18b: mp 170-171 °C (MeOH); ^{1}H NMR δ 1.12 (dm, H_7, $J_{7,7'}$ = 13.1), 1.34 (dm, $H_{7'}$), 1.81 (complex m, H_8), 1.98 (complex m, $H_{8'}$), 2.43 (ddt, H_{6a}, $J_{6a,7'}$ = 12.5, $J_{6a,10a}$ = 5.4, $J_{6,6a}$ = $J_{6a,7}$ = 3.0), 3.73 (br t, H_{10a}, $J_{10,10a}$ = 5.8), 4.75 (br s, H_5), 5.11 (d, H_6), 5.73 (complex d, H_9, $J_{9,10}$ = 10.1, $J_{8,9}$ = $J_{8',9}$ = 3.6), 6.19 (ddt, H_{10}, $J_{8,10}$ = $J_{8',10}$ = 2.4), 6.61 (d, H_4, $J_{3,4}$ = 8.5), 6.97 (dd, H_3, $J_{1,3}$ = 2.4), 7.11 (dd, H_1, $J_{1,10a}$ = 1.1), 7.51 (m, COPh, H_m), 7.63 (m, COPh, H_p), 7.93 (m, COPh, H_o). Anal. Found: C, 74.11; H, 5.59; Cl, 11.07; N, 4.23.

Cyclodehydration Reactions of Tetrahydropyridines 8a,b and 12a,b. A solution of 0.1 g of the tetrahydropyridine derivative and 1 equiv of BF_3·Et_2O in 10 mL of toluene was heated at reflux for 4 h. One more equivalent of Lewis acid was added to the cold solution, which was further refluxed for 4 h. The solution was then poured in 20 mL of 5% aqueous $NaHCO_3$. The organic layer was washed with water, dried, and concentrated in vacuo. The residue was chromatographed (toluene as eluant).

From **8a**, 21% of 6,7-dihydro-8-methyl-2-nitro-10-phenylpyrido[1,2-*a*]indole (**11a**): mp 195-197 °C (EtOH); ^{1}H NMR δ 2.03 (dt, Me_8, $J_{Me,9}$ = 1.5, $J_{Me,7}$ = 1.1), 2.66 (tdq, H_7, $J_{6,7}$ = 7.1, $J_{7,9}$ = 1.3), 4.23 (t, H_6), 6.54 (sextet, H_9), 7.36 (dd, H_4, $J_{3,4}$ = 9.0, $J_{1,4}$ = 0.5), 7.37 (m, Ph, H_p), 7.52 (m, Ph, H_o and H_m), 8.12 (dd, H_3, $J_{1,3}$ = 2.2), 8.67 (dd, H_1). Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.99; H, 5.30; N, 9.21. Found: C, 74.68; H, 5.28; N, 9.05.

From **8b**, 64% of 2-chloro-6,7-dihydro-8-methyl-10-phenylpyrido[1,2-*a*]indole (**11b**): mp 151 °C (EtOH); ^{1}H NMR δ 1.99 (dt, Me_8, $J_{Me,9}$ = 1.5, $J_{Me,7}$ = 1.2), 2.60 (tdq, H_7, $J_{6,7}$ = 7.2, $J_{7,9}$ = 1.3), 4.12 (t, H_6), 6.49 (sextet, H_9), 7.14 (dd, H_3, $J_{3,4}$ = 8.5, $J_{1,3}$ = 1.8), 7.17 (dd, H_4, $J_{1,4}$ = 0.9), 7.35 (m, Ph, H_p), 7.48 (m, Ph, H_o and H_m), 7.65 (dd, H_1). Anal. Calcd for $C_{19}H_{16}ClN$: C, 77.68; H, 5.49; Cl, 12.07; N, 4.77. Found: C, 77.36; H, 5.42; Cl, 12.05; N, 4.72.

From **12a**, 21% of 6,9-dihydro-7,8-dimethyl-2-nitro-10-phenylpyrido[1,2-*a*]indole (**13a**): mp 197-198 °C (EtOH); ^{1}H NMR δ 1.87 and 1.90, (2 br s, Me_7 and Me_8), 3.63 (br s, t when {Me}, H_9, $J_{6,9}$ = 3.6), 4.58 (br s, t when {Me}, H_6), 7.37 (dd, H_4, $J_{3,4}$ = 9.0, $J_{1,4}$ = 0.4), 7.38 (m, Ph, H_p), 7.51 (m, Ph, H_o and H_m), 8.13 (dd, H_3, $J_{1,3}$ = 2.2), 8.68 (dd, H_1). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.46; H, 5.70; N, 8.80. Found: C, 75.32; H, 5.58; N, 8.72.

From **12b**, 40% of 2-chloro-6,9-dihydro-7,8-dimethyl-10-phenylpyrido[1,2-*a*]indole (**13b**): mp 135-137 °C (EtOH); ^{1}H NMR δ 1.84 (br s, Me_7 and Me_8), 3.57 (br s, t when {Me}, H_9, $J_{6,9}$ = 3.7), 4.46 (br s, t when {Me}, H_6), 7.14 (dd, H_3, $J_{3,4}$ = 8.5 $J_{1,3}$ = 2.1), 7.23 (d, H_4), 7.28 (m, Ph, H_p), 7.48 (m, Ph, H_o and H_m), 7.70 (d, H_1). Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; Cl, 11.52; N, 4.55. Found: C, 78.12; H, 5.78; Cl, 11.48; N, 4.48.

Rearrangements of Azabicyclooctenes 16a,b and 17a,b. A solution of 0.1 g of the azabicyclooctene and 1 equiv of BF_3·Et_2O in 10 mL benzene was refluxed (2 h for chloro derivatives, 8 h for nitro derivatives) and then poured in 20 mL of 5% aqueous $NaHCO_3$. The organic layer was washed with water, dried, and evaporated to dryness. From **16a,b** only **18a,b** were quantitatively formed and identified by NMR spectra. From the reaction of **17a,b**, chromatograhic separation (toluene as eluant) of the crude led to isolation of phenanthridines **18a,b** and **19a,b**.

From **17a**, 83% of (6α,6aα,10aα)-6-benzoyl-5,6,6a,7,8,10a-hexahydro-2-nitrophenanthridine (**19a**) and 13% of 6α,6aβ,10aβ isomer **18a**.

19a: mp 165-166 °C (MeOH); ^{1}H NMR δ 1.69 (dm, H_7, $J_{7,7'}$ = 13.0), 1.86 (complex d, $H_{7'}$), 2.17 (complex m, H_8 and $H_{8'}$), 2.43 (ddt, H_{6a}, $J_{6a,7'}$ = 11.6, $J_{6a,10a}$ = 5.5, $J_{6,6a}$ = $J_{6a,7}$ = 2.7), 3.19 (br t, H_{10a}, $J_{10,10a}$ = 5.5), 4.88 (d, H_6), 4.97 (br s, H_5), 5.80 (complex d, H_9, $J_{9,10}$ = 10.1, $J_{8,9}$ = $J_{8',9}$ = 3.5), 6.14 (ddt, H_{10}, $J_{8,10}$ = $J_{8',10}$ = 2.1), 6.58 (d, H_4, $J_{3,4}$ = 8.9), 7.52 (m, COPh, H_m), 7.64 (m, COPh, H_p), 7.92 (m, COPh, H_o), 7.94 (dd, H_3, $J_{1,3}$ = 2.5), 8.03 (dd, H_1, $J_{1,10a}$ = 1.2). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.66; H, 5.41; N, 8.33.

From **17b**, 94% of (6α,6aα,10aα)-6-benzoyl-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridine (**19b**) and 5% of 6α,6aβ,10aβ isomer **18b**.

19b: mp 176-177 °C (MeOH); ^{1}H NMR δ 1.75 (complex m, H_7), 1.82 (complex m, $H_{7'}$), 2.12 (complex m, H_8 and $H_{8'}$), 2.44 (dddd, H_{6a}, $J_{6a,7'}$ = 10.2, $J_{6a,10a}$ = 5.2, $J_{6,6a}$ = 3.9, $J_{6a,7}$ = 3.4), 3.17 (br t, H_{10a}, $J_{10,10a}$ = 5.1), 4.72 (d, H_6), 5.75 (dtd, H_9, $J_{9,10}$ = 9.9, $J_{8,9}$ = $J_{8',9}$ = 3.7, $J_{9,10a}$ = 1.6), 6.01 (ddt, H_{10}, $J_{8,10}$ = $J_{8',10}$ = 2.1), 6.78 (d, H_4, $J_{3,4}$ = 6.6), 6.98 (ddd, H_3, $J_{1,3}$ = 2.4, $J_{3,10a}$ = 0.8), 7.05 (dd, H_1, $J_{1,10a}$ = 1.1), 7.49 (m, COPh, H_m), 7.61 (m, COPh, H_p), 7.93 (m, COPh, H_o). Anal. Calcd for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; Cl, 10.95; N, 4.33. Found: C, 74.32; H, 5.56; Cl, 10.89; N, 4.38.

Acknowledgment. We thank a reviewer for calling our attention to the papers cited under ref 16.

Registry No. **4a**, 113628-30-1; **4b**, 113628-31-2; **4c**, 113628-32-3; **4d**, 113628-33-4; **5a**, 91851-06-8; **5b**, 91851-05-7; **5c**, 79866-41-4; **6a**, 113628-34-5; **7a**, 113628-35-6; **7b**, 113628-36-7; **8a**, 113628-38-9; **8b**, 113628-39-0; **9**, 113628-37-8; **11a**, 113628-45-8; **11b**, 113628-46-9; **12a**, 113628-40-3; **12b**, 113628-41-4; **13a**, 113628-47-0; **13b**, 113628-48-1; **14a**, 113667-68-8; **14b**, 113667-69-9; **15a**, 113628-42-5; **16a**, 113628-43-6; **16b**, 113628-44-7; **16c**, 113628-49-2; **16d**, 113628-50-5; **17a**, 113667-70-2; **17b**, 113667-71-3; **17c**, 113667-72-4; **17d**, 113667-73-5; **18a**, 107209-59-6; **18b**, 107297-72-3; **18c**, 107209-61-0; **18d**, 107209-60-9; **19a**, 107297-74-5; **19b**, 107297-73-4; CH_2=CHCH=CH_2, 106-99-0; CH_2=$C(CH_3)$CH=CH_2, 78-79-5; CH_2=$C(CH_3)C(CH_3)$=CH_2, 513-81-5; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4.

Supplementary Material Available: Detailed description of NOE and structural analyses for compounds **4b**, **8b**, **11a**, **13a**, **14a**, **15a**, **16a**, **17a**, **18a**, and **19a** (4 pages). Ordering information is given on any current masthead page.

Regioselective Synthesis of Isoquinuclidin-6-ones. Synthesis of an Ibogamine Intermediate

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Addition of benzeneselenenyl chloride to 5,6-dehydroisoquinuclidines **8** followed by dehydrohalogenation and hydrolysis of the derived vinyl selenides **11** affords isoquinuclidin-6-ones **7** regioselectively. The method has been applied to the synthesis of 7-*syn*-ethylisoquinuclidin-6-one **16**, an intermediate in the synthesis of ibogamine **2a**.

Isoquinuclidin-6-ones **1** have served as key intermediates in several general approaches to the alkaloids *dl*-ibogamine (**2**) and catharanthine (**3**).[3,4] Depending upon the group R of **1**, the versatile carbonyl group has been utilized either

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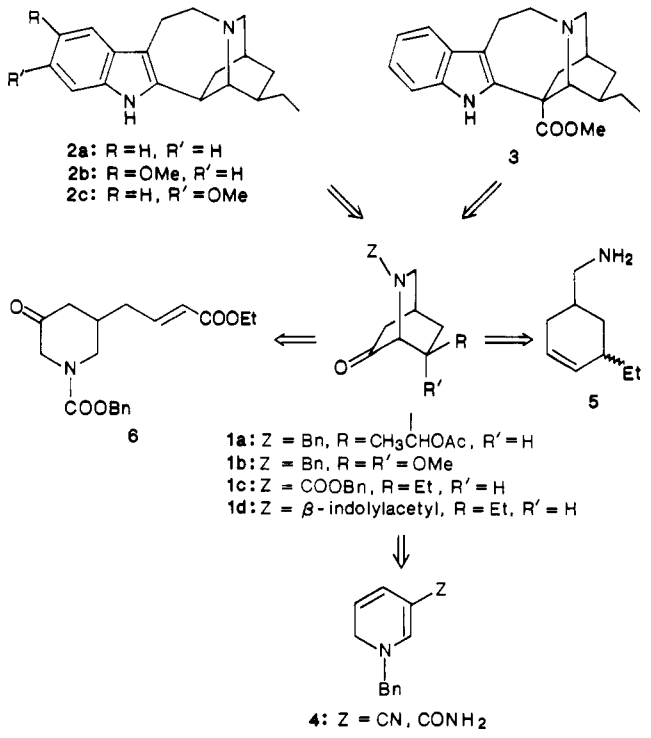
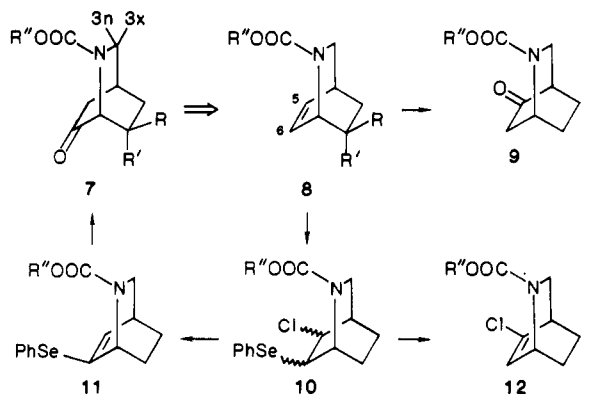
Scheme I



as a site for formation of the C–C bond between the indole and isoquinuclidine rings of **2** or **3**[3] or as a handle for introduction of the ethyl substituent.[4] The successful regioselective synthetic routes to **1a** and **1b** (Scheme I) have been based upon cycloadditions of methyl vinyl ketone with 5-cyano- or 5-carbamoyl-*N*-benzyl-1,2-dihydropyridines **4**.[3a,4] Ring closure methodology utilizing 3-ethyl-5-(aminomethyl)cyclohexene (**5**)[3b] provided **1c**, and intramolecular Michael reaction of *N*-[(benzyloxy)-carbonyl]-5-[[3-(ethyloxy)carbonyl]-2-propyl]piperidin-3-one (**6**)[3d] afforded **1d**. The syntheses of *1a-d* have not been trivial, however, and each approach has some drawbacks.

Retrosynthetic analysis of the isoquinuclidin-6-one heterocycle **7**[5] suggested the 5,6-dehydroisoquinuclidine **8** as a potential synthetic precursor (Scheme II). Numerous structures **8** are readily available via Diels–Alder routes involving iminium ions and cyclohexa-1,3-diene[6] or

Scheme II



through an alternative reaction of *N*-acyl-1,2-dihydropyridines with suitable dienophiles.[7] However, prior to this work, attempts to develop regioselective functionalization reactions for the olefinic bond of **8** leading to 6-keto derivatives **7** had not been successful.[1] Hydroboration of **8a** followed by oxidation gave in 63% yield a mixture of 55–60% **9** and 45–40% **7a**.[6a] Epoxidation of **8a** followed by reduction with lithium aluminum hydride was reported to lead in 45% yield to a mixture containing 65% of the 6-hydroxy isomers, which upon oxidation provided the *N*-methyl analogue of ketone **7a**.[8] However, this report was put into question by Borne et al.[5e] when they found only 10% of the 6-hydroxyisoquinuclidine regioisomers upon reduction of the epoxide mixture from **8a**.

In an effort to develop a regioselective synthesis of isoquinuclidin-6-ones **7** from **8**, we took advantage of our earlier observation that oxymercuration can be used to regioselectively functionalize **8a** (R = R' = H) to give isoquinuclidin-5-one **9**.[9] Since the bridging electrophilic moiety ultimately became bonded to the 6-position of **8a**, we reasoned that addition of benzeneselenenyl chloride should introduce the electrophilic phenylselenyl group at the 6-position and chloride at the 5-position in a structure of type **10**. Basic elimination would afford vinyl selenide **11**, which upon hydrolysis would give the desired isoquinuclidin-6-one **7**.

Addition of benzeneselenenyl chloride to olefin **8a** afforded chloro selenide **10a** of undefined stereochemistry. Significantly, however, it was found that only the regioisomer having the phenylselenyl group at C-6 was obtained. Elimination of hydrogen chloride from **10a** by heating to reflux in neat DBU afforded solely the vinyl selenide **11a**. In NMR decoupling experiments with **11a** irradiation of

(1) For a preliminary communication, see: Krow, G. R.; Shaw, D. A. *Synth. Commun.* **1982**, *12*, 313–318.

(2) Portions of this paper was taken from the doctoral thesis of D. A. Shaw (present address: FMC Corporation, P.O. Box 8, Princeton, NJ 08540) and from a paper presented at the 29th National Medicinal Chemistry Symposium, The University of North Carolina at Chapel Hill, NC, Abstract No. 33, June 16, 1986.

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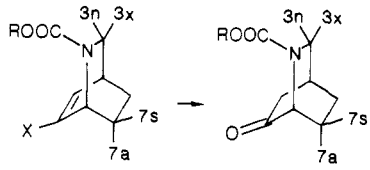
Table I. Yields of Vinyl Selenides 11 and Ketones 7 in the Regioselective 6-Ketofunctionalization Sequence from Olefins 8[a]



8, X = H
11, X = PhSe

7

olefin 8	R	yield (%) (%) vinyl selenide 11	ketone 7
(a) parent	Et	78	69
(b) 3x-Me	Et	68	57
(c) 3n-Me	Et	81	80
(d) 3x-Ph	Et	79	66
(e) 7s-Et	Me	94	65
(f) 7a-Et	Me	45	72
(g) 7s-COMe	Me	*a*	
(h) 7a-COMe	Me	*a*	
(i) 3n-CCl_3	Et	*b*	

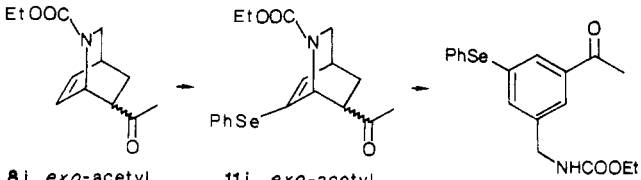
[a] Addition of benzeneselenenyl chloride to a **8g/8h** mixture followed by elimination afforded **13** rather than vinyl selenides **11g/11h**. [b] See Experimental Section.

the multiplet at δ 2.45 (H-4) caused the doublet (J = 8 Hz) at δ 6.45 (H-5) to simplify to a singlet; irradiation of the multiplet at δ 4.70 (H-1) did not affect H-5.

In order to show that isomerization of chloro selenides **10a** had not occurred during the thermal elimination process, **10a** was reacted at room temperature with 30% hydrogen peroxide to give the single vinyl chloride **12**. NMR decoupling experiments confirmed structure **12** following collapse of the major 6 Hz couplings for conformers of H-6 at δ 5.96 and 5.90 upon irradiation of H-1 at δ 4.78 and 4.80.

The results following application of the synthetic method to the formation of vinyl selenides **11a–f** and the corresponding ketone hydrolysis[10] products **7a–f**, from a series of 3- and 7-substituted-5,6-dehydroisoquinuclidines **8a–f**, are shown in Table I. As found for the parent **8a**, the functionalization method was totally regioselective for 6-keto isomers **7a–f** at the level of detection by ^{1}H NMR and TLC; no evidence for known isomeric 5-keto isomers **9** was found.[9] Significantly, endo-C-3 and anti-C-7 alkyl substituents, which lie over the 5,6-double bond in structures **8c** and **8f**, did not hinder addition of benzeneselenenyl chloride. However, an endo-C-3 trichloromethyl group in **8i** was sufficient to block reaction with benzeneselenenyl chloride or bromide.

Phenylselenium chloride added to a mixture of 7-acetyl isomers **8j** and **8k**;[7b] however, elimination with DBU at 25 °C for 144 h in toluene afforded primarily the diaryl selenide **13**. Presumably, in the basic medium the vinyl selenides **11j/11k** underwent subsequent elimination of carbamate anion β to the ketone carbonyl, which was then air-oxidized to give **13**.



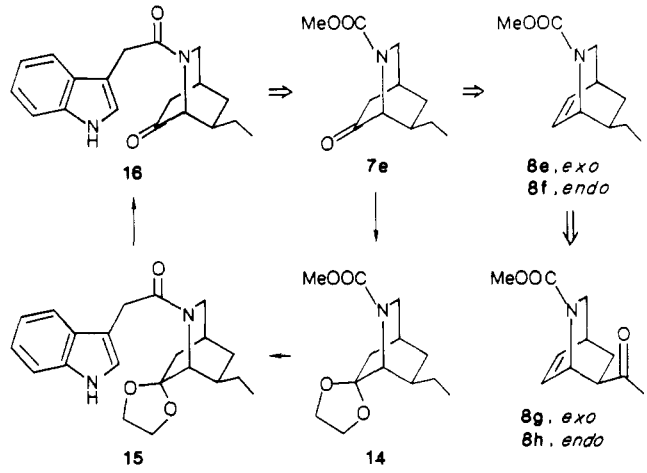
8j, *exo*-acetyl
8k, *endo*-acetyl

11j, *exo*-acetyl
11k, *endo*-acetyl

13

(10) Marino, J. P.; Landick, R. C. *Tetrahedron Lett.* **1975**, 4531–4534.

Scheme III



16 7e 8e, *exo* 8f, *endo*

15 14 8g, *exo* 8h, *endo*

Previously, *dl*-ibogamine (**2a**) has been synthesized from ketone **16** by Hanaoka et al.[3d] Retrosynthetic analysis suggests ketone **7e** as a precursor (Scheme III). The 7-acetyl isomer **8g**,[7b] although reported only as a mixture with its epimer **8h**, would be a suitable precursor to ketone **7e**, since only a carbonyl reduction and ketofunctionalization at C-6 is required. Nevertheless, the necessity to separate an epimeric mixture of the 7-acetyl (**8g/8h**) or 7-ethyl (**8e/8f**) stereoisomers remained. Upon preparation of the tosylhydrazones from a mixture of ketones **8g** and **8h** in tetrahydrofuran, an unexpected bonus was received. A crystalline tosylhydrazone was obtained, which was easily separated from an oily tosylhydrazone which remained. Reduction of the crystalline tosylhydrazone with sodium cyanoborohydride[11] afforded a single ethyl stereoisomer. This could be assigned as the 7-syn isomer **8e** on the basis of high field ^{1}H NMR coupling parameters; proton H-8s (dd, J = 12 Hz, 3 Hz, NOE with H-3x) exhibited coupling only to H-4 and H-8a, indicating a syn relationship to the 7-ethyl substituent. In confirmation of this assignment proton H-8s (dt, J = 13 Hz, 3 Hz, 3 Hz, NOE with H-3x) in the 7-anti-ethyl isomer **8f** was coupled to H-4, H-8a, and H-7s.

Olefin **8e** was converted to ketone **7e** by using the present regioselective 6-ketofunctionalization methodology. In order to remove the *N*-methoxycarbonyl group, the ketone **7e** was first protected as its ketal with ethylene glycol to give **14**. Methyllithium cleavage of the carbamate and subsequent acylation of the resulting amine with β-indolylacetyl chloride provided **15**. Ketal hydrolysis afforded the keto amide **16**, previously converted to ibogamine by Hanaoka et al.,[3d] in 34% overall yield from olefin **8e**.

In the present paper we have shown that a carbonyl moiety can be introduced β to the nitrogen atom of 5,6-dehydroisoquinuclidine **8** to afford isoquinuclidin-6-ones **7**. The method involves hydrolysis of vinyl selenides **11**, which are derived from structures **10**, formed by regioselective addition of benzeneselenenyl chloride to the olefinic bond of **8**. Further applications of this selenium-based methodology will be reported in due course.

Experimental Section

General. Infrared spectra were measured with a Perkin-Elmer 137 sodium chloride spectrophotometer as methylene chloride solutions unless otherwise indicated. Exact mass measurements were taken on an RMH-2 Hitachi Perkin Elmer or UG Micromass 7035 mass spectrometer. Unless otherwise noted, proton NMR

(11) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668.

spectra were obtained in deuteriochloroform solutions with tetramethylsilane as an internal standard using either a Perkin-Elmer R-32 or a Varian EM-390 90-MHz NMR. Carbon NMR spectra were recorded on a Varian XL-100 instrument operating at 25.2 MHz using a Nicolet NTCFT 1180 pulse system; deuteriochloroform was used as solvent and peak locations were determined relative to δ 76.910 for chloroform. Thin layer chromatography was conducted by using Analtech silica gel GF plates containing a fluorescent indicator. Olefins **8a**,[6a] **8b**,[6b] **8c**,[7c] **8d**,[6c] **8g**,[7b] **8h**,[7b] and **8i**[6d] were prepared as previously described.

***N*-(Methoxycarbonyl)-7-*syn*-ethyl-2-azabicyclo[2.2.2]-oct-5-ene (8e) and *N*-(Methoxycarbonyl)-7-*anti*-ethyl-2-azabicyclo[2.2.2]oct-5-ene (8f).** A mixture of *N*-(methoxycarbonyl)-7-acetyl-2-azabicyclo[2.2.2]oct-5-enes **8g** and **8h**[7b] (2.8 g, 0.013 mol) was dissolved in dry tetrahydrofuran (10 mL), tosylhydrazine (2.5 g, 0.013 mol) was added, and the resulting solution was warmed to 50 °C for 48 h to give a milky yellow solution. Following cooling, filtration afforded 3.9 g (77%) of white crystals, R_f 0.33 (1:1 hexane/ethyl acetate), mp 178–180.5 °C (nearly pure by ^{1}H NMR) increasing to mp 192–193.5 °C after two recrystallizations from methanol: ^{1}H NMR δ 7.8–7.4 (m, 5 H), 6.2–6.0 (br, H-5, H-6), 4.9 (br, H-1), 3.7 (s, OMe), 3.5–2.8 (m, 4 H), 2.4 (s, Me), 1.8 (s, Me), 1.7 (br, 2 H); IR 3700–3200, 1700 cm^{-1}. Anal. Calcd for $C_{18}H_{23}N_3O_4S$: C, 57.28; H, 6.14; N, 11.13. Found: C, 57.30; H, 6.04; N, 11.19. Removal of solvent from the filtrate in vacuo afforded an oily residue (1.2 g), which was mainly the isomeric tosylhydrazone, R_f 0.33 (1:1 hexane/ethyl acetate), which failed to crystallize: ^{1}H NMR δ 7.8–7.3 (m, 5 H), 6.42 (m, 2 H), 4.75 (br, H-1), 3.70–3.60 (br, OMe), 3.2–2.8 (m, H-3's), 2.75–2.10 (m, 2 H), 2.40 (s, Me), 1.90 and 1.75 (3 H, Me), 1.9–1.5 (br, 2 H). The ratio of crystalline to noncrystalline tosylhydrazones varied from trial to trial.

A sample of crystalline tosylhydrazone (27.1 g, 0.072 mol) was dissolved in tetrahydrofuran (225 mL) and heated at reflux under nitrogen for 1 h with a catalytic amount of *p*-toluenesulfonic acid (1 g) and sodium cyanoborohydride (18.0 g, 0.28 mol). After cooling, the reaction mixture was poured into water and extracted with methylene chloride (3 × 150 mL). The combined organic layers were washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and filtered, and solvent was removed in vacuo to afford crude olefin. Vacuum distillation (133–136 °C, 0.2 mm) afforded 13.4 g (96%) of isomerically pure olefin **8e**: 360-MHz ^{1}H NMR (some of the peaks are due to sets of conformers) δ 6.40 (m, H-5), 6.35 and 6.25 (two m, H-6), 4.7 and 4.5 (br, H-1), 3.70 (s, 3 H), 3.20 (dd, 10 Hz, 2 Hz, H-3x), 2.95 (m, H-3n), 2.70 (br, H-4), 1.98 (br, H-7a), 1.80 (dd, 12 Hz, 3 Hz, H-8s), 1.2 (m, 1 H), 1.0-0.9 (br, H-8a and C*H*), 0.85 (t, J = 7 Hz, Me), an NOE is observed between H-3x and H-8s; ^{13}C NMR δ 155.336, 133.789, 130.340, 51.749, 48.657, 46.330, 40.577, 30.900, 29.808, 28.086, 11.006; IR 2980, 1700, 1475, 1380 cm^{-1}; m/e 195.1259, found m/e 195.1265. Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.70; H, 8.78; N, 6.99.

The oily tosylhydrazone (12.58 g, 0.033 mol) was dissolved in dimethylformamide (75 mL) and sulfolane (75 mL); sodium cyanoborohydride (8.37 g, 0.133 mol) and *p*-toluenesulfonic acid (750 mg) were added and the mixture was heated under argon to 105 °C for 20 h. The reaction mixture was cooled, diluted with water (50 mL), and extracted with cyclohexane (4 × 100 mL). The combined organic extracts were washed with saturated sodium chloride (10 mL) and water (10 mL), dried over magnesium sulfate, and filtered; solvent was removed in vacuo and the residue was distilled as above to afford 4.21 g (65%) of olefin **8f**: 500-MHz ^{1}H NMR (sets of conformers) δ 6.42, 6.47 (dt, J = 7.9, 6.2, 1.6 Hz, H-6), 6.34, 6.31 (ddd, J = 7.9, 6.4, 1.6 Hz, H-5), 4.60, 4.45 (dt, J = 6.2, 1.5, 1.6 Hz, H-1), 3.68 (s, OMe), 3.20 (dd, J = 9.9 Hz, 2.2 Hz, H-3x), 2.99, 2.94 (dt, J = 9.9, 2.7, 2.7 Hz, H-3n), 2.67, 2.64 (m, H-4), 1.64, 1.62 (dt, J = 13, 3, 2.7 Hz, H-8a), 1.45 (m, H-7s), 1.35 (m, CH_2), 1.0 center of two conformers (ddd, J = 13.0, 2.7, 2.4 Hz, H-8s; in benzene-d_6 the resonance for H-8s is upfield at δ 0.65 and can be observed more clearly), 0.95, 0.92 (t, J = 7.2 Hz, Me), and NOE was observed between H-8s and H-3x; ^{13}C NMR δ 155.889 (s), 132.952 (d, overlapping C-5 and C-6), 51.381 (q), 48.505 (d), 47.807 (t), 40.399 (d), 30.450 (d), 29.563 (t), 26.955 (t), 11.393 (q); IR (neat) 1700, 1460, 1400 cm^{-1}; high resolution mass spectrum, calcd for $C_{11}H_{17}NO_2$ m/e 195.1259, found m/e 195.1279.

***N*-(Ethoxycarbonyl)-5-chloro-6-(phenylselenenyl)-2-azabicyclo[2.2.2]octane (10a).** The olefin **8a** (800 mg, 4.4 mmol) was dissolved in dry methylene chloride (30 mL) and stirred at −78 °C under nitrogen. To this solution was added benzeneselenenyl chloride (0.92 g, 4.84 mmol). After stirring at room temperature for 13 h, the solvent was removed in vacuo and the residue was chromatographed (1:1 hexane/ether) to give 1.60 g (98%) of **10a** as a viscous oil: NMR δ 7.60 (m, 2 H), 7.25 (m, 3H), 4.15 (q, J = 8 Hz, 5 H), 3.70–3.50 (m, 2 H), 2.20–1.50 (m, 5 H), 1.25 (t, J = 8 Hz, 3 H); IR (neat) 2950, 1705 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_2ClSe$: C, 51.54; H, 5.37; N, 3.76. Found: C, 51.26; H, 5.40; N, 3.86.

Formation of Vinyl Selenides (11). General Procedure. The olefin 8 (4.4 mmol) was converted to the 5-chloro-6-phenylselenenyl adduct exactly as described above for formation of **10a**. The adduct **10** was refluxed under nitrogen with 4.4 mL of DBU for 15 h. After being cooled to room temperature, the mixture was diluted with water, the aqueous solution was extracted with ether (3 × 70 mL), the ether extracts were washed with 2% hydrochloric acid, dried over magnesium sulfate, and filtered, and the solvent was removed to give *N*-(ethoxycarbonyl)-6-(phenylselenenyl)-5,6-dehydroisoquinuclidine (**11**). The crude vinyl selenides **11** could be hydrolyzed directly to ketones **7** without further purification.

***N*-(Ethoxycarbonyl)-6-(phenylselenenyl)-2-azabicyclo-[2.2.2]oct-5-ene (11a).** Olefin **8a** (1.33 g, 7.3 mmol) afforded 1.74 g (78%) of vinyl selenide **11a**: ^{1}H NMR (separate carbamate conformers are observed) δ 7.50 (m, 2 H), 7.30 (m, 3 H), 6.45 (d, J = 6 Hz, H-5), 4.70 (m, 1 H), 4.00 (q, J = 8 Hz, 2 H), 3.40–2.95 (m, 2 H), 2.80 (m, 1 H), 2.00–1.30 (m, 4 H), 1.20 (t, J = 8 Hz, 3 H); IR (neat) 2920, 1705 cm^{-1}; mass spectrum, m/e (relative intensity) 337 (5), 236 (55).

***N*-(Ethoxycarbonyl)-3-*exo*-methyl-6-(phenylselenenyl)-2-azabicyclo[2.2.2]oct-5-ene (11b).** Olefin **8b** (0.45 g, 2.3 mmol) afforded 0.24 g (68%) of oily vinyl selenide **11b**: ^{1}H NMR δ 7.45 (m, 2 H), 7.30 (m, 3 H), 6.40 (m, 1 H), 4.65 (m, 1 H), 4.05 (q, J = 8 Hz, 2 H), 3.40 (m, 1 H), 2.50 (m, 1 H), 2.00–1.40 (m, 4 H), 1.15 (m, 6 H); IR 2950, 1705 cm^{-1}; mass spectrum, m/e (relative intensity) 351 (15), 236 (61).

***N*-(Ethoxycarbonyl)-3-*endo*-methyl-6-(phenylselenenyl)-2-azabicyclo[2.2.2]oct-5-ene (11c).** Olefin **8c** (0.15 g, 0.8 mmol) gave 0.22 g (81%) of oily vinyl selenide **11c**: ^{1}H NMR δ 7.50 (m, 2 H), 7.30 (m, 3 H), 6.40 (m, 1 H), 4.70 (br, 1 H), 3.70 (m, 1 H), 2.60 (m, 1 H), 1.90–1.40 (m, 4 H), 1.20 (t, J = 8 Hz, 6 H); IR 2950, 1705 cm^{-1}; mass spectrum, m/e (relative intensity) 351 (21), 236 (100).

***N*-(Ethoxycarbonyl)-3-*exo*-phenyl-6-(phenylselenenyl)-2-azabicyclo[2.2.2]oct-5-ene (11d).** Olefin **8d** (0.80 g, 3.0 mmol) gave 1.01 g (79%) of vinyl selenide **11d**: ^{1}H NMR δ 7.50 (m, 2 H), 7.30 (m, 3 H), 6.55 (m, 1 H), 4.90 (br, 1 H), 4.50 (m, 1 H), 3.85 (br, 2 H), 2.70 (m, 1 H), 2.10–1.30 (m, 4 H), 1.00 (br, 3 H); IR 2950, 1705 cm^{-1}; mass spectrum, m/e (relative intensity) 413 (7), 236 (100).

***N*-(Methoxycarbonyl)-7-*syn*-ethyl-6-(phenylselenenyl)-2-azabicyclo[2.2.2]oct-5-ene (11e).** Olefin **8e** (2.40 g, 12.3 mmol) afforded 3.90 g (94%) of vinyl selenide **11e**: ^{1}H NMR δ 7.60, 7.35 (br, 5 H), 6.40 (d, J = 8 Hz, 1 H), 4.70 (br, 1 H), 3.60 (s, 3 H), 3.40–2.90 (br, 2 H), 2.80 (m, 1 H), 2.20–1.70 (m, 3 H), 1.40–0.75 (m, 5 H); IR 2920, 1710, 1440, 1385 cm^{-1}; high resolution mass spectrum, calcd for $C_{17}H_{21}NO_2Se$, m/e 351.0737, found 351.0737.

***N*-(Methoxycarbonyl)-7-*anti*-ethyl-6-(phenylselenenyl)-2-azabicyclo[2.2.2]oct-5-ene (11f).** Olefin **8f** (0.96 g, 4.26 mmol) gave 0.68 g (45%) of vinyl selenide **11f**; ^{1}H NMR δ 7.50, 7.25 (br, 5 H), 6.25 (d, J = 8 Hz), 4.4 (br, H-1), 3.45 (s, OMe), 3.2–2.9 (m, H-3's), 2.70 (m, H-4), 1.8–1.0 (m, 5 H), 0.85 (q, J = 7 Hz, 3 H); IR (neat) 2900, 1700, 1420, 1380 cm^{-1}; high resolution mass spectrum, calcd for $C_{17}H_{21}NO_2Se$ m/e 351.0737, found 351.0733.

***N*-(Ethoxycarbonyl)-5-chloro-2-azabicyclo[2.2.2]oct-5-ene (12).** The 5-chloro-6-phenylselenenyl adduct **10a** (1.10 g, 2.95 mmol) was dissolved in tetrahydrofuran (20 mL) and 30% hydrogen peroxide (5 mL) solution was added in one portion. The reaction mixture was stirred at room temperature for 17 h, then diluted with ether (20 mL), and poured into a separatory funnel containing 10% aqueous sodium sulfite solution (10 mL). The layers were separated and the organic portion was washed with

saturated aqueous sodium bicarbonate (10 mL), water (10 mL), and brine (10 mL) and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a quantitative yield of a pale yellow oil, R_f 0.41 (4:1 hexane/ether), whose 300-MHz ^{1}H NMR [δ 5.94 (two conformational isomers, dd, J = 6.6 Hz, 2.0 Hz, H-6, coupled large to H-1 and small to H-4)] is consistent only with a single structural isomer. Flash column chromatography (4:1 hexane–ether) provided 462 mg (73%) of pale yellow oil; 300-MHz ^{1}H NMR (benzene-d_6) δ 5.96 and 5.90 (two dd, J = 6.6 Hz, 2.0 Hz, H-6), 4.78 and 4.40 (two m, H-1), 4.00 (q, J = 7 Hz, OCH_2), 3.00–2.84 (m, H-3exo and H-3endo), 2.77 (m, H-4), 1.58 (m, H-8), 1.15–0.65 (m, H-7's, H-8, CH_3); IR (neat) 2950, 1710 cm^{-1}; high resolution mass spectrum, calcd for $C_{10}H_{14}NO_2Cl$ m/e 215.0714, found m/e 215.0713.

Attempted Preparation of *N*-(Ethoxycarbonyl)-7-*exo*/*endo*-acetyl-6-(phenylselenenyl)-2-azabicyclo[2.2.2]oct-5-enes (11j and 11k). Formation of 1-Acetyl-3-[(ethoxycarbonyl)-aminomethyl]-5-(phenylselenenyl)benzene (13). A mixture of 7-acetyl olefins **8j** and **8k** (0.625 g, 2.7 mmol) after addition of benzeneselenenyl chloride, DBU elimination for 1 week at 25 °C in toluene, and flash chromatography afforded trace amounts of minor products and 240 mg (27%) of oily **13**: ^{1}H NMR δ 7.80–7.40 (m, 8 H), 5.55 (br, 1 H), 4.35 (d, J = 7 Hz, 2 H), 4.10 (q, J = 7 Hz, 2 H), 2.50 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 197.608, 156.563, 139.380, 137.452, 131.905, 128.735, 128.642, 60.936, 44.686, 26.388, 14.463; IR 3300, 1725, 1700 cm^{-1}; high resolution mass spectrum, calcd for $C_{18}H_{17}NO_3Se$ m/e 377.0507, found m/e 377.0527.

Attempted Additions of Benzeneselenenyl Halide to 3-*endo*-Trichloromethyl Olefin 8i. Benzeneselenenyl bromide failed to add to olefin **8i** (86% recovery) after 50 h in refluxing chloroform. Benzeneselenenyl chloride failed to add to olefin **8i** (90% recovery) after reflux for 15 h in refluxing 88% formic acid.

Vinyl Selenide Hydrolysis. General Procedure. The vinyl selenide **11** (5.2 mmol) was dissolved in dioxane (25 mL) and refluxed with an equal volume of 20% hydrochloric acid. After 48 h, the reaction mixture was cooled to room temperature and was extracted with ether (3 × 50 mL). The combined ether extracts were washed with water, followed by saturated sodium carbonate, dried over magnesium sulfate, and filtered, and solvent was removed in vacuo to give, after flash chromatography (2:1 hexane/ethyl acetate), the corresponding ketone **7**.

***N*-(Ethoxycarbonyl)-2-azabicyclo[2.2.2]octan-6-one (7a).** Vinyl selenide **11a** (1.74 g, 5.2 mmol) afforded 693 mg (69%) of colorless oil, which crystallized from ether/hexane to give ketone **7a**: mp 68–70 °C (lit.[5a] mp 69–70 °C); ^{1}H NMR δ 4.35 (m, 1 H), 4.20 (q, J = 8 Hz, 2 H), 3.50 (s, 2 H), 2.45 (br s, 3 H), 2.10–1.60 (m, 4 H), 1.26 (t, J = 8 Hz, 3 H); ^{13}C NMR δ 206.089 (s, C-6), 154.879 (s), 60.962 (t), 54.753 (d, C-1), 47.957 (t, C-3), 42.773 (t, C-5), 28.189 (d, C-4), 24.561, 22.787 (both t, C-7, C-8), 14.187 (q); IR (neat) 2950, 1725, 1705, 1120 cm^{-1}; mass spectrum, m/e 197.

***N*-(Ethoxycarbonyl)-3-*exo*-methyl-2-azabicyclo[2.2.2]octan-6-one (7b).** Vinyl selenide **11b** (0.55 g, 1.5 mmol) afforded 0.19 g (57%) of oily ketone **7b**: ^{1}H NMR δ 4.30 (m, 1 H), 4.17 (q, J = 7 Hz, 2 H), 3.90 (m, 1 H), 2.80 (m, 1 H), 2.55–2.30 (m, 2 H), 2.10–1.70 (m, 4 H), 1.45–1.20 (br, 6 H); ^{13}C NMR δ 206.802, 155.590, 61.341, 55.808, 52.887, 44.847, 34.256, 24.091, 19.105, 18.210, 14.445; IR 2950, 1725, 1705 cm^{-1}; high resolution mass spectrum, calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found m/e 211.1200.

***N*-(Ethoxycarbonyl)-3-*endo*-methyl-2-azabicyclo[2.2.2]-octan-6-one (7c).** Vinyl selenide **11c** (0.17 g, 0.5 mmol) afforded 0.08 g (80%) of oily ketone **7c**; ^{1}H NMR δ 4.32 (br, 1 H), 4.20 (q, J = 8 Hz, 2 H), 3.85 (m, 1 H), 2.80 (m, 1 H), 2.60–2.30 (m, 2 H), 2.10–1.70 (m, 4 H), 1.44 (d, J = 8 Hz, 3 H), 1.27 (t, J = 8 Hz, 3 H); ^{13}C NMR δ 209.370, 155.310, 61.240, 56.090, 53.590, 37.940, 33.440, 24.280; IR 2950, 1725, 1705, 1290, 1095 cm^{-1}; high resolution mass spectrum, calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found m/e 211.1207.

***N*-(Ethoxycarbonyl)-3-*exo*-phenyl-2-azabicyclo[2.2.2]octan-6-one (7d).** Vinyl selenide **11d** (0.10 g, 0.25 mmol) gave 0.045 g (66%) of oily ketone **7d**: ^{1}H NMR δ 7.30 (s, 5 H), 4.95 (m, 1 H), 4.55 (m, 1 H), 4.07 (q, J = 8 Hz, 2 H), 2.55 (m, 1 H), 2.30–0.95 (br, 8 H); ^{13}C NMR δ 206.582, 155.682, 61.590, 55.530, 51.094, 44.186, 35.946, 23.677, 17.814, 14.264; IR 2950, 1750, 1700, 1405, 1290, 1095 cm^{-1}; high resolution mass spectrum, calcd for $C_{16}H_{19}NO_3$ m/e 273.1350, found m/e 273.1376.

***N*-(Methoxycarbonyl)-7-*syn*-ethyl-2-azabicyclo[2.2.2]octan-6-one (7e).** Vinyl selenide **11e** (1.01 g, 2.8 mmol) gave 0.39 g (65%) of oily ketone **7e**: ^{1}H NMR δ 4.20 (m, 1 H), 3.70 (s, 3 H), 3.45 (s, 3 H), 2.40 (m, 1 H), 2.35 (s, 2 H), 2.05 (m, 2 H), 1.40–1.05 (br, 3 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 205.574 (s), 155.186 (s), 58.668 (d), 52.081 (q), 47.222 (t), 43.115 (t), 39.099 (d), 30.980 (t), 28.041 (d), 27.167 (t), 10.785 (q); IR 2950, 1725, 1700, 1450, 1400 cm^{-1}; high resolution mass spectrum, calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found m/e 211.1196.

***N*-(Methoxycarbonyl)-7-*anti*-ethyl-2-azabicyclo[2.2.2]octan-6-one (7f).** Vinyl selenide **11f** ((0.44 g, 1.26 mmol) gave 0.193 g (72%) of oily ketone **7f**: ^{1}H NMR δ 4.20 (m, H-1), 3.7 (s, OMe), 3.45 (s, H-3's), 2.40 (m, 3 H), 2.1–1.7 (m, 2 H), 1.65–1.15 (m, 3 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 206.846 (s), 155.900 (s), 58.098 (d), 52.178 (q), 48.204 (t), 41.704 (t), 37.475 (t), 30.744 (d), 28.020 (d), 26.591 (t), 10.851 (q); IR (neat) 2905, 1725, 1705, 1450, 1395 cm^{-1}; high resolution mass spectrum, calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found m/e 211.1206.

***N*-(Methoxycarbonyl)-7-*syn*-ethyl-2-azabicyclo[2.2.2]octan-6-one Ethylene Ketal (14).** Ketone **7e** (0.26 g, 1.23 mmol) was dissolved in dry toluene (50 mL) and heated to reflux for 48 h under nitrogen with ethylene glycol (0.1 g) and *p*-toluenesulfonic acid (10 mg) during which time a Dean–Stark water separator was used to collect azeotroped water. After being cooled to room temperature, the reaction mixture was diluted with 2% sodium hydroxide (75 mL) and extracted with ether (2 × 25 mL). The ether was dried over sodium sulfate and filtered, and solvent was removed in vacuo to afford 0.295 g (99%) of **14**: ^{1}H NMR δ 3.95 (br s, 5 H), 3.70 (s, 3 H), 3.25 (s, 2 H), 2.05 (m, 1 H), 1.95–1.45 (br, 5 H), 1.35–1.05 (br, 2 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 155.742 (s), 108.360 (s), 64.282 (t), 63.041 (q), 51.496 (d), 46.223 (d), 39.667 (t), 38.618 (t), 31.003 (d), 27.178 (t), 27.036 (t), 11.614 (q); IR 2950, 1700 cm^{-1}; high resolution mass spectrum, calcd for $C_{13}H_{21}NO_4$ m/e 255.1473, found m/e 255.1467.

***N*-(β-Indolylacetyl)-7-*syn*-ethyl-2-azabicyclo[2.2.2]octan-6-one (16).** Ketal **14** (100 mg, 0.4 mmol) was dissolved in dry ether (10 mL) and stirred at 0 °C under nitrogen. Methyllithium (2.5 equiv) was added, and the solution was stirred at 25 °C for 12 h and then quenched with saturated ammonium chloride. Ether extraction (3 × 20 mL), addition of sodium bicarbonate until basic, ether extraction (3 × 20 mL), drying over magnesium sulfate, and removal of solvent afforded an amine which was immediately condensed with β-indolylacetyl chloride (85 mg, 0.44 mmol) in methylene chloride (20 mL). After stirring at 25 °C for 24 h, solvent was removed in vacuo and the crude ketal **15** was dissolved in tetrahydrofuran (10 mL), diluted with 5% hydrochloric acid (10 mL), and stirred at 25 °C for 24 h. Ether extraction afforded, after drying, removal of solvent in vacuo, and reverse phase HPLC (C_{18} column, 85:15 methanol/water), 0.07 g (56%) of pure **16**: ^{1}H NMR δ 8.15–8.30 (br, 1 H), 7.70–7.00 (m, 5 H), 4.80, 4.00 (d, J = 4.5 Hz), 3.80 (q, J = 16 Hz), 3.65 (dt, J = 12, 2 Hz), 3.40 (dd, J = 12, 2 Hz), 1.40–0.90 (m, 5 H), 0.85 (m, 3 H); ^{13}C NMR δ 206.253, 170.783, 136.062, 126.843, 122.165, 119.608, 118.732, 111.031, 108.658, 66.691, 61.396, 46.935, 39.309, 33.894, 28.808, 27.261, 24.372, 10.916; IR 3450, 2920, 1730, 1640, 1460, 1420, 1260 cm^{-1}; high resolution mass spectrum, calcd for $C_{19}H_{22}N_2O_2$ m/e 310.1686, found m/e 310.1683.

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