3.96 (m, 4 H, OCH_2CH_2O), 4.17 (t, J = 1.8 Hz, 1 H, H-1), 7.23 (br s, 5 H, aromatic), 7.37 (dd, J = 6.7, 1.6 Hz, 1 H, H-5); ^{13}C NMR 22.1 (CH_3), 23.6 (C-8), 32.3 (C-4), 47.1 (C-7), 51.6 (OCH_3), 53.7 (C-1), 54.1 (C-3), 62.1 (benzylic), 64.5, 64.9 (OCH_2CH_2O), 111.3 (OCO), 126.7, 128.0, 128.8, 136.6 (aromatic), 139.3 (C-6), 143.2 (C-5), 165.1 (C=O); IR ($CHCl_3$) 1700, 1610, 1250, 1070 cm^{-1}; mass spectrum, m/e (relative intensity) 343 (P, 1), 229 (23), 228 (68), 138 (16), 91 (100); high-resolution mass spectrum, m/e 343.1779 ($C_{20}H_{25}NO_4$ requires 343.1783).

2-Benzyl-6-carbomethoxy-7-acetylisoquinuclidene (23). A solution containing 369 mg (1.07 mmol) of the isoquinuclidine **22** (mixture of exo and endo isomers) in 1.4 mL of 1:1 10% hydrochloric acid/tetrahydrofuran was stirred for 24 h at 25 °C. The resulting yellow solution was neutralized with saturated aqueous sodium bicarbonate and extracted with chloroform. The combined extracts were dried and concentrated in vacuo, giving a tan solid, which was purified by Florisil chromatography (1:1 hexanes/ethyl acetate), yielding 200 mg (62%) of the 7-acetylisoquinuclidene **23** as a white solid (mp 112.5–114 °C, hexane): ^{1}H NMR 1.58–1.84 (m, 2 H, H-8), 1.90 (dt, J = 10.1, 2.5 Hz, 1 H, H-3 endo), 2.13 (s, 3 H, CH_3), 2.72–2.81 (m, 1 H, H-4), 2.98 (dd, J = 10.0, 2.0 Hz, 1 H, H-3 exo), 3.26–3.32 (m, 1 H, H-7), 3.51 (AB quartet, 2 H, benzylic), 4.38 (dd, J = 2.8, 1.8 Hz, 1 H, H-1), 7.26 (br s, 5 H, aromatic), 7.40 (dd, J = 7.0, 1.6 Hz, 1 H, H-5); ^{13}C NMR 23.9 (C-8), 28.5 (CH_3), 31.9 (C-4), 51.6 (OCH_3), 52.8 (C-7), 53.5 (C-3), 53.9 (C-1), 61.5 (benzylic), 127.0, 128.2, 128.7, 132.9 (aromatic), 139.0 (C-6), 144.1 (C-5), 164.9 (C=O ester), 207.1 (C=O ketone); IR ($CHCl_3$) 1700, 1200, 1080 cm^{-1}; mass spectrum, m/e (relative intensity) 299 (P, 1), 268 (2), 229 (44), 228 (47), 198 (2), 138 (22), 91 (100); high-resolution mass spectrum, m/e 299.1507 ($C_{18}H_{21}NO_3$ requires 299.1521).

2-Benzyl-6-carbomethoxy-7-acetyl-7-hydroxyisoquinuclidene (24). A solution of 498 mg (4.44 mmol) of potassium *tert*-butoxide in 3.0 mL of *tert*-butyl alcohol was combined with 120 mL (0.72 mmol) of triethylphosphite in 960 mL of 1,2-dimethoxyethane and cooled to −20 °C. To this mixture was added 135 mg (0.045 mmol) of the 7-acetylisoquinuclidene **23**, and the mixture was stirred at −20 °C under a stream of dry oxygen for 1.5 h. The resulting yellow solution was poured into cold 5% hydrochloric acid and washed with benzene. The aqueous layer was made basic (pH 11) with saturated aqueous sodium bicarbonate and extracted with chloroform. The combined organic extracts were dried and concentrated in vacuo, giving an orange oil, which was subjected to preparative TLC (1:1 hexanes/ethyl acetate), yielding 47 mg (33%) of the 7-hydroxyisoquinuclidene **24** as a yellow oil: ^{1}H NMR 1.21 (ddd, J = 13.9, 2.9, 2.4 Hz, 1 H, H-8 endo), 1.84 (ddd, J = 9.9, 2.4, 1.9 Hz, 1 H, H-3 endo), 2.37 (s, 3 H, CH_3), 2.51 (dd, J = 13.9, 2.4 Hz, 1 H, H-8 exo), 2.89 (m, 1 H, H-4), 3.00 (dd, J = 9.9, 2.2 Hz, 1 H, H-3 exo), 3.1 (s, 1 H, OH), 3.43 (AB quartet, 2 H, benzylic), 3.81 (s, 3 H, OCH_3), 4.06 (d, J = 1.5 Hz, 1 H, H-1), 7.26 (br s, 5 H, aromatic), 7.57 (dd, J = 6.8, 1.5 Hz, 1 H, H-5); ^{13}C NMR 25.1 (C-4), 32.2 (CH_3), 34.7 (C-8), 51.8 (OCH_3), 51.8 (C-3), 59.2 (C-1), 61.0 (benzylic), 81.3 (C-7), 127.2, 128.3, 129.0, 132.9 (aromatic), 138.3 (C-6), 144.1 (C-5), 165.4 (C=O ester), 210.1 (C=O ketone); IR ($CHCl_3$) 3400, 1700, 1250, 1090 cm^{-1}; mass spectrum, m/e (relative intensity) 315 (P, 4), 284 (7), 272 (4), 242 (9), 228 (28), 138 (11), 91 (100); high-resolution mass spectrum, m/e 315.1470 ($C_{18}H_{21}NO_4$ requires 315.1470).

1-Carbethoxy-7-acetoxy-7-cyanoisoquinuclidene (32). A mixture of 1-carbethoxy-1,2-dihydropyridine[6] (15.0 g, 0.0981 mol) and 1-cyanovinyl acetate (16.3 g, 0.147 mol) was heated at 100 °C for 2.5 days. After cooling, the crude reaction mixture was diluted with chloroform and passed through a short Florisil column (4:1 hexanes/ethyl acetate). Repurification using Florisil (2:1 hexanes/ethyl acetate) afforded 7.47 g (30%) of the blocked isoquinuclidene **32** as a C-7 epimeric mixture. The epimers could be separated chromatographically. The less polar epimer (7-*endo*-cyano, 7-*exo*-acetoxy) was isolated as an oil: ^{1}H NMR 1.19 (m, J = 7.1 Hz, 3 H, CH_3), 1.80 (m, J = 14.4 Hz, 1 H, H-8 exo), 2.03 (s, 3 H, $COCH_3$), 2.30 (dt, J = 13.7, 3.1 Hz, 1 H, H-8 endo), 2.86 (br m, 1 H, H-4), 2.94 (dq, J = 10.2, 2.4 Hz, 1 H, H-3 endo), 3.34 (dt, J = 10.2, 2.6 Hz, 1 H, H-3 exo), 4.07 (m, J = 7.1 Hz, 2 H, OCH_2), 5.25 (d, J = 6.3 Hz, 0.5 H, H-1), 5.32 (d, J = 6.3 Hz, 0.5 H, 1 H, H-6), 6.42 (m, J = 6.7, 6.3, 1.5 Hz, 1 H, H-6), 6.61 (q, J = 6.7 Hz, 1 H, H-5); ^{13}C NMR 14.5 (CH_3), 20.6 (O_2CCH_3), 29.8/30.0 (C-4), 37.1 (C-8), 46.5 (C-3), 50.1/50.6 (C-1), 61.5 (OCH_2), 72.3 (C-7), 117.8 (C=N), 128.4/128.8 (C-6), 137.1/137.6 (C-5), 155.1/156.0 (C=O (carbamate)), 168.7 (C=O (ester)); IR ($CHCl_3$) 1753, 1690, 1425 cm^{-1}; mass spectrum, m/e (relative intensity) 264 (P, 1), 221 (4), 153 (66), 124 (100); high-resolution mass spectrum, m/e 264.1101 ($C_{13}H_{16}N_2O_4$ requires 264.1110).

The more polar epimer (7-*endo*-acetoxy, 7-*exo*-cyano) was isolated as an oil: ^{1}H NMR 1.20 (t, J = 7.1 Hz, 1.5 H, CH_3), 1.26 (t, J = 7.1 Hz, 1.5 H, CH_3), 1.80 (dd, J = 14.6, 2.4 Hz, 1 H, H-8 exo), 2.01 (s, 1 H, O_2CCH_3), 2.47 (ddd, J = 14.8, 7.4, 2.0 Hz, 1 H, H-8 endo), 2.89 (br m, 1 H, H-4), 2.91 (dd, J = 9.9, 2.0 Hz, 1 H, H-3 endo), 3.34 (dd, J = 10.1, 2.1 (Hz, 1 H, H-3 exo), 4.11 (m, J = 7.1 Hz, 2 H, OCH_2), 5.29 (d, J = 6.0 Hz, 0.5 H, H-1), 5.32 (d, J = 6.0 Hz, 0.5 H, H-1), 6.25 (dd, J = 12.0, 8.0 Hz, 1 H, H-6), 6.54 (m, J = 12.0 Hz, 1 H, H-5); ^{13}C NMR 14.5 (CH_3), 20.6 (O_2CCH_3), 30.6 (C-4), 39.3 (C-8), 45.5 (C-3), 49.9 (C-1), 61.9 (OCH_2), 72.7 (C-7), 118.2 (C=N), 127.6/128.4 (C-6), 136.6 (C-5), 155.6 (C=O (carbamate)), 168.3 (C=O (ester)); IR ($CHCl_3$) 1751, 1695 cm^{-1}; mass spectrum, m/e (relative intensity) 264 (P, 1), 221 (6), 195 (1), 166 (1), 153 (100), 124 (68); high-resolution mass spectrum, m/e 264.1107 ($C_{13}H_{16}N_2O_4$ requires 264.1110).

1-Carbethoxy-7-ketoisoquinuclidene (33). A methanol (70 mL) solution of sodium methoxide (from 1.61 g, 7.0 mg-atoms, of sodium) was added to a flask containing the 7-acetoxy-7-cyanoisoquinuclidene **32** (9.2 g, 0.035 mol). The reaction mixture was stirred at 25 °C for 4 h, poured into ice water, and extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil, which was subjected to Florisil chromatography (2:1 hexanes/ethyl acetate) to yield the 7-ketoisoquinuclidene **33** (74%) as an oil: ^{1}H NMR 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 2.18 (dd, J = 2.7, 0.9 Hz, 2 H, H-8), 3.16 (br m, J = 9.2 Hz, 2 H, H-3 endo, H-4), 3.46 (m,

J = 9.8 Hz, 1 H, H-3 exo), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.85 (m, 0.5 H, H-1), 4.97 (m, 0.5 H, H-1), 6.40 (t, J = 6.6 Hz, 1 H, H-6), 6.64 (t, J = 6.7 Hz, 1 H, H-5); ^{13}C NMR 14.6 (CH_3), 32.3 (C-4), 36.6 (C-8), 46.4 (C-3), 57.6 (C-1), 61.7 (OCH_2CH_3), 128.3 (C-6), 139.5 (C-5), 155.1 (C=O (carbamate)), 202.6 (C=O (ketone)); IR ($CHCl_3$) 1730, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 195 (P, 2), 167 (23), 153 (42), 138 (38), 124 (35), 108 (100), 94 (79); high-resolution mass spectrum, m/e 195.0886 ($C_{10}H_{13}NO_3$ requires 195.0895).

1-Carbethoxy-7,7-diethoxyisoquinuclidene (34). A mixture of the 7-ketoisoquinuclidine **33** (4.90 g, 0.0251 mol), ethanol (12.7 g, 0.276 mol), triethyl orthoformate (38.7 g, 0.261 mol), and *p*-toluenesulfonic acid (0.478 g, 0.252 mol) was stirred at 70 °C for 24 h. After cooling, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, and concentrated to give an oil, which was subjected to Florisil chromatography (4:1 hexanes/ethyl acetate), to afford 6.20 g (92%e of the ketal **34** as an oil: ^1H NMR 1.11 (t, J = 7.1 Hz, 6 H, 7-OCH_2CH_3), 1.22 (td, J = 7.1, 2.3 Hz, 3 H, ($O_2CH_2CH_3$), 1.56 (ddd, J = 13.0, 5.5, 2.6 Hz, 1 H, H-8 exo), 1.72 (ddd, J = 13.0, 5.7, 3.2 Hz, 1 H, H-8 endo), 2.74 (br m, 1 H, H-4), 2.97 (tt, J = 8.6, 2.5 Hz, 1 H, H-3 endo), 3.26 (dd, J = 10.1, 2.0 Hz, 1 H, H-3 exo), 3.34–3.67 (m, 4 H, 7-OCH_2CH_3), 4.09 (qd, J = 7.1, 1.1 Hz, 1 H, $CO_2CH_2CH_3$), 4.10 (m, 1 H, $O_2CH_2CH_3$), 4.70 (dd, J = 3.71, 3.70 Hz, 0.55 H, H-1), 4.85 (dd, J = 5.8, 1.6 Hz, 0.45 H, H-1), 6.35 (br m, 2 H, H-5, H-6); ^{13}C NMR 14.8 (CH_3), 15.2 (CH_3(2)), 31.3/31.6 (C-4), 36.6/36.8 (C-8), 45.9/46.2 (C-3), 50.3/51.0 (C-1), 55.6 (7-OCH_2CH_3), 5.65/5.67 (7-OCH_2CH_3), 60.9 ($O_2CH_2CH_3$), 104.7/104.8 (C-7), 131.1/131.8 (C-5 or C-6), 133.4/134.0 (C-5 or C-6), 155.3/155.7 (C=O); IR ($CHCl_3$), 1665 cm^{-1}; mass spectrum, m/e (relative intensity) 269 (P, 1), 224 (6), 166 (5), 153 (91), 124 (100), 108 (17), 94 (36); high-resolution mass spectrum, m/e 269.1624 ($C_{14}H_{23}NO_4$ requires 269.1627).

1-Methyl-7-*endo*-hydroxyisoquinuclidene (35). To a solution of the isoquinuclidene carbamate **33** (0.190 g, 0.974 mmol) in 31 mL of anhydrous ether was added $LiAlH_4$ (0.370 g, 9.4 mmol). The resulting suspension was stirred at 25 °C for 6 h. After cooling to 0 °C, the reaction was quenched with 20% aqueous NaOH (0.65 mL). After 5 min of stirring, the suspension was filtered through Celite. The filtrate was concentrated in vacuo to afford 0.135 g (87%) of the 7-*endo*-hydroxyisoquinuclidene **35** (with minor amounts of the exo isomer) as an oil: ^1H NMR 1.03 (ddd, J = 13.3, 5.5, 2.5 Hz, 1 H, H-3 exo), 1.64 (dt, J = 9.4, 2.4 Hz, 1 H, H-3 endo), 1.96 (ddd, J = 13.4, 8.2, 2.4 Hz, 1 H, H-3 endo), 2.20 (s, 3 H, NCH_3), 2.50 (br m, 1 H, H-4), 2.79 (br s, 1 H, OH), 2.84 (dd, J = 9.5, 2.3 Hz, 1 H, H-3 exo), 3.37 (ddd, J = 4.5, 4.5, 1.4 Hz, 1 H, H-1), 4.17 (m, 1 H, H-7), 6.12 (dd, J = 7.9, 5.2 Hz, 1 H, H-6), 6.54 (td, J = 7.4, 1.3 Hz, 1 H, H-5); ^{13}C NMR 31.5 (C-4), 35.5 (C-8), 44.3 (NCH_3), 54.4 (C-3), 59.8 (C-1), 69.4 (C-7), 127.9 (C-6), 136.3 (C-5); IR ($CHCl_3$) 3610 (sharp), 3580 (br).

1-Methyl-7,7-diethoxyisoquinuclidene (36). To a solution of $LiAlH_4$ (1.34 g, 0.035 mol) in 550 mL of anhydrous ether was added a solution of the carbamate **34** (6.00 g, 0.022 mol) in 110 mL of anhydrous ether. The reaction mixture was stirred at 25 °C for 6 h and then was cooled to 0 °C. After the dropwise addition of 20% aqueous NaOH solution (7.5 mL), the resulting suspension was filtered through Celite. Concentration of the filtrate in vacuo afforded 4.66 g (99%) of the 1-methylisoquinuclidene **36** as an oil: ^1H NMR 1.05 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.15 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.44 (ddd, J = 12.8, 3.5, 2.2 Hz, 1 H, H-8 endo), 1.54 (dd, J = 12.8, 2.5 Hz, 1 H, H-8 exo), 1.74 (dt, J = 9.4, 2.2 Hz, 1 H, H-3 endo), 2.20 (s, 3 H, NCH_3), 2.49 (br m, 1 H, H-4), 3.05 (dd, J = 9.3, 2.2 Hz, 1 H, H-3 exo), 3.28–3.52 (m, 3 H, OCH_2CH_3, H-1), 3.51 (br q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.14 (ddd, J = 7.8, 5.5, 1.5 Hz, 1 H, H-6), 6.31 (td, J = 7.2, 1.1 Hz, 1 H, H-5); ^{13}C NMR 15.1 (CH_2CH_3), 15.3 (CH_2CH_3), 31.7 (C-4), 35.3 (C-8), 44.4 (NCH_3), 54.9 (C-3), 55.4 (OCH_2CH_3), 60.0 (C-1), 105.5 (C-7), 129.5 (C-5 or C-6), 132.8 (C-5 or C-6); IR ($CHCl_3$) 1245 cm^{-1}; mass spectrum, m/e (relative intensity) 211 (P, 1), 182 (16), 166 (24), 123 (26), 108 (34), 95 (100); high-resolution mass spectrum, m/e 211.1567 ($C_{12}H_{21}NO_2$ requires 211.1572).

1-Methyl-7-*endo*-[(*tert*-butyldimethylsilyl)oxy]isoquinuclidene (37). In a flask containing 1.2 mL of DMF were combined *tert*-butyldimethylsilyl chloride (0.117 g, 0.777 mmol) and diisopropylethylamine (0.126 g, 0.971 mmol). This solution was stirred at 25 °C for 5 min and then was transferred to a flask containing the 7-hydroxyisoquinuclidene **35** (0.090 g, 0.648 mmol). Afterin stirring for 12 h at 25 °C, the mixture was cooled to 0 °C and water was added followed by ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with water, and dried (Na_2SO_4) and concentrated in vacuo to afford a residue, which was subjected to chromatographic separation on alumina, giving 0.125 g (77%) of the silyl ether **37** as a pale yellow oil: ^1H NMR 0.02 (s, 6 H, $Si(CH_3)_2$), 0.83 (s, 9 H $C(CH_3)_3$), 1.07 (ddd, J = 12.9, 5.7, 2.7 Hz, 1 H, H-8 exo), 1.66 (dt, J = 9.3, 2.4 Hz, 1 H, H-3 endo), 1.89 (ddd, J = 12.9, 8.0, 2.5 Hz, 1 H, H-8 endo), 2.23 (s, 3 H, NCH_3), 2.49 (br m, 1 H, H-4), 2.86 (dd, J = 9.3, 2.3 Hz, 1 H, H-3 exo), 3.25 (ddd, J = 4.5, 4.5, 1.3 Hz, 1 H, H-1), 4.17 (dt, J = 8.0, 3.2 Hz, 1 H, H-7), 6.09 (dd, J = 7.0, 5.2 Hz, 1 H, H-6), 6.45 (td, J = 7.0, 5.2 Hz, 1 H, H-5); ^{13}C NMR −4.6 ($Si(CH_3)_2$), 18.0 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 31.3 (C-4), 35.7 (C-8), 44.3 (NCH_3), 54.5 (C-3), 59.9 (C-1), 70.4 (C-7), 128.3 (C-6), 134.1 (C-5); IR ($CHCl_3$) 1455 cm^{-1}.

2-Methyl-7-ketoisoquinuclidene (38). A solution of 652 mg (3.09 mmol) of the ketal **36** in 2.0 mL of ether and 2.0 mL of 10% hydrochloric acid was stirred for 24 h at 25 °C. The mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with ether. The ether extracts were dried and concentrated by fractional distillation, yielding 284 mg (67%) of the isoquinuclidene **38** as a yellow oil: ^1H NMR 2.04 (m, 2 H, H-8), 2.40 (s, 3 H, NCH_3), 2.58 (dt, J = 9.4, 1.7 Hz, 1 H, H-3 endo), 2.78 (dd, J = 9.4, 2.5 Hz, 1 H, H-3 exo), 3.01 (m, 1 H, H-4), 3.52 (d, J = 6.0 Hz, 1 H, H-1), 6.36 (ddd, J = 7.9, 6.2, 1.7 Hz, 1 H, H-6), 6.60 (t, J = 7.3 Hz, 1 H, H-5); ^{13}C NMR 33.1 (C-4), 36.8 (C-8), 43.5 (NCH_3), 53.7 (C-3), 66.3 (C-1), 127.8 (C-6), 138.2 (C-5), 205.9 (C=O); IR ($CHCl_3$), 1720 cm^{-1}; mass spectrum, m/e (relative intensity) 137 (P, 7), 109 (63), 108 (100), 94 (66), 82 (20), 67 (13); high-resolution mass spectrum, m/e 137.0835 ($C_8H_{11}NO$ requires 137.0841).

7-Ketoisoquinuclidene 38 + Methyl Propiolate. A solution of 200 mg (1.46 mmol) of isoquinuclidene **38** and 491 mg (5.84 mmol) of methyl propiolate in 7.0 mL of dry acetonitrile was stirred for 3 h at 25 °C. The resulting brown mixture was concentrated in vacuo, giving a brown oil, which was subjected to silica gel chromatography (2:1 hexanes/ethyl acetate), yielding 52 mg (12%) of **58** as an unstable yellow oil: ^1H NMR 1.23 (dt, J = 13.6, 2.7 Hz, 1 H, H-8 endo), 1.61 (dt, J = 8.6, 2.1 Hz, 1 H, H-3 endo), 2.05 (br s, 1 H, OH), 2.09 (s, 3 H, NCH_3), 2.78 (dd, J = 13.9, 2.1 Hz, 1 H, H-8 exo), 2.62 (m, 1 H, H-4), 2.83 (dd, J = 8.6, 2.6 Hz, 1 H, H-3 exo), 3.26 (dd, J = 5.2, 1.2 Hz, 1 H, H-1), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.18 (s, 1 H, C=C-H), 6.25 (m, J = 8.0, 5.4, 1.3 Hz, 1 H, H-6), 6.68 (td, J = 7.3, 1.3 Hz, 1 H, H-5); ^{13}C NMR 31.5 (C-4), 38.9 (C-8), 42.8 (NCH_3), 51.7, 52.6 (OCH_3), 52.9 (C-3), 62.0 (C-1), 78.0 (C-7), 82.6 (=CCO_2CH_3), 84.9 (C=CCO_2CH_3), 105.8 (C=CH), 127.8 (C-6), 137.5 (C-5), 154.2 (C=O), 157.9 (CH_3O_2CC=C), 166.6 (C=O); IR ($CHCl_3$) 2200, 1710, 1620, 1435, 1260 cm^{-1}; mass spectrum, m/e (relative intensity) 305 (P, 18), 290 (8), 274 (25), 244 (43), 230 (11), 217 (16), 202 (15), 189 (24), 175 (15), 158 (20), 108 (50), 94 (100); high-resolution mass spectrum, m/e 305.1238 ($C_{16}H_{19}NO_5$ requires 305.1263).

General Procedure for Amino-Claisen Rearrangements. Solutions (0.2 M) of the allylamines in anhydrous acetonitrile containing the alkyl propiolate (0.8 M) were heated at 70 °C until the starting amine was consumed (TLC monitoring). Purification involved concentration in vacuo followed by either column chromatography on Florisil or silica gel, or preparative TLC on silica gel. All products isolated in these reactions were oils. Listed below are the allylic amines (with references to their source) and propiolate esters used in these processes along with the products obtained and their spectroscopic data.

Isoquinuclidene 47[17] + Methyl Propiolate. Reaction gave hydroisoquinoline **51** (46%) and dimer **39** (R = Me) (30%). Spectroscopic data for **51**: ^1H NMR 1.47–2.17 (m, 5 H, H-8, H-8a, H-7), 2.79 (ddd, J = 11.9, 4.4, 1.2 Hz, 1 H, H-1 eq), 2.94 (s, 3 H, N-CH_3), 3.08 (t, J = 11.8 Hz, 1 H, H-1 ax), 3.18 (m, 1 H, H-4a),

(17) Cava, M. P.; Wilkins, C. K.; Dalton, D. R.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772.

3.67 (s, 3 H, OCH_3), 5.48 (dt, J = 10.1, 3.1 Hz, 1 H, H-6), 5.67 (d, J = 10.9 Hz, 1 H, H-5), 7.35 (s, 1 H, H-3); ^{13}C NMR 20.7 (C-8), 24.6 (C-7), 29.7 (C-8a), 31.1 (C-4a), 42.7 (NCH_3), 48.0 (C-1), 50.7 (OCH_3), 97.9 (C-4), 122.7 (C-5), 131.3 (C-6), 146.0 (C-3), 168.6 (CO_2CH_3); IR ($CHCl_3$) 1670 (NC=CCO), 1620, 1260, 1180 cm^{-1}; mass spectrum, m/e (relative intensity) 207 (P, 82), 192 (26), 178 (16), 176 (26), 148 (57), 128 (52), 91 (40); high-resolution mass spectrum, m/e 207.1257 ($C_{12}H_{17}NO_2$ requires 207.1259).

Isoquinuclidene 47[17] + Ethyl Propiolate. Reaction gave hydroisoquinoline **52** (40%) and dimer **39** (R = Et) (29%). Spectroscopic data for **52**: ^1H NMR 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.70–2.19 (m, 5 H, H-7, H-8, H-8a), 2.79 (ddd, J = 11.9, 4.4, 1.2 Hz, 1 H, H-1 eq), 2.94 (s, 3 H, NCH_3), 3.07 (t, J = 11.7 Hz, 1 H, H-1 ax), 3.20 (m, 1 H, H-4a), 4.15 (q, J = 7.0 Hz, 2 H, OCH_2), 5.46 (dt, J = 10.1, 3.1 Hz, 1 H, H-6), 5.67 (d, J = 10.2 Hz, 1 H, H-5), 7.35 (s, 1 H, H-3); ^{13}C NMR 14.5 (OCH_2CH_3), 20.7 (C-8), 24.5 (C-7), 29.5 (C-8a), 31.1 (C-4a), 42.3 (NCH_3), 48.2 (C-1)e, 58.5 (OCH_2CH_3), 98.0 (C-4), 122.4 (C-5), 131.1 (C-6), 146.0 (C-3), 168.1 (CO_2Et); IR ($CHCl_3$) 1670 (NC=CCO), 1620, 1250, 1170 cm^{-1}; mass spectrum, m/e (relative intensity) 221 (P, 81), 192 (100), 176 (48), 164 (8), 142 (47), 132 (9), 114 (16), 91 (12); high-resolution mass spectrum, m/e 221.1417 ($C_{13}H_{19}NO_2$ requires 221.1416).

Isoquinuclidene 47[17] + *tert*-Butyl Propiolate. Reaction gave hydroisoquinoline **53** (39%), dimer **39** (R = tBu) (12%), and ether **40** (R = tBu) (2%). Spectroscopic data for **53**: ^1H NMR 1.48 (s, 9 H, tBu), 1.26–2.17 (m, 5 H, H-7, H-8, H-8a), 2.75 (dd, J = 11.3, 3.3 Hz, 1 H, H-1 eq), 2.91 (s, 3 H, NCH_3), 3.04 (t, J = 11.7 Hz, 1 H, H-1 ax), 3.16 (br m, 1 H, H-4a), 5.44 (dd, J = 11.3, 2.5 Hz, 1 H, H-6), 5.68 (d, J = 10.3 Hz, 1 H, H-5), 7.26 (s, 1 H, H-3); ^{13}C NMR 21.4 (C-8), 24.7 (C-7), 28.7 ($C(CH_3)_3$), 30.0 (C-8a), 31.8 (C-4a), 42.7 (NCH_3), 48.0 (C-1), 78.2 ($CO_2C(CH_3)_3$), 100.0 (C-4), 122.7 (C-5), 131.8 (C-6), 145.3 (C-3), 168.2 (CO_2tBu); IR ($CHCl_3$) 1660 (NC=CCO), 1620, 1140 cm^{-1}; mass spectrum, m/e (relative intensity) 249 (P, 29), 193 (74), 176 (30), 164 (19), 148 (100), 114 (64), 91 (20); high-resolution mass spectrum, m/e 249.1729 ($C_{15}H_{23}NO_2$ requires 249.1729).

Isoquinuclidene 48[10b] + Methyl Propiolate. Reaction gave hydroisoquinoline **54** (51%), dimer **39** (R = Me) (65%), and ether **40** (R = Me) (2%). Spectroscopic data for **54**: ^1H NMR 1.26 (s, 3 H, CH_3), 1.82 (m, J = 10.8, 4.2 Hz, 1 H, H-8), 2.25 (br m, 2 H, H-7, H-8a), 2.78 (ddd, J = 12.0, 5.2, 1.0 Hz, 1 H, H-1 eq), 2.91 (s, 3 H, N-CH_3), 3.01 (t, J = 12.0 Hz, 1 H, H-1 ax), 3.16 (br m, 1 H, H-4a), 3.66 (s, 3 H, CO_2CH_3), 3.94 (m, 4 H, OCH_2CH_2O), 5.49 (d, J = 11.0 Hz, 1 H, H-6), 5.74 (d, J = 11.0 Hz, 1 H, H-5), 7.33 (s, 1 H, H-3); ^{13}C NMR 20.9 (CH_3), 26.8 (C-8 or C-7), 29.8 (C-8a), 31.2 (C-7 or C-8), 40.2 (C-4a or NCH_3), 42.6 (NCH_3 or C-4a), 48.3 (C-1), 50.4 (OCH_3), 64.6, 64.8 (OCH_2CH_2O), 97.4 (C-4), 111.6 (OCO), 122.4 (C-5), 133.1 (C-6), 146.6 (C-3), 168.7 (CO_2CH_3); IR ($CHCl_3$) 1671 (NC=CCO), 1618, 1170 cm^{-1}; mass spectrum, m/e (relative intensity) 293 (P, 31), 262 (10), 248 (20), 153 (4), 149 (13), 128 (42), 87 (100); high-resolution mass spectrum, m/e 293.1622 ($C_{16}H_{23}NO_4$ requires 293.1627).

Isoquinuclidene 49[10b] + Methyl Propiolate. Reaction gave hydroisoquinoline **55** (36%), dimer **39** (R = Me) (18%), and ether **40** (R = Me) (1%). Spectroscopic data for **55**: ^1H NMR 1.19 (s, 3 H, CH_3), 1.61 (m, 2 H, H-8), 2.10 (m, 1 H, H-8a), 2.45 (m, 1 H, H-7), 2.82 (dd, J = 13.3, 3.3 Hz, 1 H, H-1 ax), 2.89 (s, 3 H, NCH_3), 3.07 (m, 1 H, H-4a), 3.15 (dd, J = 12.3, 3.2 Hz, 1 H, H-1 eq), 3.63 (s, 3 H, OCH_3), 3.93 (m, 4 H, OCH_2CH_2O), 5.63 (d, J = 10.0 Hz, 1 H, H-6), 6.34 (ddd, J = 10.0, 4.6, 2.8 Hz, 1 H, H-5), 7.34 (s, 1 H, H-3); ^{13}C NMR 20.7 (CH_3), 26.2 (C-8), 31.5 (C-7 or C-8a), 32.4 (C-7 or C-8a), 42.9 (NCH_3 or C-4a), 44.6 (NCH_3 or C-4a), 50.3 (OCH_3), 53.4 (C-1), 64.6, 64.7 (OCH_2CH_2O), 98.3 (C-4), 111.5 (OCO), 125.7 (C-5), 131.8 (C-6), 145.9 (C-3), 168.6 (CO_2CH_3); IR ($CHCl_3$), 1670 (NC=CCO), 1611, 1175 cm^{-1}; mass spectrum, m/e (relative intensity) 293 (P, 10), 153 (11), 87 (100); high-resolution mass spectrum, m/e 293.1622 ($C_{16}H_{23}NO_4$ requires 293.1621).

Isoquinuclidene 14 + Methyl Propiolate. Reaction gave hydroisoquinoline **46** (61%). Spectroscopic data for **46**: ^1H NMR 1.28 (s, 3 H, CH_3), 1.81 (m, 2 H, H-19), 2.17 (br m, 1 H, H-18 or H-20), 2.29 (br m, 1 H, H-18 or H-20), 2.76–3.03 (m, 3 H, H-6, H-21 eq), 3.12 (t, J = 12.0 Hz, 1 H, H-21 ax), 3.18 (br s, 1 H, H-15), 3.41 (t, J = 7.0 Hz, 2 H, H-5), 3.66 (s, 3 H, OCH_3), 3.96 (br m, 4 H, OCH_2CH_2O), 5.52 (dd, J = 10.0, 2.4 Hz, 1 H, H-17), 5.78 (d, J = 10.0 Hz, 1 H, H-16), 6.93 (d, J = 2.3 Hz, 1 H, H-2), 7.08–7.37 (m, 4 H, H-3, H-9, H-10, H-11), 7.56 (dd, J = 7.9, 1.0 Hz, 1 H, H-12), 8.28 (br s, 1 H, NH); ^{13}C NMR 20.9 (CH_3), 24.8 (C-6 or C-19), 26.8 (C-6 or C-19), 30.0 (C-18 or C-20), 31.5 (C-18 or C-20), 40.2 (C-15), 46.6 (C-21), 50.4 (OCH_3), 56.3 (C-5), 64.6, 64.8 (OCH_2CH_2O), 96.8 (C-14), 111.3 (C-12), 111.6 (C-7 or OCO), 112.3 (C-7 or OCO), 118.4 (C-9), 119.4 (C-10), 122.1 (C-2 or C-11), 122.2 (C-2 or C-11), 122.5 (C-16), 127.1 (C-8), 133.1 (C-17), 136.3 (C-13), 146.1 (C-3)e, 168.9 (CO_2CH_3); IR ($CHCl_3$) 3475 (NH), 1670 (NC=CCO), 1615, 1160 cm^{-1}; mass spectrum, m/e (relative intensity) 422 (P), 264 (9), 233 (2), 187 (2), 149 (2), 115 (2), 87 (5); high-resolution mass spectrum, m/e 422.2190 ($C_{25}H_{30}N_2O_4$ requires 422.2385).

Isoquinuclidene 15 + Methyl Propiolate. Reaction gave hydroisoquinoline **45** (22%). Spectroscopic data for **45**: ^1H NMR 1.26 (s, CH_3), 1.81 (m, 2 H, H-19), 2.10 (br m, 1 H, H-18 or H-20), 2.28 (br m, 1 H, H-18 or H-20), 2.75–2.98 (m, 3 H, H-6, H-21 eq), 3.10 (t, J = 12.0 Hz, 1 H, H-21 ax), 3.18 (br s, 1 H, H-15), 3.41 (t, J = 7.0 Hz, 2 H, H-5), 3.67 (s, 3 H, OCH_3), 3.94 (br m, 4 H, OCH_2CH_2O), 5.51 (d, J = 10.0 Hz, 1 H, H-17), 5.77 (d, J = 10.0 Hz, 1 H, H-16), 7.18–7.54 (m, 8 H, H-3, aromatic H), 7.82 (dd, J = 7.9, 1.0 Hz, 1 H, aromatic H), 8.00 (dd, J = 7.9, 1.0 Hz, 1 H, H-12); ^{13}C NMR 20.9 (CH_3), 24.5 (C-6 or C-19), 26.9 (C-6 or C-19), 30.1 (C-18 or C-20), 31.7 (C-18 or C-20), 40.4 (C-15), 46.7 (C-21), 50.4 (OCH_3), 55.2 (C-5), 64.7, 64.9 (OCH_2CH_2O), 98.2 (C-14), 111.6 (OCO), 122.7 (C-16), 126.7 (C-8), 132.9 (C-17), 113.9, 119.2, 123.3, 123.5, 125.0, 129.3, 130.5, 133.7, 135.4, 138.5 (aromatic H), 145.5 (C-3), 168.6 (CO_2CH_3); IR ($CHCl_3$) 1680 (NC=CCO), 1621, 1175 cm^{-1}; mass spectrum, m/e (relative intensity) 562 (P, 5), 422 (5), 292 (16), 87 (58); high-resolution mass spectrum, m/e 562.2156 ($C_{31}H_{34}N_2O_6S$ requires 562.1437).

2-Methyl-2-azabicyclo[2.2.1]hept-5-ene (55a)[18] + Methyl Propiolate. Reaction gave the hydropyrindine **56** (19%) and dimer **39** (R = Me) (3%). Spectroscopic data for **56**: ^1H NMR 1.97 (br d, J = 13.0 Hz, 1 H, H-7), 2.33–2.53 (m, 1 H, H-7 or H-7a), 2.53–2.73 (m, 1 H, H-7 or H-7a), 2.63 (t, J = 11.7 Hz, 1 H, H-1 ax), 2.73–2.87 (m, 1 H, H-1 eq), 2.90 (s, 3 H, NCH_3), 3.52 (m, 1 H, H-4a), 3.68 (s, 3 H, OCH_3), 5.60 (m, 1 H, H-6), 5.90 (m, 1 H, H-5), 7.40 (s, 1 H, H-3); ^{13}C NMR 34.3 (C-7a), 36.4 (C-7), 41.4 (C-4a), 42.8 (NCH_3), 50.0 (C-1), 50.1 (OCH_3), 98.6 (C-4), 126.4 (C-5), 137.8 (C-6), 148.9 (C-3), 169.3 (CO_2Me); IR ($CHCl_3$), 1680 (NC=CC=O), 1630, 1260, 1170 cm^{-1}; mass spectrum, m/e (relative intensity) 193 (P, 5), 178 (6), 162 (3), 134 (12), 82 (5), 32 (100); high-resolution mass spectrum, m/e 193.1101 ($C_{11}H_{15}NO_2$ requires 193.1103).

Reaction of 2-Methyl-7-*endo*-[(*tert*-butyldimethylsilyl)oxy]isoquinuclidene (37) + Methyl Propiolate. Reaction under the conditions described above gave hydroisoquinoline **57** (25%) and dimer **39** (R = Me) (27%). Spectroscopic data for hydroisoquinoline **57**: ^1H NMR 0.05 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $(CCH_3)_3$), 1.88 (ddd, J = 13.3, 13.2, 3.9 Hz, 1 H, H-8 ax), 2.01 (m, J = 13.3, 5.0 Hz, 1 H, H-8 eq), 2.25 (br m, 1 H, H-8a), 2.82 (ddd, J = 12.3, 3.9, 1.0 Hz, 1 H, H-1 eq), 2.90 (s, 3 H, NCH_3), 2.97 (t, J = 11.6 Hz, 1 H, H-1 ax), 3.19 (br m, 1 H, H-4a), 3.64 (s, 3 H, CO_2CH_3), 4.22 (m, 1 H, H-7), 5.41 (m, J = 11.3 Hz, 1 H, H-6), 5.74 (ddd, J = 9.0, 1.8, 1.2 Hz, 1 H, H-5), 7.30 (s, 1 H, H-3); ^{13}C NMR −4.54 ($Si(CH_3)_2$), 18.2 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 31.2 (C-4a or C-8a), 31.3 (C-4a or C-8a), 35.3 (C-8), 42.6 (NCH_3), 48.6 (C-1), 50.5 (OCH_3), 64.7 (C-7), 97.2 (C-2), 127.1 (C-6), 132.6 (C-5), 146.7 (C-3), 168.6 (C=O); IR ($CHCl_3$) 1672 (NC=CCO), 1622 cm^{-1}; mass spectrum, m/e (relative intensity) 337 (P, 6), 177 (50), 118 (100); high-resolution mass spectrum, m/e 337.2074 ($C_{18}H_{31}NO_3Si$ requires 337.2073).

2-Methyl-4-carbomethoxy-7-ketohydroisoquinoline (59) from 7,7-Diethoxyisoquinuclidene 36 + Methyl Propiolate. A solution of 1-methylisoquinuclidene **36** (2.50 g, 0.012 mol) and methyl propiolate (3.98 g, 0.047 mol) in 59 mL of anhydrous CH_3CN was heated at 70 °C for 20 h. The reaction mixture was cooled to 25 °C, and the solvent and excess methyl propiolate were removed by concentration in vacuo to afford a residue, which was dissolved in 59 mL of 1:1 (v/v) 1% aqueous acetic acid/THF solution and stirred at 25 °C for 3 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with brine, and dried (Na_2SO_4) and concentrated in vacuo to afford a residue, which was subjected to silica gel chromatography (1:1 hex-

(18) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

anes/ethyl acetate) to yield 1.59 g (61%) of enone **59** as a low-melting white solid: ^{1}H NMR (400 MHz) 2.34 (ddd, J = 16.8, 2.6, 0.9 Hz, 1 H, H-8 eq), 2.54 (br m, 1 H, H-8a), 2.77 (dd, J = 16.8, 5.4 Hz, 1 H, H-8 ax), 2.78 (ddd, J = 11.8, 5.6, 1.2 Hz, 1 H, H-1 eq), 2.89 (s, 3 H, NCH_3), 3.05 (t, J = 11.8 Hz, 1 H, H-1 ax), 3.62 (br s, 1 H, H-4a), 3.63 (s, 3 H, OCH_3), 5.77 (ddd, J = 10.0, 1.0, 1.0 Hz, 1 H, H-6), 6.80 (ddd, J = 10.0, 2.1, 1.8 Hz, 1 H, H-5), 7.34 (s, 1 H, H-3); ^{13}C NMR 32.3 (C-4a or C-8a), 32.4 (C-4a or C-8a), 40.6 (C-8), 42.5 (NCH_3), 48.4 (C-1), 50.6 (OCH_3), 94.9 (C-4), 125.9 (C-6), 147.3 (C-3), 155.0 (C-5), 167.9 (C=O (ester)), 197.1 (C=O (enone)); IR ($CHCl_3$) 1665, 1615 cm^{-1}; mass spectrum, m/e (relative intensity) 221 (P, 75), 206 (26), 190 (35), 178 (24), 162 (100), 149 (13), 134 (41); high-resolution mass spectrum, m/e 221.1051 ($C_{12}H_{15}NO_3$ requires 221.1051).

2-Methyl-4-carbomethoxy-5-cyano-7-[(trimethylsilyl)-oxy]hydroisoquinoline (62). To a solution of enone **59** (1.056 g, 4.78 mmol) in 12.5 mL of anhydrous benzene at 25 °C was added dropwise a solution of diethylaluminum cyanide in benzene (1.0 M, 5.73 mL, 5.73 mmol). The reaction mixture was stirred at 0 °C for 4 h. At this time, pyridine (1.89 g, 23.9 mmol) and trimethylsilyl chloride (1.035 g, 9.55 mmol) were added sequentially and the reaction mixture was stirred at 0 °C for another 2 h, diluted with benzene (20 mL), quenched by the addition of cold saturated aqueous NH_4Cl, and filtered through Celite. The filtrate was washed with cold saturated aqueous NH_4Cl and cold saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to afford 1.528 g (91%) of the β-cyano silyl enol ether **62** (b:a ratio of >6:1) as a foam: ^{1}H NMR 0.12 (s, 9 H, $Si(CH_3)_3$), 1.76 (d, J = 18.2 Hz, H-8 eq), 2.20 (br m, 1 H, H-8a), 2.42 (ddt, J = 18.1, 7.8, 7.0 Hz, 1 H, H-8 ax), 2.87 (s, 3 H, NCH_3), 3.33 (m, 1 H, H-1 eq), 3.33 (t, J = 12.9 (Hz, 1 H, H-1 ax), 3.56 (s, 3 H, OCH_3), 3.58 (br m, 1 H, H-4a), 3.62 (m, J = 5.5 Hz, 1 H, H-5), 4.63 (dd, J = 5.3, 1.5 Hz, 1 H, H-6), 7.39 (s, 1 H, H-3); ^{13}C NMR 0.0 ($Si(CH_3)_3$), 29.5, 29.6, 30.2 (C-4a, C-8a, or C-5), 31.5 (C-8), 42.5 (NCH_3), 49.2 (C-1), 50.3 (OCH_3), 94.1 (C-4), 95.5 (C-6), 120.6 (CN), 147.4 (C-3), 151.6 (C-7), 167.7 (C=O); mass spectrum, m/e (relative intensity) 320 (P, 6), 295 (7), 221 (13), 167 (7), 153 (39), 152 (44), 83 (100); high-resolution mass spectrum, m/e 320.1555 ($C_{16}H_{24}N_2O_3Si$ requires 320.1556).

In attempts to purify this substance by alumina chromatography or when it was treated with 1:1 25% aqueous HOAc/THF at 25 °C, the β-cyano ketone **63** was formed: ^{1}H NMR 2.31 (dt, J = 15.0, 2.0 Hz, 1 H, H-8 eq), 2.55 (dt, J = 14.6, 2.2 Hz, 1 H, H-6 eq), 2.55 (br m, 1 H, H-8a), 2.69 (ddd, J = 14.6, 7.2, 0.5 Hz, 1 H, H-6 ax), 2.75 (dd, J = 15.0, 7.5 Hz, 1 H, H-8 ax), 2.90 (s, 3 H, NCH_3), 2.91 (ddd, J = 13.3, 5.3, 1.7 Hz, 1 H, H-1 eq), 3.11 (td, J = 5.2, 1.7 Hz, 1 H, H-4a), 3.36 (t, J = 13.3 Hz, 1 H, H-1 ax), 3.59 (s, 3 H, OCH_3), 3.60 (m, 1 H, H-4a), 3.68 (m, J = 6.3 Hz, 1 H, H-5), 7.45 (s, 1 H, H-3); ^{13}C NMR 32.1 (C-4a or C-8a), 32.7 (C-4a or C-8a), 33.7 (C-5), 41.9 (C-6 or C-8), 42.6 (NCH_3), 42.8 (C-6 or C-8), 48.9 (C-1), 50.6 (OCH_3), 92.7 (C-4), 120.5 (CN), 147.7 (C-3), 167.6 (C=O (ester)), 204.9 (C=O (ketone); IR ($CHCl_3$) 1715, 1660, 1440, 1410 cm^{-1}; mass spectrum, m/e (relative intensity) 248 (P, 54), 217 (44), 208 (44), 166 (100), 152 (54); high-resolution mass spectrum, m/e 248.1158 ($C_{13}H_{16}N_2O_3$ requires 248.1161).

2-Methyl-4-carbomethoxy-5-cyano-6-hydroxy-7-[(trimethylsilyl)oxy]hydroisoquinoline (64). A solution of freshly prepared silyl enol ether **62** (1.20 g, 3.75 mmol) in anhydrous THF was cooled to 0 °C. To the cooled solution was added dropwise a THF solution of BH_3 (1.0 M, 5.62 mL, 5.6 mmol). The reaction mixture was stirred at 0 °C for 30 min and at 25 °C for 20 h. The mixture was cooled to −10 °C, and 18.5 mL of 3 N NaOH and 18.5 mL of 30% H_2O_2 solution were added. After being stirred for 20 min at −10 °C, the mixture was extracted with dichloromethane. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo, giving a residue, which was subjected to flash alumina chromatography to afford 0.625 g (49%) of the siloxy alcohol **64** as a foam: ^{1}H NMR (400 MHz) 0.13 (s, 9 H, $Si(CH_3)_3$), 1.60 (d, J = 14.7 Hz, 1 H, H-8 eq), 2.12 (br m, 1 H, H-8a), 2.23 (ddd, J = 14.6, 5.0, 3.0 Hz, 1 H, H-8 ax), 2.80 (ddd, J = 13.2, 5.0, 1.6 Hz, 1 H, H-1 eq), 2.96 (s, 3 H, NCH_3), 3.09 (td, J = 4.5, 1.0 Hz, 1 H, H-4a), 3.31 (dd, J = 5.5, 2.5 Hz, 1 H, H-5), 3.63 (s, 3 H, OCH_3), 3.91 (m, J = 3.0, 2.9 Hz, 1 H, H-7), 4.12 (m, 1 H, H-6), 4.15 (t, J = 13.2 Hz, H-1 ax), 7.49 (s, 1 H, H-3); ^{13}C NMR 0.25 ($Si(CH_3)_3$), 27.2 (C-4a or C-8a), 29.5 (C-8), 29.7 (C-4a or C-8a), 33.1 (C-5), 42.8 (NCH_3), 49.9 (C-1), 50.4 (OCH_3), 68.4 (C-7), 69.9 (C-6), 92.7 (C-4), 120.2 (CN), 148.5 (C-3), 168.5 (C-O_2CH_3); IR ($CHCl_3$) 3490, 1605 cm^{-1}; mass spectrum, m/e (relative intensity) 338 (P, 29), 323 (32), 307 (20), 231 (7), 208 (22), 166 (100), 152 (100); high-resolution mass spectrum, m/e 338.1639 ($C_{16}H_{26}N_2O_4Si$ requires 338.1661). Further elution afforded 0.071 g (7%) of the 2-methyl-4-carbomethoxy-5-cyano-6,7-dihydroxy analogue of **64** as a film: ^{1}H NMR (400 MHz) 1.71 (br d, J = 14.7 Hz, 1 H, H-8 eq), 2.12 (br m, 1 H, H-8a), 2.21 (m, J = 14.7, H-8 ax), 2.90 (dd, J = 13.3, 4.1 Hz, 1 H, H-1 eq), 2.96 (s, 3 H, NCH_3), 3.07 (t, J = 4.8 Hz, 1 H, H-4a), 3.30 (m, J = 2.6 Hz, 1 H, H-5), 3.62 (s, 3 H, OCH_3), 3.65 (br s, 2 H, 6-OH, 7-OH), 3.97 (br d, J = 2.9 Hz, 1 H, H-5), 4.04 (t, J = 13.0 Hz, 1 H, H-1 ax), 4.20 (br s, 1 H, H-6), 7.52 (s, 1 H, H-3); ^{13}C NMR 27.3 (C-4a or C-8a), 28.6 (C-8), 29.5 (C-4a or C-8a), 33.5 (C-5), 42.9 (NCH_3), 50.2 (C-1), 50.6 (OCH_3), 68.6 (C-7), 70.4 (C-6), 92.5 (C-4), 121.0 (CN), 148.8 (C-3), 168.7 (C=O); IR ($CHCl_3$) 3396 (br), 2210, 1640, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 226 (P, 33), 265 (38), 251 (6), 235 (22), 207 (5), 166 (61), 152 (100); high-resolution mass spectrum, m/e 266.1272 ($C_{13}H_{18}NO_4$ requires 266.1267).

2-Methyl-4-carbomethoxy-5-cyano-6-methoxy-7-hydroxyhydroisoquinoline (65). To a flask containing the silyl enol ether **66** (0.400 g, 1.13 mmol) was added a solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 2.83 mL, 2.84 mmol). The solution was stirred at 25 °C for 1 h and then concentrated in vacuo to afford a residue, which was dissolved in benzene. The benzene solution was washed with water, dried (Na_2SO_4), and concentrated in vacuo to afford an oil, which was chromatographed on a flash alumina column to afford 0.167 g (53%) of the hydroxyhydroisoquinoline **65** as a foam: ^{1}H NMR (400 MHz) 1.71 (dd, J = 13.1, 3.4 Hz, 1 H, H-8 eq), 2.15 (br m, 2 H, H-8a, H-8 ax), 2.87 (ddd, J = 13.0, 5.0, 1.8 Hz, 1 H, H-1 eq), 2.95 (s, 3 H, NCH_3), 2.97 (m, 1 H, H-4a), 3.41 (s, 3 H, 6-OCH_3), 3.55 (dd, J = 5.2, 2.2 Hz, 1 H, H-5), 3.64 (s, 3 H, CO_2CH_3), 3.67 (br t, J = 2.5 Hz, 1 H, H-6), 4.04 (t, J = 13.0 Hz, 1 H, H-1 ax), 4.05 (m, J = 3.4, 2.5 Hz, 1 H, H-7), 7.50 (s, 1 H, H-3); ^{13}C NMR 27.6 (C-4a or C-8a), 29.1 (C-8), 29.3 (C-4a or C-8a, C-5), 42.8 (NCH_3), 50.1 (C-1), 50.4 (CO_2CH_3), 57.2 (6-OCH_3), 67.2 (C-5), 79.6 (C-6), 92.9 (C-4), 120.9 (C=N), 148.3 (C-3), 168.2 (C=O); IR ($CHCl_3$) 3490 (br), 1650, 1605 cm^{-1}; mass spectrum, m/e (relative intensity) 380 (P, 11), 249 (11), 217 (6), 196 (5), 166 (14), 152 (52); high-resolution mass spectrum, m/e 280.1424 ($C_{14}H_{20}N_2O_4$ requires 280.1423).

2-Methyl-4-carbomethoxy-5-cyano-6-methoxy-7-[(trimethylsilyl)oxy]hydroisoquinoline (66). To a solution of the alcohol **64** (0.550 g, 1.62 mmol) in 11.6 mL of anhydrous THF at −78 °C was added nBuLi (1.5 M, 1.2 mL, 1.49 mmol). After stirring for 30 min, methyl triflate (0.400 g, 2.44 mmol) was added, and stirring was continued at −78 °C for 30 min and at −40 °C for 4 h. The reaction was quenched by the addition of 10% aqueous NH_4OH and water at 0 °C. This solution was extracted with dichloromethane. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo, giving a residue, which was subjected to flash alumina column chromatography to afford 0.406 (71%) of the 6-methoxy-7-silyloxy hexahydroisoquinoline **66** as a foam: ^{1}H NMR (400 MHz) 1.58 (dd, J = 13.4, 3.0 Hz, 1 H, H-8 eq), 2.11 (m, 2 H, H-8a, H-8 ax), 2.77 (ddd, J = 13.0, 4.8, 1.8 Hz, 1 H, H-1 eq), 2.94 (s, 3 H, NCH_3), 2.96 (m, J = 1.0 Hz, H-4a), 3.39 (s, 3 H, 6-OCH_3), 3.51 (dd, J = 5.3, 2.5 Hz, 1 H, H-5), 3.55 (br t, J = 2.7 Hz, 1 H, H-6), 3.64 (s, 3 H, CO_2CH_3), 3.93 (dd, J = 2.8, 2.7 Hz, 1 H, H-7), 4.13 (t, J = 13.0 Hz, 1 H, H-1 ax), 7.48 (s, 1 H, H-3); ^{13}C NMR −0.14 ($Si(CH_3)_3$), 27.6 (C-4a or C-8a), 28.9 (C-4a or C-8a), 29.7 (C-5), 30.2 (C-8), 42.9 (NCH_3), 50.0 (C-1), 50.4 (CO_2CH_3), 57.1 (6-OCH_3), 67.2 (C-7), 79.2 (C-6), 93.2 (C-4), 120.4 (CN), 148.2 (C-3), 168.1 (C=O); IR ($CHCl_3$) 1650, 1610, 1590 cm^{-1}; mass spectrum, m/e (relative intensity) 352 (P, 18), 337 (14), 321 (9), 263 (4), 222 (14), 196 (9), 166 (78), 152 (80); high-resolution mass spectrum, m/e 352.1822 ($C_{17}H_{28}N_2O_4Si$ requires 352.1818).

2-Methyl-4-carbomethoxy-5-cyano-6-methoxy-7-[(3′,4′,5′-trimethoxybenzoyl)oxy]hydroisoquinoline (67). A mixture of the hydroisoquinoline **65** (0.024 g, 0.086 mmol), 3,4,5-trimethoxybenzoyl chloride (0.099 g, 0.43 mmol), and 4-(N,N-dimethylamino)pyridine (0.002 g, 0.019 mmol) in 0.32 mL of ethanol-free chloroform and 0.8 mL of pyridine was stirred at 50 °C for 2 days, cooled to 25 °C, diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concen-

trated in vacuo, giving a solid, which was subjected to flash alumina chromatography to afford 0.011 g (30%) of the desired ester **67** as a white solid (mp 204.5–206.0 °C, acetone): ^{1}H NMR 1.94 (d, J = 15.5 Hz, 1 H, H-8 eq), 2.23 (br m, 1 H, H-8a), 2.36 (ddd, J = 15.5, 6.6, 3.7 Hz, 1 H, H-8 ax), 2.82 (ddd, J = 12.9, 5.2, 1.6 Hz, 1 H, H-1 eq), 2.91 (s, 3 H, NCH_3), 3.11 (td, J = 5.3, 1.3 Hz, 1 H, H-4a), 3.47 (s, 3 H, CO_2CH_3), 3.66 (s, 3 H, 6-OCH_3), 3.68 (m, J = 5.2, 1.8 Hz, 1 H, H-5), 3.83 (dd, J = 2.3, 1.8 Hz, 1 H, H-6), 3.86 (s, 6 H, aromatic 3,5-OCH_3), 3.89 (s, 1 H, aromatic 4-OCH_3), 3.96 (t, J = 12.9 Hz, 1 H, H-1 ax), 5.37 (dd, J = 3.7, 2.6 Hz, 1 H, H-7), 7.46 (s, 2 H, aromatic H), 7.52 (s, 1 H, H-3); ^{13}C NMR 26.9 (C-8), 27.4 (C-4a or C-8a), 29.0 (C-4a or C-8a), 29.9 (C-5), 42.8 (NCH_3), 49.5 (C-1), 50.5 (CO_2CH_3), 56.5 (aromatic 3-OCH_3, 5-OCH_3), 57.5 (6-OCH_3 or aromatic 4-OCH_3 or 6-OCH_3), 60.8 (6-OCH_3 or aromatic 4-OCH_3), 68.3 (C-7), 76.3 (C-6), 93.5 (C-4), 107.6 (aromatic C-2 and C-6), 120.6 (CN), 124.4 (aromatic C-1), 142.7 (aromatic C-4), 148.1 (C-3), 153.2 (aromatic C-3 and C-5), 165.4 (O(C=O)Ar), 167.9 (CO_2CH_3); IR ($CHCl_3$) 1685, 1650, 1590 cm^{-1}; mass spectrum, m/e (relative intensity) 474 (P, 11), 459 (6), 294 (12), 279 (8), 263 (19), 240 (47), 222 (26), 195 (58), 166 (72), 152 (100); high-resolution mass spectrum, m/e 474.1977 ($C_{24}H_{30}N_2O_8$ requires 474.2002).

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Registry No. (±)-**14**, 87371-63-9; (±)-**15**, 120230-10-6; (±)-**16**, 120230-11-7; (±)-**18** (isomer 1), 120328-40-7; (±)-**18** (isomer 2), 120230-09-3; (±)-**19**, 120230-13-9; (±)-*exo*-**21**, 120328-39-4; (±)-*endo*-**21**, 120328-41-8; (±)-*exo*-**22**, 120328-42-9; (±)-*endo*-**22**, 120230-14-0; (±)-*exo*-**23**, 120328-43-0; (±)-*endo*-**23**, 120230-15-1; (±)-*exo*-**24**, 120328-44-1; (±)-*endo*-**24**, 120230-16-2; **30**, 3061-65-2; **31**, 57956-33-9; (±)-**32** (*exo*-CN), 120328-45-2; (±)-**32** (*endo*-CN), 120230-17-3; (±)-**33**, 120230-18-4; (±)-**34**, 120230-19-5; (±)-**35**, 120230-20-8; (±)-**36**, 120230-21-9; (±)-**37**, 120230-22-0; (±)-**38**, 120230-23-1; (±)-**39** (R = *t*-Bu), 120230-28-6; (±)-**45**, 120262-54-6; (±)-**46**, 120230-30-0; (±)-**47**, 119594-50-2; (±)-**48**, 120328-46-3; (±)-**49**, 120328-47-4; (±)-**51**, 120230-25-3; (±)-**52**, 120230-26-4; (±)-**53**, 120230-27-5; (±)-**54**, 120230-29-7; (±)-**55**, 120328-48-5; (±)-**55a**, 119594-57-9; (±)-**56**, 120230-31-1; (±)-**57**, 120230-32-2; (±)-**58**, 120230-24-2; (±)-**59**, 120230-33-3; (±)-**62**, 120230-34-4; (±)-**63**, 120230-35-5; (±)-**64**, 120230-36-6; (±)-**64** (diol), 120230-37-7; (±)-**65**, 120230-39-9; (±)-**66**, 120230-38-8; (±)-**67**, 120230-40-2; $MeO_2CC{\equiv}CH$, 922-67-8; $EtO_2CC{\equiv}CH$, 623-47-2; *t*-$BuO_2CC{\equiv}CH$, 13831-03-3.

A Comparison of the Radical-Stabilizing Ability of Aromatic Groups. $\gamma^\bullet$ Values for Aromatic Groups

Xavier Creary,* M. E. Mehrsheikh-Mohammadi, and Steven McDonald

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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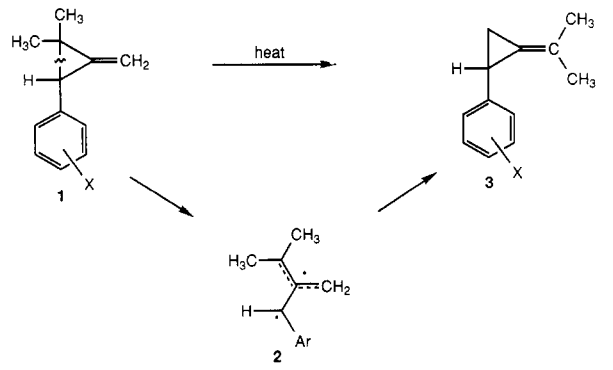
A series of 15 2-aryl-3,3-dimethyl-1-methylenecyclopropanes, **1**, have been prepared and thermally rearranged in C_6D_6 to the corresponding 2-aryl-1-isopropylidenecyclopropanes, **3**. Rearrangement rates give a measure of the ability of various aromatic groups to stabilize the transition state leading to a biradical intermediate. The 4-pyridine *N*-oxide group was found to be the most effective of the aromatic groups in stabilizing the radical intermediate. This has been rationalized by considering the mode of spin delocalization in such radicals. Resonance interactions result in an intermediate which is stabilized due to nitroxide radical character. The 2-furanyl and 2-thienyl groups are also very effective radical stabilizing groups. Rearrangement rates of **1** were converted to $\gamma^\bullet$ values, which are a quantitative measure of the relative abilities of various groups to stabilize free radicals.

Interest in the chemistry of free radicals has remained high over the years.[1] We[2] and others[3-9] have developed quantitative methods of probing the factors that promote their stability. $\sigma^\bullet$ substituent constants[2d,4-7] have been developed that factor out polar effects, which can often dominate free-radical reactions. These substituent constants attempt to measure the pure radical stabilizing ability of substituents on benzylic radicals. Our $\sigma^\bullet$ sub-

Scheme I



(1) For discussions of many current aspects of free-radical chemistry, see: *Substituent Effects in Free Radical Chemistry*; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; D. Reidel Publishing Co.: Dordrecht, Holland, 1986.

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