(1 M, 3.2 mL, 3.2 mmol). After being stirred at 0 °C for 3 h, the solution was neutralized by addition of Amberlite IR-120 (H^+). The resin was removed and washed with MeOH. The combined filtrate and washing were concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 30:1). The fractions corresponding to R_f 0.25 (EtOH/toluene, 1:5) were concentrated to give **17** (86 mg, 24%) as a colorless oil. The fractions corresponding to R_f 0.23 were concentrated in vacuo to give **16** (136 mg, 39%) as white crystals, mp 105–106.5 °C. **16**: $[\alpha]^{21}_D$ −32.4° (c 0.96, MeOH); IR ν_{max}^{KBr} 3380, 2940, 2900 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.73–1.87 (m, 2 H, H-5, H-5′), 2.07–2.17 (m centered at δ 2.11, H-1), 3.51 (dd, 1 H, J = 6.5 and 11.0 Hz, CH_2OH), 3.63–3.75 (m, 3 H, H-2, H-3, CH_2OH), 4.02 (ddd, 1 H, J = 4.9, 4.9, and 7.3 Hz, H-4), 4.72 (s, 2 H, $OCH_2C_6H_5$), 7.23–7.40 (m, 5 H, $OCH_2C_6H_5$). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.47; H, 7.52. **17**: $[\alpha]^{21}_D$ −12.1° (c 0.92, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.20–1.28 (m centered at δ 2.14, 1 H, H-5), 2.04–2.10 (m centered at δ 2.06, 1 H, H-1), 2.18–2.26 (m centered at δ 2.22, 1 H, H-5′), 3.50–3.66 (m, 3 H, H-3, CH_2OH), 3.95 (dd, 1 H, J = 5.4 and 5.4 Hz, H-2), 4.16 (dd, J = 6.8 and 12.2 Hz, H-4), 4.64, 4.70 (each d, each 1 H, J = 12.0 Hz, $OCH_2C_6H_5$), 7.23–7.41 (m, 5 H, $OCH_2C_6H_5$); high-resolution mass spectra, calcd for $C_{13}H_{18}O_4$ m/z 238.1203, found (M) 238.1187.

(1*S*,2*S*,3*S*,4*R*)-2,3,4-Triacetoxy-1-(acetoxymethyl)cyclopentane (18). A solution of **16** (117 mg, 0.49 mmol) in EtOH (10 mL) was hydrogenolyzed in the presence of 10% Pd on charcoal (234 mg) under 1 atm of hydrogen for 15 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated in vacuo. The residue was acetylated with acetic anhydride (3 mL) in pyridine (3 mL) for 15 h. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (AcOEt/hexane, 1:6). The fractions corresponding to R_f 0.72 (AcOEt/hexane, 1:1) were concentrated in vacuo to give **18** (155 mg, quantitative) as a colorless oil: $[\alpha]^{21}_D$ −46.9° (c 0.72); IR ν_{max}^{neat} 2950, 1750, 1440 cm^{-1}; ^1H NMR (90 MHz) δ 1.91–2.01 (m, 3 H, H-1, H-5, H-5′), 2.05 (s, 12 H, 4 $OCOCH_3$), 4.05 (d, 2 H, J = 6 Hz, CH_2OAc), 4.87–5.30 (m, 3 H, H-2, H-3, H-4). Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.34; H, 6.33.

(1*R*,2*R*,3*S*,4*R*)-2,3,4-Triacetoxy-1-(acetoxymethyl)cyclopentane (19). Compound **17** (68 mg, 0.28 mmol) was hydrogenolyzed in the presence of 10% Pd on charcoal (204 mg) as described in the case of **18**. After acetylation of the products and chromatographic purification (AcOEt/hexane, 1:6), 84 mg (95%) of **19** was obtained as a colorless oil. **19**: TLC R_f 0.72 (AcOEt/hexane, 1:1); $[\alpha]^{21}_D$ −5.3° (c 0.79); IR ν_{max}^{neat} 2975, 1750, 1440, 1380 cm^{-1}; ^1H NMR (90 MHz) δ 2.09, 2.10 (each s, 3 H and 9 H, 4 $OCOCH_3$), 2.40–2.81 (m, 3 H, H-1, H-5, H-5′), 4.28 (d, 2 H, J = 6 Hz, CH_2OAc), 5.20–5.60 (m, 3 H, H-2, H-3, H-4). Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.28; H, 6.33.

(1*S*,2*S*,3*S*,4*R*)-2,3,4-Trihydroxycyclopentane-1-methanol, Pseudo-α-L-arabinofuranose (1). A solution of **18** (60 mg, 0.19 mmol) in MeOH (5 mL) containing sodium methoxide in MeOH (1 M, 0.57 mL, 0.57 mmol) was stirred at 0 °C for 2.5 h. The solution was neutralized with Amberlite IR-120 (H^+). The resin was removed and washed with MeOH, and the combined filtrate and washing were concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 9:1 to 8:1), and the fractions corresponding to R_f 0.41 ($CHCl_3$/MeOH, 2:1) were concentrated in vacuo to give **1** (27 mg, 95%) as a colorless oil: $[\alpha]^{16}_D$ −40.5° (c 0.84, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.69–1.88 (m, 2 H, H-5, H-5′), 2.00–2.08 (m, 1 H, H-1), 3.47–3.67 (m, 4 H, H-2, H-3, CH_2OH), 3.81 (ddd, 1 H, J = 6.4, 6.4, and 8.3 Hz, H-4); ^{13}C NMR (100 MHz, CD_3OD) δ 33.02, 44.90, 64.50, 75.45, 78.53, 85.56; high-resolution mass spectrum calcd for $C_6H_{13}O_4$ m/z 149.0812, found (M + H) 149.0795.

(1*R*,2*R*,3*S*,4*R*)-2,3,4-Trihydroxycyclopentane-1-methanol, Pseudo-β-D-ribofuranose (2). By the analogous procedure described in the preparation of **1**, **19** (59 mg) was deacetylated to give **2** (27 mg, 98%) after silica gel chromatography ($CHCl_3$/MeOH, 2:1) as a colorless oil: TLC R_f 0.46 ($CHCl_3$/MeOH, 2:1); $[\alpha]^{16}_D$ +6.6° (c 1.00, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.21–1.28 (m, 1 H, H-5), 1.99–2.08 (m, 1 H, H-1), 2.18–2.25 (m, 1 H, H-5′), 3.54 (dd, 1 H, J = 6.3 and 10.7 Hz, CH_2OH), 3.63 (dd, 1 H, J = 5.6 and 10.7 Hz, CH_2OH), 3.68 (dd, 1 H, J = 4.9 and 5.4 Hz, H-3), 3.85 (dd, 1 H, J = 5.4 and 5.4 Hz, H-2), 3.98 (ddd, 1 H, J = 4.4, 4.9 and 6.6 Hz, H-4); ^{13}C NMR (100 MHz, CD_3OD) δ 33.69, 45.98, 65.30, 74.52, 76.64, 79.59; high-resolution mass spectrum calcd for $C_6H_{13}O_4$ m/z 149.0812, found (M + H) 149.0798.

(1*R*,2*R*,3*S*,4*R*)-4-Acetoxy-1-(acetoxymethyl)-2,3-(isopropylidenedioxy)cyclopentane (20). To a solution of **2** (5 mg, 0.04 mmol) in DMF (0.5 mL) were added 2,2-dimethoxypropane (0.03 mL) and camphorsulfonic acid (2 mg). After being stirred for 6 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ and concentrated in vacuo. The residue was acetylated with acetic anhydride (0.5 mL) in pyridine (0.5 mL) for 2 h. After concentration of the mixture, the residue was chromatographed on silica gel (AcOEt/hexane, 1:10). The fractions corresponding to R_f 0.62 (AcOEt/hexane, 2:3) were concentrated in vacuo to give **20** (7.5 mg, 82%) as a colorless oil: $[\alpha]^{24}_D$ −20.1° (c 0.33); IR ν_{max}^{neat} 3000, 2950, 1750, 1380 cm^{-1}; ^1H NMR (400 MHz) δ 1.30, 1.46 (each s, each 3 H, $C(CH_3)_2$), 1.59–1.65 (m, 1 H, H-5), 2.05, 2.08 (each s, each 3 H, 2 $OCOCH_3$), 2.33–2.40 (m, 1 H, H-5′), 2.45–2.52 (m, 1 H, H-1), 4.01–4.09 (m, 2 H, CH_2OAc), 4.52–4.56 (m, 2 H, H-2, H-3), 5.06–5.08 (m, 1 H, H-4). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.42; H, 7.71.

Acknowledgment. We thank Hisao Arita of our university for performing elemental analyses.

Registry No. **1**, 118013-55-1; **2**, 118013-56-2; **3**, 22529-61-9; **4**, 23558-05-6; **5**, 117918-35-1; **6**, 117918-36-2; α-**7**, 117918-37-3; β-**7**, 117918-42-0; **9**, 117918-38-4; **9′**, 118013-63-1; **10**, 117940-39-3; **10′**, 118014-53-2; **11**, 117918-39-5; **12**, 118013-57-3; **14**, 118013-58-4; **15**, 118013-59-5; **16**, 117918-40-8; **17**, 118013-60-8; **18**, 118013-61-9; **19**, 118013-62-0; **20**, 117918-41-9; $CH_2(COOMe)_2$, 108-59-8.

α-Acylamino Radical Cyclizations: Application to the Synthesis of a Tetracyclic Substructure of Gelsemine

Joong-Kwon Choi, Deok-Chan Ha, David J. Hart,* Chih-Shone Lee, Subban Ramesh, and Shung Wu

Department of Chemistry, The Ohio State University, 120 W. 18th Ave., Columbus, Ohio 43210

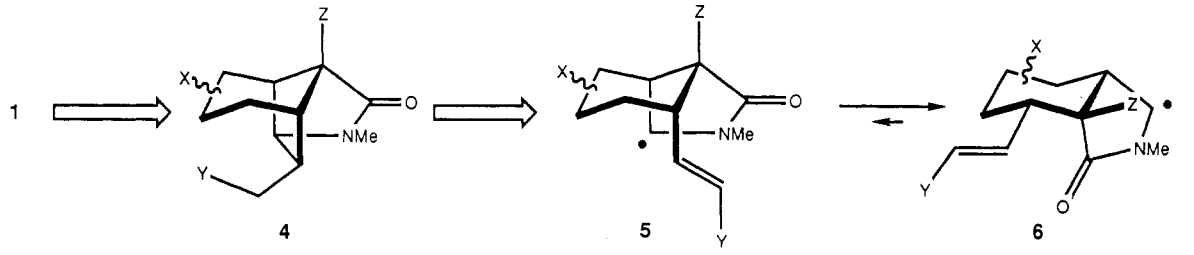
Received July 6, 1988

Syntheses of gelsemine substructures **2** and **3** are described. Free-radical precursors **14**, **18**, **35**, and **38** were prepared, and their behavior upon treatment with tri-*n*-butyltin hydride and AIBN was examined. The radical derived from **14** afforded reduction product **15**, whereas the radicals derived from **18**, **35**, and **38** gave cyclization products **23**, **37**, and **39**, respectively. Aspects of these free-radical cyclizations as well as the conversion of **23** and **37** to **2** and **3**, respectively, are presented.

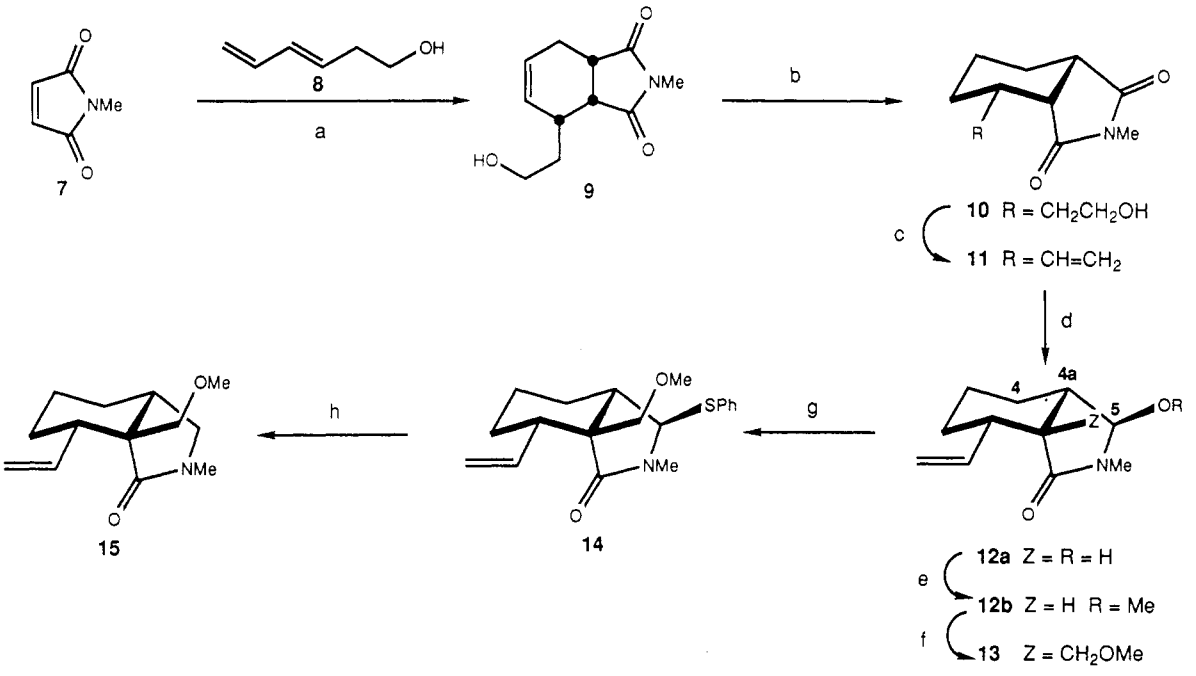
Gelsemine (**1**) is an oxindole alkaloid that has eluded synthesis since its structure was reported nearly 30 years ago.[1-3] This has not, however, been due to a lack of effort. In fact, numerous studies that have been reported in the

0022-3263/89/1954-0279$01.50/0

Scheme I

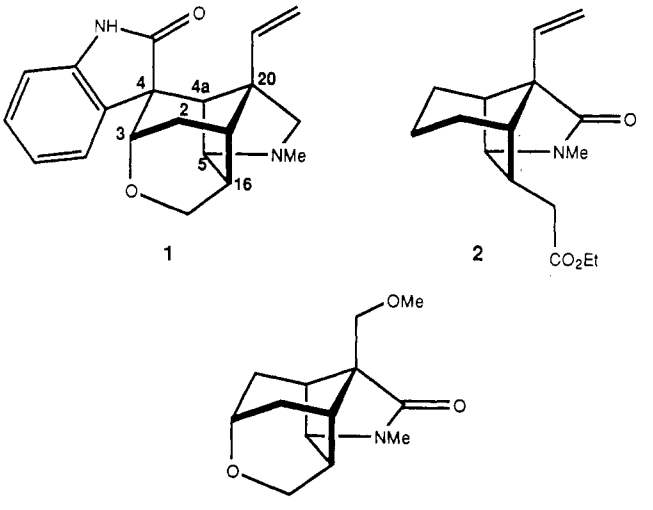


Scheme II[a]



[a] (a) $PhCH_3$, Δ, 7 h; (b) H_2, Pd/C, EtOH; (c) *o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF; H_2O_2; (d) $NaBH_4$, MeOH, 0 °C; (e) MeOH, Dowex-50 (H^+); (f) LDA, THF; $ClCH_2OMe$; (g) PhSH, TsOH (cat.), CH_2Cl_2; (h) *n*-Bu_3SnH, AIBN, PhH, Δ.

past few years suggest that this synthetic challenge will eventually be met with a variety of solutions.[4-9] This paper describes our own progress toward gelsemine within the context of syntheses of the tricyclic and tetracyclic substructures 2 and 3.[10]



Our approach to gelsemine follows a retrosynthetic analysis (Scheme I) that is closely related to that recently presented by Hiemstra and Speckamp.[8] We projected that

(1) Conroy, H.; Chakrabarti, J. K. *Tetrahedron Lett.* **1959** (4), 6. Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. *Tetrahedron Lett.* **1959** (4), 1.

(2) Gelsevirine (Wenkert, E. *Experientia* **1972**, *28*, 377) and 21-oxogelsemine (Nikiforov, A. J.; Latzel, J.; Varmuza, K.; Wichtl, M. *Monatsh. Chem.* **1974**, *105*, 1292) are structurally related to gelsemine.

(3) For reviews of literature related to *Gelsemium* alkaloids, see: Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, pp 93–117. Luzio, M. J. Ph.D. Thesis, University of Rochester, 1987.

(4) Fleming, I.; Loreto, M. A.; Michael, J. P.; Wallace, I. H. M. *Tetrahedron Lett.* **1982**, *23*, 2053. Clarke, C.; Fleming, I.; Fortunak, J. M. D.; Gallagher, P. T.; Honan, M. C.; Mann, A.; Nubling, C. O.; Raithby, P. R.; Wolff, J. J. *Tetrahedron* **1988**, *44*, 3991.

(5) Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115.

(6) Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett.* **1987**, *28*, 1035. Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

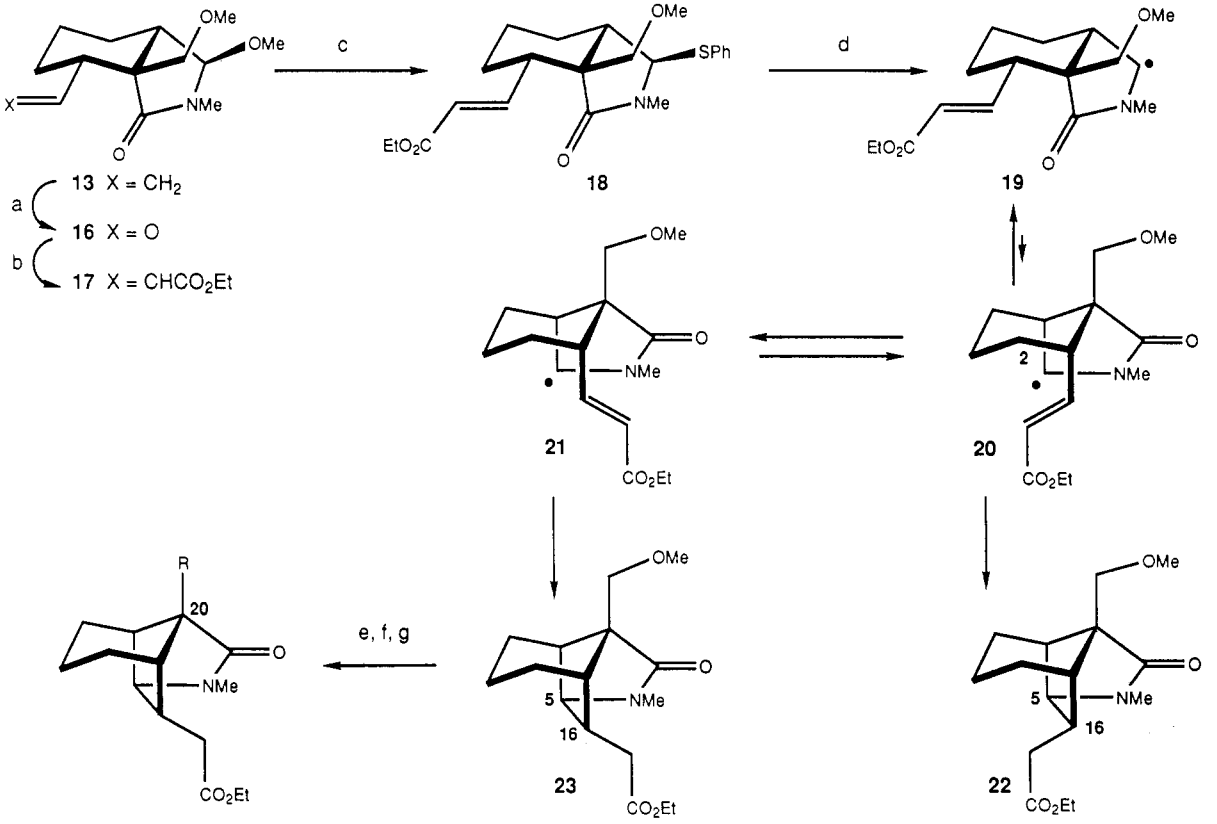
(7) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. Earley, W. G.; Jacobsen, E. J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781. Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785.

(8) Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019. Hiemstra, H.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1988**, *53*, 3884.

(9) (a) Guthrie, R. D. Ph.D. Thesis, University of Rochester, 1963; *Diss. Abstr.* **1963**, *24*, 1834. (b) Tahk, R. C. Ph.D. Thesis, University of Rochester, 1966; *Diss. Abstr.* **1966**, *27B*, 118. (c) Landeryon, V. A. Ph.D. Thesis, University of Rochester, 1965; *Diss. Abstr.* **1965**, *26*, 2477. (d) Lovett, E. G. Ph.D. Thesis, University of Rochester, 1967; *Diss. Abstr.* **1967**, *27*, 110–B.

(10) Taken in part from the following: Ha, D.-C. Ph. D. Thesis, Ohio State University, 1987. Lee, C.-S. Ph.D. Thesis, Ohio State University, 1988.

Scheme III[a]



[a] (a) $NaIO_4$, OsO_4 (cat.); (b) $Ph_3P{=}CHCO_2Et$; (c) PhSH, TsOH; (d) *n*-Bu_3SnH, AIBN (cat.), PhH; (e) BBr_3; (f) DMSO, $(COCl)_2$; Et_3N; (g) $Ph_3P{=}CH_2$.

gelsemine might be prepared from hypothetical intermediate **4**, where X, Y, and Z were suitable for introduction of the oxindole, tetrahydropyran, and vinyl moieties, respectively. We have previously shown that α-acylamino radical cyclizations are of some use in the construction of carbon–carbon bonds adjacent to nitrogen, and thus we imagined that **4** might be prepared through cyclization of a radical of type **5**.[11,12] An interesting conformational issue arises, however, when this projected cyclization (**5** → **4**) is considered. One would expect radical **5** to be in conformational equilibrium with radical **6**. In fact, one would expect **6**, a conformation from which cyclization cannot take place, to be more stable than **5**. Thus, the success of the proposed construction of the incipient C_5–C_{16} bond of gelsemine would depend on a sensitive balance of cyclization rates (**5** → **4**), conformational equilibria (**5** ⇄ **6**), and rates of other radical processes (**5** or **6** → noncyclized products). We felt this was an interesting issue which might be of general value as organic chemists continue to increase their use of radical cyclizations in synthesis design.[13]

Synthesis of Compound 2: Preparation and Attempted Cyclization of Perhydroisoindoles 14 and 18. Our initial studies, which ignored the need for a functional handle to introduce the oxindole and tetrahydropyran moieties, focused on the synthesis of radical cyclization precursor **14** using the reaction sequence outlined in Scheme II. A Diels–Alder reaction between *N*-methylmaleimide (**7**) and the known dienol **8** gave hexahydroisoindole **9** in 97% yield.[14] A catalytic hydrogenation followed by application of the Grieco dehydration sequence to **10** afforded imide **11** (84% overall).[15] Reduction of imide **11** with sodium borohydride in methanol followed by hydroxy–methoxy exchange gave lactam **12b** in 88% yield.[16] The stereochemical assignment at C_5 of lactam **12b** was based on the appearance of the C_5 methine as a singlet at δ 4.16, an indication of a 90° H_{4a}–C_{4a}–C_5–H_5 dihedral angle. The regiochemical course of this reduction is remarkable, but is explained by the popular antiperiplanar effect. In this case, antiperiplanar alignment of the HOMO of the incoming nucleophile and the C_4–C_{4a} σ* orbital appears to be important.[17] Hiemstra and Speck-

(11) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430. Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959.

(12) For other studies using α-acylamino radical cyclizations, see: Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2693. Kametani, T.; Honda, T. *Heterocycles* **1982**, *19*, 1861. Kanō, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1988**, *27*, 253.

(13) For an excellent introduction to the use of free-radical reactions in organic synthesis, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1986. Also see: Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Curran, D. P. *Synthesis* **1988**, 417. Curran, D. P. *Synthesis* **1988**, 489.

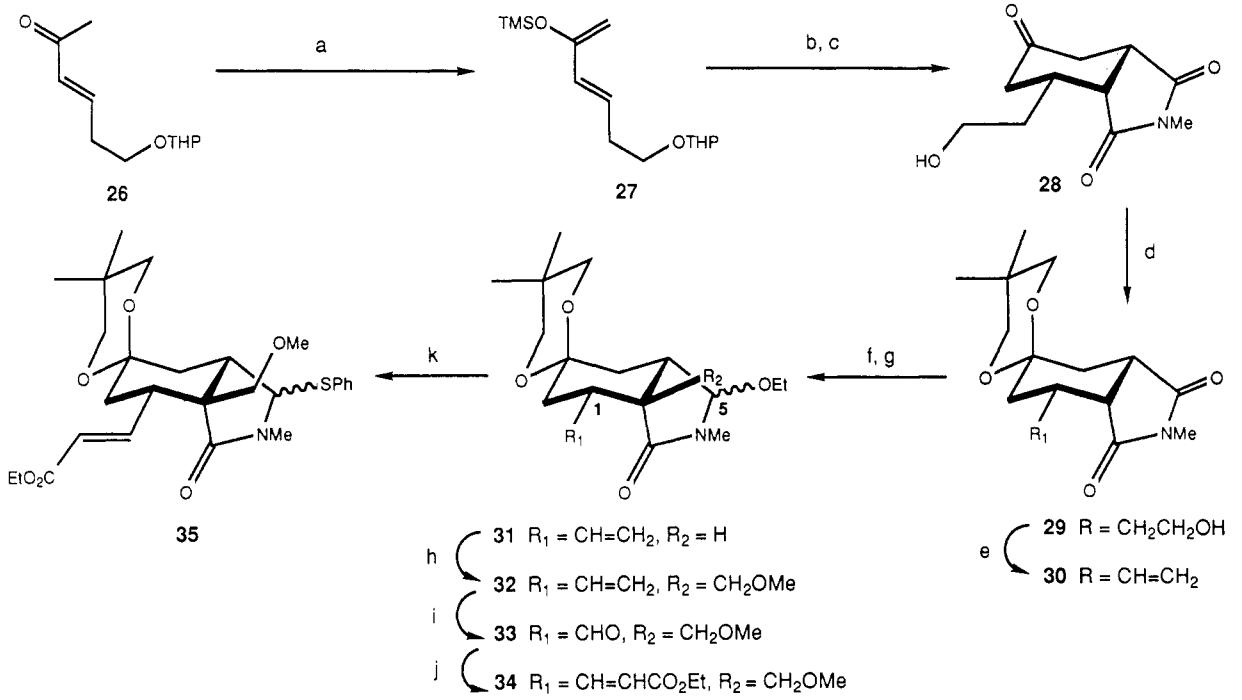
(14) Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 5274. Howden, M. E. H.; Maercker, A.; Burdon, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1732.

(15) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1975**, *30*, 3760.

(16) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619. Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.

(17) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192. Kayser, M. M.; Salvador, J.; Morand, P.; Krishnamurty, H. G. *Can. J. Chem.* **1982**, *60*, 1199. Kayser, M. M.; Salvador, J.; Morand, P. *Can. J. Chem.* **1983**, *61*, 439. Anh, N. T.; Eisentein, O. *Nouv. J. Chim.* **1977**, *1*, 61. Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

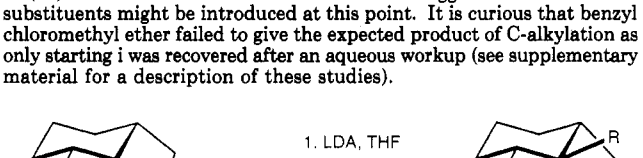
Scheme IV[a]



[a] (a) LDA, THF; Me_3SiCl; (b) *N*-methylmaleimide (**7**), $PhCH_3$; Δ, 3 h; (c) Dowex-50 (H^+), THF, H_2O, Δ; (d) 2,2-dimethylpropane-1,3-diol, Dowex-50 (H^+), PhH; (e) *o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF; H_2O_2; (f) $NaBH_4$, MeOH, −23 °C; (g) EtOH, Dowex-50 (H^+); (h) LDA, THF; $ClCH_2OMe$; (i) OsO_4 (cat.), $NaIO_4$, *t*-BuOH, H_2O; (j) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, Δ; (k) PhSH, Dowex-50 (H^+), CH_2Cl_2.

amp have recently reported a definitive study which strongly supports this notion.[8] Alkylation of the lithium enolate of **12** with chloromethyl methyl ether gave lactam **13** (84%), and subsequent methoxy–thiophenoxy exchange afforded radical precursor **14**.[18,19] It was not surprising to find that treatment of **14** with tri-*n*-butytin hydride and AIBN under high dilution conditions gave only reduction product **15** (93%).[20] Thus, the conformational issue alluded to above appears to be real.

Several strategies could be used to combat this apparent conformational problem. For example, one might be able to reduce the rate of reduction of radicals of type **5** and **6** by using a trialkylgermanium hydride in place of tri-*n*-butyltin hydride.[21] The use of hydride-free sources of tin radicals might also be of some value.[22] Since we also had to face the issue of incorporating functionality which would be suitable for constructing the tetrahydropyran substructure of gelsemine, we decided to pursue a different strategy which involved increasing the rate of the projected radical cyclization.[23] Thus we next prepared unsaturated ester **18** as outlined in Scheme III. Johnson–Lemieux oxidation of **13** followed by treatment of the resulting aldehyde **16** (65%) with (carbethoxymethylidene)triphenylphosphorane gave unsaturated ester **17** (83%).[24,25] Methoxy–thiophenoxy exchange once again proceeded smoothly to give **18** (89%). Treatment of **18** with tri-*n*-butyltin hydride and AIBN under conditions identical with those used with **14** gave a 92% yield of inseparable cyclization products **23** and **22** (10:1, respectively).[26] The regiochemical course of the cyclization (exo rather than endo) was apparent from the ^1H NMR spectrum (CH_2CO_2Et in **23** at δ 2.26 and 2.29 as AB portion of ABX system, J_{AB} = 16.5 Hz), mass spectrum ($M^+ - CH_2CO_2Et$), and deuterium exchange experiments (two exchangeable hydrogens). The stereochemistry at C_{16} was inferred from a series of difference NOE experiments which revealed the proximate nature of the NCH_3 and CH_2CO_2Et groups.[27]



i

ii R = $CH_2CH{=}CH_2$
iii R = CH_2CO_2tBu
iv R = CH_2OCH_3

(18) Durst, T.; LeBelle, M. J. *Can. J. Chem.* **1972**, *50*, 3196. Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2475. Hullot, P.; Cuvigny, T.; Larcheveque, M.; Normant, H. *Can. J. Chem.* **1976**, *54*, 1098. Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *J. Org. Chem.* **1984**, *49*, 1149.

(19) Model studies conducted with lactam **i** suggest that a number of substituents might be introduced at this point. It is curious that benzyl chloromethyl ether failed to give the expected product of C-alkylation as only starting **i** was recovered after an aqueous workup (see supplementary material for a description of these studies).

(20) For reviews of tin hydride chemistry, see: Neumann, W. P. *Synthesis* **1987**, 665. Kuivila, H. G. *Synthesis* **1970**, 499. Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.

(21) Pike, P.; Hershberger, S.; Hershberger, J. *Tetrahedron Lett.* **1985**, *26*, 6289. Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

(22) Kuivila, H. G.; Pian, C. H.-C. *Tetrahedron Lett.* **1973**, 2561. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. Hart, D. J.; Seely, F. S. *J. Am. Chem. Soc.* **1988**, *110*, 1631.

(23) For a quantitative study, see: Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240.

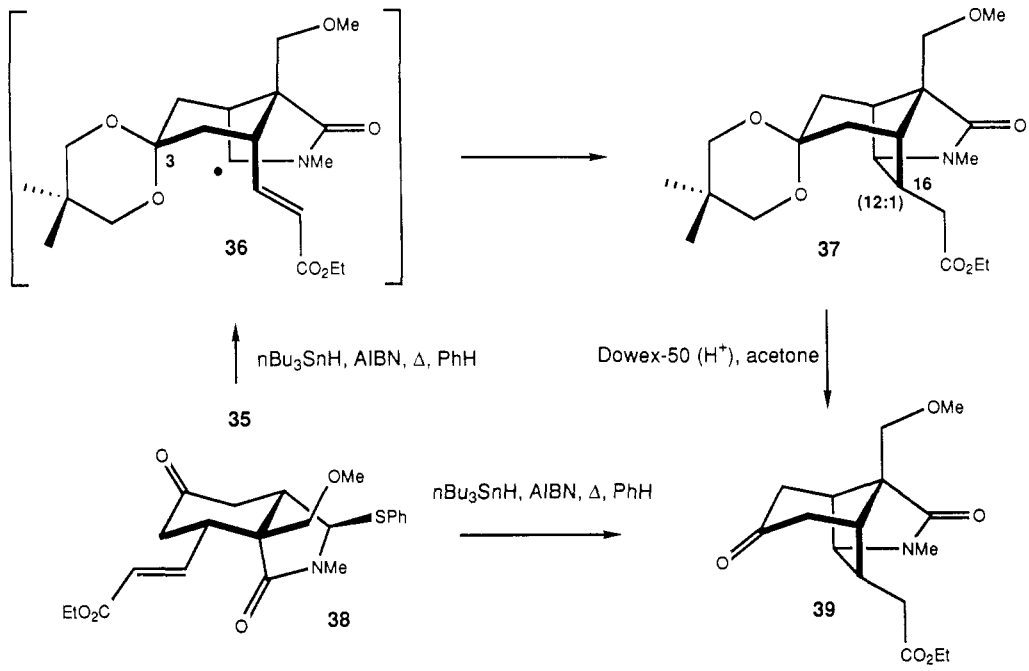
(24) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(25) Isler, O.; Gutmann, H.; Montavon, M.; Ruegg, R.; Ryser, G. Zeller,; P. *Helv. Chim. Acta* **1957**, *40*, 1242.

(26) Signals in the ^1H NMR spectrum of **23** suggested that a small amount of **22** was present [δ 1.27 (t, *J* = 7 Hz, CH_3), 2.75 (s, NCH_3), 3.43 (s, OCH_3), 3.95 (d, *J* = 10 Hz, CHOMe)]. The ratio of **23** to **22** was estimated by integration of signals assigned to the *N*-methyl groups [δ 2.88 (**23**) and δ 2.75 (**22**)].

(27) This stereochemical assignment is consistent with the stereochemical course of related cyclizations of **35** and **38** (vide infra), established by X-ray crystallography.

Scheme V



There are two interesting aspects to this cyclization (**18** → **22** + **23**). First, it is clear that the carbethoxy group provides the cyclization rate enhancement needed to overcome the bimolecular reduction problem.[23] Second, the cyclization does not provide the C_{16} stereochemistry required for gelsemine. Current transition-state models for 5-hexenyl radical cyclizations suggest that chair-like transition states (e.g., **20**) are preferred over the corresponding boat-like transition states (e.g., **21**).[28] In the current example, however, it is obvious that cyclization takes place through conformation **21** rather than **20**. One explanation of this observation is that $A^{(1,3)}$ interactions between the vinyl hydrogen α to the carbethoxy group and the C_3 and/or C_2 methylenes introduce strain into the transition state arising from **20** that is absent in the transition state arising from **21**.[29]

With a tricyclic substructure of gelsemine in hand, we next established that the C_{20} methoxymethyl group could be converted to the required vinyl group. Thus, treatment of **23** with boron tribromide gave alcohol **24** (98%), and a Swern oxidation afforded aldehyde **25** in 86% yield.[30,31] Finally, Wittig olefination of **25** gave **2** in 74% yield.[32]

Although the study described in Scheme III suggested that the basic plan for constructing major portions of gelsemine was viable, it was also clear that several critical issues still had to be addressed. The remainder of this paper will describe one variant of this route which incorporates a functional group which may be of use for introduction of the tetrahydropyran and oxindole moieties and also addresses the issue of adjusting stereochemistry at C_{16}.

Synthesis of Compound 3: Preparation and Cyclization of Perhydroisoindole 35. With the aforementioned issues in mind, we set free-radical precursor **35** as our next objective (Scheme IV). The synthesis began with the preparation of enone **26** (87%) using a Wittig reaction between (2-oxopropylidene)triphenylphosphorane and the tetrahydropyranyl ether of β-hydroxypropanal.[33,34] Treatment of **26** with lithium diisopropylamide followed by chlorotrimethylsilane gave diene **27** (93%).[35] The remainder of the synthesis closely paralleled the synthesis of **18**. Thus, **27** was treated with *N*-methylmaleimide, and the resulting cycloadduct was subjected to hydrolysis conditions to give **28** in 95% overall yield. Ketalization of **28** using 2,2-dimethylpropane-1,3-diol and formal dehydration of the resulting alcohol **29** (81%) gave olefin **30** (76%). Reduction of **30** with sodium borohydride followed by hydroxy–ethoxy exchange gave the expected lactam **31** (84%), contaminated with diastereomeric materials. Sequential treatment of **31** with lithium diisopropylamide and chloromethyl methyl ether gave **32** (84%).[36] Johnson–Lemieux oxidation of **32** gave aldehyde **33** (73%). Finally, treatment of **33** with the appropriate stabilized phosphorane followed by ethoxy–thiophenoxy exchange of the resulting unsaturated ester **34** (91%) gave free-radical precursor **35** (83%).[37]

The cyclization of **35** is sterically more demanding than the cyclization of **18** due to the additional axial substituent at C_3. Nonetheless, when **35** was submitted to standard

(28) For a description of what we mean by "chair-like" and "boat-like", see: Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. Also see: Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.

(29) This result suggests that 5-hexenyl radicals constrained such that a substituent must occupy an axial site at C_4 in the traditional "chair" transition state will cyclize predominantly via "boat" transition states. See: Rajanbabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522. Rajanbabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609.

(30) Kutney, J. P.; Abdurahman, N.; LeQuesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656.

(31) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(32) The viability of using a Wittig reaction as a final step in projected syntheses of gelsemine has been demonstrated (see ref 9c).

(33) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41.

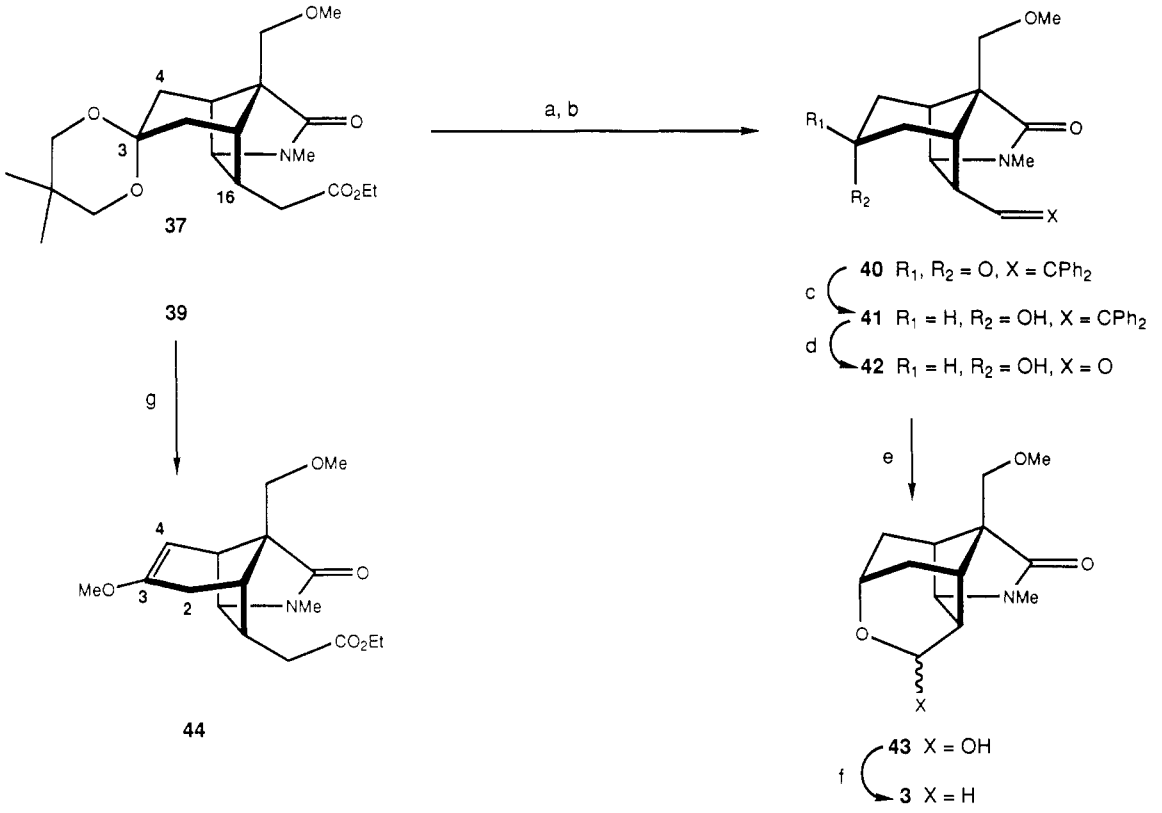
(34) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037.

(35) Girard, C.; Amice, P.; Barnier, J. P.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3329. Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459.

(36) It was clear that **31** and **32** were the major diastereomers present in these mixtures. Signals in the ^1H NMR spectra of the mixtures indicated the presence of unidentified isomers (15–25%; see Experimental Section).

(37) Lactams **33** and **34** were obtained as mixtures of diastereomers (presumably at C_5, although small amounts of isomerization at C_1 of aldehyde **33** may have occurred). Thioether **35** was contaminated by a small amount of material that also appeared to be a diastereomer.

Scheme VI[a]



[a] (a) PhMgBr, THF; (b) TsOH, MeOH; (c) $NaBH_4$, MeOH, 0 °C; (d) O_3; Me_2S; (e) DBU, CH_2Cl_2; (f) Et_3SiH, TFA, CH_2Cl_2; (g) $(MeO)_3CH$, MeOH, TsOH.

high dilution cyclization conditions, **37** was obtained as a 12:1 mixture of C_{16} diastereomers in yields ranging from 60% to 90% (Scheme V). Conversion of **37** to crystalline ketone **39** proceeded in 87% yield.[38] The structure of **39** was proven by X-ray crystallographic analysis.[39] On one occasion, allowing a sample of **35** to stand on silica gel for several hours afforded a sample of ketone **38**. Cyclization of this material also afforded **39** (86%) as a 6:1 mixture of C_{16} diastereomers. This result suggests that the hybridization state at C_3 has a small, but not overwhelming, effect on the stereochemical course of the cyclization.

Finally, we have performed two unrelated studies which suggest that **37** and **39** may ultimately be useful intermediates in a synthesis of gelsemine. First, we have developed a protocol for adjusting stereochemistry at C_{16}. Our plan was to degrade the C_{16} acetic acid residue to the nor-aldehyde and use a C_3 hydroxyl group to trap the epimerizable aldehyde as a tetrahydropyran.[40] We were able to accomplish this objective by using a Barbier–Wieland degradation (Scheme VI).[41] Thus, treatment of **37** with an excess of phenylmagnesium bromide followed by an acid workup afforded keto olefin **40** (76%). Reduction of **40** with sodium borohydride gave a separable mixture of alcohols **41** (81%) and its C_3 epimer (7%). Ozonolysis of **41** followed by isomerization of the resulting aldehyde **42** using DBU in dichloromethane gave tetrahydropyran **43** (72%). Treatment of **43** with triethylsilane and trifluoroacetic acid afforded gelsemine substructure **3** in 84% yield.[42]

In a second study, we have discovered that subjecting **39** to standard ketalization conditions [$(MeO)_3CH$, MeOH, Dowex-50 (H^+)] affords only enol ether **44** (75%). The structure of **44** was based on ^1H NMR studies which ultimately established the relationship between the C_4 vinylic and C_5 methine protons. The reluctance of **39** to form a ketal can be rationalized on steric grounds while the regiochemical course of the enol ether formation is most likely related to less torsional strain being introduced in **44** relative to its $\Delta^{2,3}$ isomer.[43] From a practical standpoint, this result shows that the pseudosymmetrical ketone **39** enolizes toward C_4, the ultimate point of attachment of the oxindole moiety of gelsemine.

In summary, we have demonstrated the viability of a route to gelsemine which involves construction of the C_5–C_{16} bond using a sterically demanding α-acylamino radical cyclization. The major issue that remains to be addressed is installation of the oxindole portion of the alkaloid. It appears that the thermodynamically controlled enolization of keto ester **39** may be useful in this regard. In addition, the synthesis design does allow for incorporation of the aryl portion of the oxindole at an early stage. Studies pursuing both of these avenues will be reported in due course.

(38) The ratio assigned to **37** and its C_{16} diastereomer was determined at this point by integration of ^1H NMR signals assigned to the NCH_3 [δ 2.92 (**39**), δ 2.80 (diastereomer)] and CH_2OMe [δ 3.73 and 3.92 (**39**) and δ 3.80 and 3.97 (diastereomer)] groups. The presence of the C_{16} diastereomer of **39** was also suggested by a small triplet at δ 1.27 (CH_3) and a small singlet at δ 3.37 (OCH_3). Pure **39** was obtained by recrystallization.

(39) The X-ray crystallographic analysis of **39** was performed by Dr. Judith C. Gallucci at The Ohio State University Department of Chemistry Crystallographic Facility. Details appear in the supplementary material.

(40) For implementation of a similar strategy, see: Ha, D.-C.; Hart, D. J. *Tetrahedron Lett.* **1987**, *28*, 4489.

(41) Riegel, B.; Moffett, R. B.; McIntosh, A. V. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 234, 237.

(42) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

(43) Velluz, L.; Valls, J.; Nomine, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 181.

Experimental Section[44]

All melting points are uncorrected. In many cases, decoupling experiments were performed to aid in the assignment of peaks in ^1H NMR spectra, although in some cases assignments are tentative. ^{13}C NMR spectra were recorded as broad-band, off-resonance-decoupled, or DEPT (distortionless enhancement by polarization transfer) spectra. Mass spectra were recorded at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at m/e values greater than those of the parent. Title compounds were at least 90% pure as judged by ^1H NMR and ^{13}C NMR with the exception of compounds **31–35**. These compounds were contaminated by diastereomeric substances as discussed in the text, footnotes, and Experimental Section.

Solvents and reagents were dried and purified prior to use when it was deemed necessary: tetrahydrofuran, benzene, and diethyl ether (distilled from sodium metal); carbon tetrachloride and dichloromethane (passed through activity I alumina); methanol (distilled from magnesium methoxide); toluene (distilled from CaH_2). All reaction temperatures refer to that of the reaction mixture unless indicated otherwise. Reactions requiring an inert atmosphere were run under a blanket of argon or nitrogen. Analytical thin-layer chromatography was performed with EM laboratories 0.25-mm-thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica 60 (70–230 mesh). Medium-pressure liquid chromatography (MPLC) was performed over EM Laboratories Lobar prepacked silica gel columns. Ethyl acetate and *n*-hexane, used as eluents in column chromatography, were distilled prior to use.

(3aα,4β,7aα)-(±)-3a,4,7,7a-Tetrahydro-4-(2-hydroxyethyl)-2-methyl-1*H*-isoindole-1,3(2*H*)-dione (9). To a solution of 4.7 g (47.9 mmol) of dienol **8** in 80 mL of toluene was added 5.33 g (47.9 mmol) of *N*-methylmaleimide (**7**) in one portion. The solution was heated under reflux for 7 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to afford 9.67 g (97%) of imide **9**: IR (neat) 3440, 1770 (weak), 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.96–2.05 (m, 1 H), 2.10–2.28 (m, 3 H), 2.52 (m, 1 H) 2.72 (ddd, J = 9.0, 7.0, 1.8 Hz, 1 H), 2.91 (s, 3 H, NCH_3), 3.14 (ddd, J = 9.0, 7.5, 1.8 Hz, 1 H, CHC(O)N), 3.28 (dd, J = 9.0, 6.5 Hz, 1 H, CHC(O)N), 3.80 (ddd, J = 12.7, 7.9, 5.0 Hz, 1 H, CHO), 3.92 (ddd, J = 11.0, 5.9, 5.0 Hz, 1 H, CHO), 5.74 (dt, J = 10.0, 3.2 Hz, 1 H, =CH), 5.89 (ddd, J = 10.0, 6.8, 3.2, 1 H, =CH); exact mass calcd for $C_{11}H_{15}NO_3$ m/e 209.1052, found 209.1010.

(3aα,4β,7aα)-(±)-Hexahydro-4-(2-hydroxymethyl)-2-methyl-1*H*-isoindole-1,3(2*H*)-dione (10). A solution of 7.60 g (36.4 mmol) of **9** and 360 mg of 5% palladium on charcoal in 220 mL of ethanol was hydrogenated in a Parr hydrogenator under 50 psi of hydrogen for 3 h. The reaction mixture was filtered through Celite, and the filter cake was washed with 50 mL of ethyl acetate. The combined organic solutions were concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (ethyl acetate) to give 7.64 (100%) of **10**: IR (neat) 3450, 1765 (weak), 1710–1680 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05–1.20 (m, 1 H), 1.47–1.57 (m, 2 H), 1.60–1.75 (m, 2 H), 1.78–1.89 (m, 1 H), 1.90–2.00 (m, 1 H), 2.05–2.20 (m, 3 H), 2.94–3.05 (m, 1 H, CHC(O)N), 2.96 (s, 3 H, NCH_3), 3.12 (dd, J = 8, 5.2 Hz, 1 H, CHC(O)N), 3.78 (ddd, J = 11, 7, 5 Hz, 1 H, CHO), 3.86 (ddd, J = 11, 6.5, 5 Hz, 1 H, CHO); exact mass calcd for $C_{11}H_{17}NO_3$ m/e 211.1208, found 211.1216.

(3aα,4β,7aα)-(±)-4-Ethenylhexahydro-2-methyl-1*H*-isoindole-1,3(2*H*)-dione (11). To a solution of 6.24 g (29.6 mmol) of alcohol **10** in 150 mL of tetrahydrofuran was added 8.06 g (35.5 mmol) of *o*-nitrophenyl selenocyanate in one portion. A solution of 7.14 g (35.5 mmol) of tri-*n*-butylphosphine in 45 mL of tetrahydrofuran was added at 0 °C over a 15-min period. The resulting solution was stirred at room temperature for 45 min followed by the addition of 26 mL of 30% aqueous hydrogen peroxide at 0 °C over a 15-min period. The reaction mixture was stirred at room temperature for 3 h and diluted with 300 mL of dichloromethane. The solution was washed with 200 mL of saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 150 g of silica gel (hexane–ethyl acetate, 10:1) to afford 4.88 g (85%) of olefin **11**: IR (neat) 1770 (weak), 1710–1690 (strong) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40–2.00 (m, 7 H), 2.50–2.70 (m, 1 H, CHC(O)), 2.96 (s, 3 H, NCH_3), 2.90–3.10 (m, 1 H, CHC(O)), 5.00–5.10 (m, 2 H, $=CH_2$), 6.20 (ddd, J = 18, 10, 8 Hz, 1 H, =CH); exact mass calcd for $C_{11}H_{15}NO_2$ m/e 193.1102, found 193.1094.

(3α,3aα,7β,7aα)-(±)-7-Ethenyloctahydro-3-hydroxy-2-methyl-1*H*-isoindol-1-one (12a). To a solution of 2.88 g (14.9 mmol) of imide **11** in 50 mL of methanol cooled in an ice bath was added 2.82 g (74.5 mmol) of sodium borohydride over a 10-min period. The reaction mixture was stirred in an ice bath for 15 min and then diluted with 200 mL of dichloromethane. The solution was washed with 80 mL of saturated aqueous sodium bicarbonate solution. The aqueous solution was extracted with two 50-mL portions of dichloromethane. The combined organic solutions were dried ($MgSO_4$) and concentrated in vacuo. The residue (2.99 g) was chromatographed over silica gel (hexane–ethyl acetate, 3:1) to give 2.78 g (96%) of **12a**: IR (neat) 3500, 1680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.0–2.7 (m, 9 H, CH and CH_2 manifold), 2.85 (s, 3 H, NCH_3), 3.7 (d, J = 8 Hz, 1 H, OH), 4.9–5.2 (m, 3 H, NCHO and $=CH_2$), 6.4–6.6 (m, 1 H, =CH); exact mass calcd for $C_{11}H_{17}NO_2$ m/e 195.1260, found 195.1250.

(3α,3aα,7β,7aα)-(±)-7-Ethenyloctahydro-3-methoxy-2-methyl-1*H*-isoindol-1-one (12b). To a solution of **12a** (525 mg, 2.69 mmol) in 10 mL of methanol was added 520 mg of acid-washed Dowex-50W resin. The solution was stirred for 0.5 h and filtered through a sintered-glass funnel. The resin was washed with 30 mL of ethyl acetate. The combined filtrates were dried (K_2CO_3) and concentrated in vacuo. The residue (580 mg) was chromatographed over 20 g of silica gel (hexane–ethyl acetate, 2:1) to afford 518 mg (92%) of ether **12b**: IR (neat) 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95–1.10 (m, 1 H), 1.20–1.35 (m, 2 H), 1.60–1.85 (m, 3 H), 2.25–2.38 (m, 2 H), 2.87 (s, 3 H, NCH_3), 2.90 (dd, J = 4, 4 Hz, 1 H, CHCO), 3.38 (s, 3 H, OCH_3), 4.16 (s, 1 H, OCHN), 4.95–5.10 (m, 2 H, $=CH_2$), 6.53 (ddd, J = 17.3, 11.3, 8.0 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 23.83 (t), 26.70 (t), 28.55 (q), 28.75 (t), 38.84 (d), 41.78 (d), 43.63 (d), 55.38 (q), 96.65 (d), 113.26 (t), 141.81 (d), 175.42 (s); exact mass calcd for $C_{12}H_{19}NO_2$ m/e 209.1416, found 209.1427.

(3α,3aα,7β,7aα)-(±)-7-Ethenyloctahydro-3-methoxy-7a-(methoxymethyl)-2-methyl-1*H*-isoindol-1-one (13). To a solution of 590 mg (5.84 mmol) of diisopropylamine in 20 mL of tetrahydrofuran cooled to −78 °C was added 3.5 mL (5.6 mmol) of 1.6 M *n*-butyllithium over a 5-min period. The reaction mixture was stirred for 15 min followed by the addition of 1.11 g (5.32 mmol) of lactam **12b** in 7 mL of tetrahydrofuran over a 10-min period. The solution was stirred at −78 °C for 10 min and then warmed to −20 °C for 15 min. The solution was cooled to −78 °C, and 850 mg (10.64 mmol) of chloromethyl methyl ether was added over a 2-min period. The solution was stirred at −78 °C for 20 min and allowed to warm to room temperature followed by stirring for 3 h. To the resulting solution was added 30 mL of saturated ammonium chloride solution followed by extraction with three 50-mL portions of ether. The combined ether extracts were washed with 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (2.0 g) was chromatographed over 50 g of silica gel (hexane–ethyl acetate, 2:1) to afford 1.12 g (84%) of lactam **13**: IR (neat) 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20–1.65 (m, 5 H), 1.75–1.85 (m, 1 H), 2.39 (td, J = 9.4, 3.8 Hz, 1 H), 2.52 (td, J = 6.1, 3.2 Hz, 1 H), 2.83 (s, 3 H, NCH_3), 3.32 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.49 (d, J = 9 Hz, 1 H, CHOMe), 3.55 (d, J = 9 Hz, 1 H, CHOMe), 4.38 (d, J = 3.2 Hz, 1 H, OCHN), 4.95–5.10 (m, 2 H, $=CH_2$), 6.10–6.15 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 19.68 (t), 24.79 (t), 27.53 (t), 27.66 (q), 37.63 (d), 41.78 (d), 51.36 (s), 54.30 (q), 59.15 (q), 74.48 (t), 95.50 (d), 115.52 (t), 139.13 (d), 176.40 (s); exact mass calcd for $C_{14}H_{23}NO_3$ m/e 253.1678, found 253.1676.

(3α,3aα,7β,7aα)-(±)-7-Ethenyloctahydro-7a-(methoxymethyl)-2-methyl-3-(phenylthio)-1*H*-isoindol-1-one (14). To a solution of 102 mg (0.403 mmol) of **13** in 2 mL of dichloro-

(44) For the sake of clarity in the discussion, the numbering system used in the schemes and text was derived from the numbering system of gelsemine. The numbering system used in the Experimental Section is derived from the IUPAC names of the compounds described therein.

(45) Mass and 500-Mz ^1H NMR spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.

methane were added 5 mg of *p*-toluenesulfonic acid and 53.2 mg (0.48 mmol) of thiophenol in one portion. The solution was stirred at room temperature for 16 h followed by the addition of 20 mL of 5% aqueous sodium carbonate solution. The solution was extracted with two 30-mL portions of dichloromethane. The combined organic extracts were washed with 20 mL of saturated brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (141 mg) was chromatographed over 5 g of silica gel (hexane–ethyl acetate, 3:1) to afford 126 mg (94%) of sulfide **14**: IR (neat) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.4–1.6 (m, 4 H), 1.6–1.7 (m, 1 H), 1.8–1.9 (m, 1 H), 2.2–2.3 (m, 1 H), 2.57 (m, 1 H, CHCSPh), 2.90 (s, 3 H, NCH_3), 3.20 (s, 3 H, OCH_3), 3.33 (d, J = 9.5 Hz, 1 H, CHOMe), 3.38 (d, J = 9.5 Hz, 1 H, CHOMe), 4.44 (d, J = 7.5 Hz, 1 H, HCSPh), 4.98 (dd, J = 10, 1 Hz, 1 H, =CH), 5.10 (dd, J = 17, 1 Hz, 1 H, =CH), 5.87 (ddd, J = 17, 10, 8.7 Hz, 1 H, =CH), 7.25–7.45 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.51 (t), 22.36 (t), 26.51 (t), 27.98 (q), 38.97 (d), 41.01 (d), 50.92 (s), 58.96 (q), 72.83 (d), 73.66 (t), 116.26 (t), 128.15 (d), 129.10 (d), 132.55 (s), 133.96 (d), 137.98 (d), 175.03 (s); exact mass calcd for $C_{13}H_{20}NO_2$ (M – SPh) m/e 222.1494, found 222.1506.

(3aα,7β,7aα)-(±)-7-Ethenyloctahydro-7a-(methoxymethyl)-2-methyl-1*H*-isoindol-1-one (15). To 62 mg (0.19 mmol) of sulfide **14** in 7 mL of benzene under reflux was added a solution of 109 mg (0.57 mmol) of tri-*n*-butyltin hydride and 5 mg of AIBN in 2 mL of benzene over a 10-h period. The resulting solution was concentrated in vacuo, and the residue was chromatographed over 6 g of silica gel (hexane–ethyl acetate, 2:1) to give 39 mg (93%) of lactam **15**: IR (neat) 1685, 1115, 1005, 915 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–2.00 (m, 7 H), 2.20–2.40 (m, 1 H), 2.40–2.60 (m, 1 H), 2.70–3.00 (m, 1 H), 2.83 (s, 3 H, NCH_3), 3.36 (s, 3 H, OCH_3), 3.39 (d, J = 8 Hz, 1 H, CH_2OMe), 3.46 (d, J = 8 Hz, 1 H, CH_2OMe), 4.90–5.10 (m, 2 H, $=CH_2$), 6.15–6.30 (m, 1 H, =CH); ^{13}C NMR δ 20.31 (t), 26.83 (t), 28.30 (q), 28.55 (t), 29.70 (d), 33.47 (d), 42.67 (s), 52.83 (t), 59.22 (q), 74.36 (t), 115.30 (t), 139.58 (d), 175.35 (s); exact mass calcd for $C_{13}H_{21}NO_2$ m/e 223.1592, found 223.1582.

(1α,3aα,4β,7aα)-(±)-Octahydro-1-methoxy-3a-(methoxymethyl)-2-methyl-3-oxo-1*H*-isoindole-4-carboxaldehyde (16). To a solution of 1.10 g (4.34 mmol) of **13** in *tert*-butyl alcohol–tetrahydrofuran–water (30 mL:15 mL:5 mL) was added 5 mL of 1% osmium tetraoxide in water. The solution was cooled in an ice–water bath, and 3.32 g (10.85 mmol) of sodium periodate was added in several portions over a 20-min period. The reaction mixture was stirred at room temperature for 9 h and then diluted with 150 mL of water. The solution was extracted with two 150-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue (1.36 g) was chromatographed over 35 g of silica gel (hexane–ethyl acetate, 1:1) to afford 718 mg (65%) of aldehyde **16** contaminated with a small amount of its C_4 diastereomer:IR (neat) 1700 (br) cm^{-1}; ^1H NMR (200 MHZ, $CDCl_3$) δ 1.00–1.45 (m, 3 H), 1.50–1.75 (m, 1 H), 1.75–1.95 (m, 2 H), 2.45 (dd, J = 9, 6 Hz, 1 H, HCCN), 2.62 (ddd, J = 11, 5, 0.6 Hz, 1 H, CHCO), 2.88 (s, 3 H, NCH_3), 3.37 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 3.63 (d, J = 9.5 Hz, 1 H, CHOMe), 3.77 (d, J = 9.5 Hz, 1 H, CHOMe), 4.23 (d, J = 1 Hz, 1 H, HCNO), 10.12 (d, J = 0.6 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 20.65 (t), 22.18 (t), 26.85 (t), 28.51 (q), 38.47 (d), 48.88 (d), 51.38 (s), 55.40 (q), 59.17 (q), 76.42 (t), 97.43 (d), 174.98 (s), 203.22 (s); exact mass calcd for $C_{12}H_{21}NO_3$ (M – CO) m/e 227.1521, found 227.1524.

(1α,3aα,4β,7aα)-(±)-Ethyl 3-[Octahydro-1-methoxy-3a-(methoxymethyl)-2-methyl-3-oxo-1*H*-isoindol-4-yl]-2-propenoate (17). To a solution of 591 mg (2.32 mmol) of aldehyde **16** in 10 mL of benzene was added 968 mg (2.78 mmol) of (carbethoxymethylidene)triphenylphosphorane. The solution was stirred under reflux for 4 h and then was concentrated in vacuo. The residue (1.83 g) was chromatographed over 35 g of silica gel (hexane–ethyl acetate, 1.25:1) to afford 628 mg (83%) of unsaturated ester **17**: IR (neat) 1700, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H, CH_3), 1.20–1.85 (m, 6 H), 2.40–2.65 (m, 2 H), 2.84 (s, 3 H, NCH_3), 3.31 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.43 (d, J = 12 Hz, 1 H, CHOMe), 3.55 (d, J = 12 Hz, 1 H, CHOMe), 4.18 (q, J = 7 Hz, 2 H, CO_2CH_2), 4.31 (d, J = 4 Hz, 1 H, HCNO), 5.80 (d, J = 16 Hz, 1 H, =CH), 7.36 (dd, J = 16, 9 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.30 (q), 20.18 (t), 25.67 (t), 27.15 (t), 27.91 (q), 37.81 (d), 40.24 (d), 51.67 (s), 54.87 (q), 59.21 (q), 60.17 (t), 74.48 (t), 96.19 (d), 122.20 (d), 149.34 (d), 166.55 (s), 174.83 (s); exact mass calcd for $C_{17}H_{27}NO_5$ m/e 325.1889, found 325.1886.

[1α,3aα,4β(*E*),7aα]-(±)-Ethyl 3-[Octahydro-3a-(methoxymethyl)-2-methyl-3-oxo-1-(phenylthio)-1*H*-isoindol-4-yl]-2-propenoate (18). To a stirred solution of 614 mg (1.89 mmol) of **17** in 8 mL of dichloromethane was added 312 mg (2.84 mmol) of thiophenol. To the solution was added 20 mg of *p*-toluenesulfonic acid followed by stirring for 15 h. To the resulting solution was added 30 mL of 5% aqueous sodium carbonate solution, and the mixture was extracted with two 40-mL portions of dichloromethane. The combined extracts were washed with 20 mL of saturated brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (830 mg) was chromatographed over 40 g of silica gel (hexane–ethyl acetate, 3:1) to afford 676 mg (89%) of phenylthio lactam **18**: IR (neat) 1695 (br), 1648 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3 H, CH_3), 1.30–1.80 (m, 6 H), 2.40–2.60 (m, 2 H), 2.88 (s, 3 H, NCH_3), 3.16 (s, 3 H, OCH_3), 3.26 (d, J = 9 Hz, 1 H, CHOMe), 3.35 (d, J = 9 Hz, 1 H, CHOMe), 4.14 (q, J = 7.5 Hz, 2 H, CO_2CH_2), 4.42 (d, J = 6 Hz, 1 H, SCHN), 5.78 (dd, J = 16, 0.5 Hz, 1 H, =CH), 7.05 (dd, J = 16, 9 Hz, 1 H, =CH), 7.20–7.45 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 14.13 (q), 17.55 (t), 22.80 (t), 25.90 (t), 28.02 (q), 39.11 (d), 39.47 (d), 51.13 (s), 59.00 (q), 60.11 (t), 72.85 (d), 73.56 (t), 122.75 (d), 128.34 (d), 129.16 (d), 132.21 (s), 134.15 (d), 147.97 (d), 166.33 (s), 174.72 (s); exact mass calcd for $C_{16}H_{24}NO_4$ (M – SPh) m/e 294.1706, found 294.1708.

(1α,3aβ,4α,7aβ,8*R)-Ethyl Octahydro-3a-(methoxymethyl)-2-methyl-3-oxo-1,4-methano-1*H*-isoindole-8-acetate (23).** To a solution of 453 mg (1.12 mmol) of 18 in 40 mL of benzene under reflux was added a solution of 654 mg (2.24 mmol) of tri-*n*-butyltin hydride and 20 mg of AIBN in 10 mL of benzene over a 10-h period. The solution was warmed under reflux for an additional 2 h and and then concentrated in vacuo. The residue was diluted with 50 mL of hexane and extracted with two 50-mL portions of acetonitrile. The acetonitrile extracts were concentrated in vacuo. The residue (563 mg) was chromatographed over 20 g of silica gel (ethyl acetate–dichloromethane, 3:1) to afford 306 mg (92%) of ester **23** and its C_8 diastereomer **22** (10:1, respectively): IR (neat) 1730, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.50–1.80 (m, 7 H), 2.26 (dd, J = 16.5, 8.5 Hz, 1 H, $CHCO_2Et$), 2.28 (m, 1 H), 2.29 (dd, J = 16.5, 8.8 Hz, 1 H, $CHCO_2Et$), 2.71 (tt, J = 7.8, 2.5 Hz, 1 H, $HCCCO_2$), 2.88 (s, 3 H, NCH_3), 3.42 (s, 3 H, OCH_3), 3.57 (dd, J = 2.2, 2.2 Hz, 1 H, NCH), 3.66 (d, J = 9.7 Hz, 1 H, CHOMe), 3.85 (d, J = 9.7 Hz, 1 H, CHOMe), 4.13 (q, J = 7.1 Hz, 2 H, CO_2CH_2); ^{13}C NMR ($CDCl_3$, major diastereomer) δ 14.02 (q), 15.38 (t), 20.47 (t), 23.74 (t), 30.34 (q), 35.98 (t), 39.81 (d), 42.15 (d), 48.92 (d), 55.93 (s), 59.51 (q), 60.28 (t), 65.79 (d), 67.88 (t), 172.38 (s), 176.75 (s); exact mass calcd for $C_{16}H_{25}NO_4$ m/e 295.1784, found 295.1786.

(1α,3aβ,4α,7aβ,8*R)-Ethyl Octahydro-3a-(hydroxymethyl)-2-methyl-3-oxo-1,4-methano-1*H*-isoindole-8-acetate (24).** To a stirred solution of 240 mg (0.814 mmol) of ester **23** in 3 mL of dichloromethane cooled to –72 °C (dry ice–isopropyl alcohol bath) was added 136 mg (0.542 mmol) of boron tribromide. The reaction mixture was stirred in a cold bath for 30 min and then warmed at room temperature for 20 min. The resulting solution was poured into 25 mL of water and stirred for 15 min. The aqueous layer was saturated with sodium chloride and extracted with two 50-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue (256 mg) was chromatographed over 6 g of silica gel (ethyl acetate–dichloromethane–methanol, 6:2:1) to afford 234 mg (100%) of alcohol **24**: IR (neat) 3450, 1730, 1675 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H, CH_3), 1.50–1.90 (m, 7 H), 2.20–2.25 (m, 1 H), 2.31 (d, J = 8 Hz, 2 H, CH_2CO_2), 2.70–2.82 (m, 1 H, $HCCCO_2$), 2.90 (s, 3 H, NCH_3), 3.40 (br t, J = 6 Hz, 1 H, OH), 3.63, (dd, J = 2.5, 2 Hz, 1 H, NCH), 3.90–4.10 (m, 2 H, CH_2O), 4.16 (q, J = 7 Hz, 2 H, CO_2CH_2); ^{13}C NMR ($CDCl_3$) δ 14.25 (q), 15.54 (t), 20.46 (t), 23.15 (t), 30.30 (q), 36.16 (t), 39.17 (d), 41.49 (d), 50.17 (d), 56.46 (s), 59.23 (t), 60.64 (t), 66.68 (d), 172.52 (s), 179.21 (s); exact mass calcd for $C_{15}H_{23}NO_4$ m/e 281.1627, found 281.1602.

(1α,3aβ,4α,7aβ,8*R)-Ethyl 3a-Formyloctahydro-2-methyl-3-oxo-1,4-methano-1*H*-isoindole-8-acetate (25).** To

a solution of 107 mg (0.85 mmol) of oxalyl chloride in 1 mL of dichloromethane cooled to −78 °C was added 132 mg (1.69 mmol) of dimethyl sulfoxide in 1 mL of dichloromethane over a 3-min period. The solution was stirred for 30 min, and 95 mg (0.338 mmol) of alcohol **24** was added in 1 mL of dichloromethane. The solution was stirred at −78 °C for 1 h, and 273 mg of triethylamine was added over a 3-min period. The resulting solution was diluted with 30 mL of dichloromethane and washed with 20 mL of saturated brine. The aqueous layer was extracted with 30 mL of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was chromatographed over 6 g of silica gel (ethyl acetate–dichloromethane–methanol, 6:2:1) to give 81 mg (86%) of aldehyde **25**: IR (neat) 1725, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H, CH_3), 1.30–2.10 (m, 7 H), 2.10–2.25 (m, 1 H), 2.35 (d, J = 8 Hz, 1 H, CH_2CO_2), 2.50–2.80 (m, 2 H), 2.87 (s, 3 H, NCH_3), 3.62 (dd, J = 1.5, 1.5 Hz, 1 H, CHN), 4.15 (q, J = 7 Hz, 2 H, CO_2CH_2), 10.04 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 14.07 (q), 15.74 (t), 20.70 (t), 24.80 (t), 30.17 (q), 35.76 (t), 40.28 (d), 42.64 (d), 50.10 (d), 60.59 (t), 64.99 (s), 65.82 (d), 172.04 (s), 173.77 (s), 201.62 (s); exact mass calcd for $C_{15}H_{21}NO_4$ m/e 279.1470, found 279.1510.

(1α,3aβ,4α,7aβ,8R*)-Ethyl 3a-Ethenyloctahydro-2-methyl-3-oxo-1,4-methano-1H-isoindole-8-acetate (2). A solution of 327 mg (0.91 mol) of methyltriphenylphosphonium bromide and 100 mg (0.91 mol) of potassium *tert*-butoxide in 5 mL of toluene was stirred for 1 h. To the resulting yellow solution was added 49 mg (0.18 mmol) of **25** in 2 mL of toluene. The reaction mixture was stirred at 60 °C for 4 h and then poured into 20 mL of water. The solution was extracted with three 40-mL portions of ether. The combined organic extracts were washed with 20 mL of saturated brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed over 6 g of silica gel (hexane–ethyl acetate, 1:1) to afford 44 mg (88%) of olefin **2**: IR (neat) 1730, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H, CH_3), 1.40–2.10 (m, 7 H), 2.32 (d, J = 7.5 Hz, 2 H, CH_2CO_2), 2.32–2.40 (m, 1 H), 2.70–2.80 (m, 1 H, $CHCCO_2$), 2.88 (s, 3 H, NCH_3), 3.58 (dd, J = 2, 2 Hz, 1 H, NCH), 4.14, (q, J = 7.5 Hz, 2 H, OCH_2), 5.27 (dd, J = 18, 2 Hz, 1 H, =CH), 5.48 (dd, J = 11, 2 Hz, 1 H, =CH), 6.03 (dd, J = 18, 11 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.01 (q), 15.39 (t), 20.53 (t), 24.16 (t), 30.42 (q), 38.54 (t), 41.74 (d), 42.07 (d), 50.67 (d) 58.21 (s), 60.31 (t), 65.71 (d), 119.22 (t), 133.66 (d), 172.31 (s), 176.91 (s); exact mass calcd for $C_{16}H_{23}NO_3$ m/e 277.1678, found 277.1674.

2-[(5-Oxo-3(E)-hexenyl)oxy]tetrahydropyran (26). A mixture of 12.2 g (77.2 mmol) of the tetrahydropyranyl ether of β-hydroxypropanal[34] and 24.7 g (77.6 mmol) of (2-oxopropylidene)triphenylphosphorane in 100 mL of dichloromethane was stirred at room temperature for 48 h. The mixture was diluted with 800 mL of hexane and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in 20 mL of dichloromethane and 300 mL of hexane and filtered, and the filtrate was concentrated in vacuo. The residual oil was distilled under reduced pressure (90–102 °C/0.5 mmHg) to give 13.3 g (87%) of **26** as a colorless oil: IR ($CHCl_3$) 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45–1.90 (m, 6 H, CH_2 manifold), 2.25 (s, 3 H, CH_3CO), 2.53 (dq, J = 6.5, 1.5 Hz, 2 H, CH_2C=), 3.54 (m, 2 H, OCH_2), 3.85 (m, 2 H, OCH_2), 4.06 (m, 1 H, OCHO), 6.14 (dt, J = 16.1, 1.5 Hz, 1 H, =CHCO), 6.84 (dt, J = 16.1, 6.8 Hz, 1 H, =CH); exact mass calcd for $C_{11}H_{18}O_3$ m/e 197.1178, found 197.1152.

2-[[5-[(Trimethylsilyl)oxy]-3(E),5-hexadienyl]oxy]tetrahydropyran (27). To a solution of 4.00 mL (28.5 mmol) of diisopropylamine in 100 mL of tetrahydrofuran cooled in a dry ice–acetone bath was added 17.8 mL (28.5 mmol) of 1.60 M *n*-butyllithium in hexane. The mixture was stirred for 30 min at −78 °C, and 5.50 g (27.8 mmol) of **26** in 30 mL of tetrahydrofuran was added over a 5-min period, followed by stirring for 30 min. Chlorotrimethylsilane (31.5 mmol) was added, and the mixture was stirred for 10 min at −78 °C, warmed to room temperature, and stirred for 10 min. The mixture was diluted with 150 mL of hexane and filtered, and the filtrate was concentrated in vacuo. The residue was distilled under reduced pressure (99–106 °C/0.1 mmHg) to give 6.96 g (93%) of **27** as a colorless oil: IR ($CHCl_3$) 1025, 850 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.23 (s, 9 H, $SiMe_3$), 1.40–2.00 (m, 6 H, CH_2 manifold), 2.41 (m, 2 H, =CCH_2), 3.50 (m, 2 H, OCH_2), 3.83 (m, 2 H, OCH_2), 4.24 (s, 2 H, =CH_2), 4.61 (m, 1 H, OCHO), 5.98 (s, 2 H, CH=CH); exact mass calcd for $C_{14}H_{26}O_3Si$ m/e 270.1655, found 270.1630.

(3aα,7β,7aα)-(±)-Tetrahydro-7-(2-hydroxyethyl)-2-methyl-1H-isoindole-1,3,5(2H,4H)-trione (28). A mixture of 5.30 g (19.6 mmol) of **27** and 2.18 g (19.6 mmol) of *N*-methylmaleimide (**7**) in 80 mL of toluene was heated at reflux for 3 h and concentrated in vacuo. The residue was dissolved in 80 mL of tetrahydrofuran and 40 mL of water. Dowex 50X8-100 ion-exchange resin (3.0 g) was added, and the mixture was heated at 60 °C for 12 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over 200 g of silica gel (ethyl acetate) to give 3.55 g of **28** as a colorless oil. Earlier fractions from the above chromatography were combined, concentrated in vacuo, and dissolved in 40 mL of tetrahydrofuran, 10 mL of methanol, and 10 mL of water. Dowex 50X8-100 ion-exchange resin (2.0 g) was added, and the mixture was heated at 60 °C for 12 h. The mixture was filtered, and the residue was chromatographed over 60 g of silica gel (ethyl acetate) to give 0.66 g (total 4.21 g, 95%) of **28**: IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (m, 1 H, OH), 1.78 (dddd, J = 14.5, 6.6, 6.6, 2.4 Hz, 1 H, $HOCH_2CH$), 1.88 (dd, J = 18.8, 13.6 Hz, 1 H, C_6H), 2.13 (dddd, J = 14.5, 7.6, 7.6, 5.1 Hz, 1 H, $HOCH_2CH$), 2.45 (ddd, J = 18.8, 3.5, 1.4 Hz, 1 H, C_6H), 2.63 (m, 1 H, C_7H), 2.73 (dd, J = 16.8, 8.2 Hz, 1 H, C_4H), 2.92 (dd, J = 16.8, 2.1 Hz, 1 H, C_4H), 3.00 (s, 3 H, NCH_3), 3.36 (dt, J = 9.4, 2.1 Hz, 1 H, $C_{7a}H$), 3.44 (ddd, J = 9.4, 5.7, 1.4 Hz, 1 H, $C_{3a}H$), 3.80 (ddd, J = 11.0, 7.6, 4.4 Hz, 1 H, HOC*H*), 3.93 (ddd, J = 11.0, 6.6, 4.5 Hz, 1 H, HOC*H*); exact mass calcd for $C_{11}H_{15}NO_4$ m/e 225.1001, found 225.0994.

(3′aα,7′β,7′aα)-(±)-7′-(2-Hydroxyethyl)tetrahydro-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5H]isoindole]-1′,3′-(2′H,4′H)-dione (29). A mixture of 7.26 g (32.3 mmol) of **28**, 3.36 g (32.3 mmol) of 2,2-dimethyl-1,3-propanediol, and 2.0 g of Dowex 50X8-100 ion-exchange resin in 150 mL of benzene was heated at reflux for 8 h with continuous removal of water using a Dean–Stark receiver. The mixture was filtered, dried (K_2CO_3), and concentrated in vacuo. The residue was heated under reduced pressure (80 °C/0.1 mmHg) to sublime the unreacted 2,2-dimethyl-1,3-propanediol. The residual oil was chromatographed over 200 g of silica gel (ethyl acetate) to give 8.10 g (81%) of **29** as a colorless oil: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.47 (t, J = 14.7 Hz, 1 H, $C_6'H$), 1.69 (br s, 1 H, OH), 1.81 (m, 1 H, $HOCH_2CH$), 1.87 (dd, J = 14.3, 6.8 Hz, 1 H, $C_4'H$), 2.02 (ddd, J = 14.7, 3.9, 0.8 Hz, 1 H, $C_6'H$), 2.17 (m, 1 H, HOC*CH*), 2.25 (m, 1 H, $C_7'H$), 2.66 (dd, J = 14.3, 3.8 Hz, 1 H, $C_4'H$), 2.92 (s, 3 H, NCH_3), 3.01 (m, 1 H, $C_{3'a}H$), 3.14 (dd, J = 8.9, 5.3 Hz, 1 H, $C_{7'a}H$), 3.23 (dd, J = 11.5, 1.6 Hz, 1 H, OCH_2), 3.37 (dd, J = 11.5, 1.6 Hz, 1 H, OCH_2), 3.49 (d, J = 11.5 Hz, 1 H, OCH_2), 3.56 (d, J = 11.5 Hz, 1 H, OCH_2), 3.77 (ddd, J = 11.0, 7.5, 4.6 Hz, 1 H, HOC*H*), 3.88 (ddd, J = 11.0, 6.3, 4.8 Hz, 1 H, HOC*H*); exact mass calcd for $C_{16}H_{25}NO_5$ m/e 311.1733, found 311.1748.

(3′aα,7′β,7′aα)-(±)-7′-Ethenyltetrahydro-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5H]isoindole]-1′,3′(2′H,4′H)-dione (30). To a solution of 7.56 g (24.3 mmol) of **29** and 6.62 g (29.2 mmol) of *o*-nitrophenyl selenocyanate in 200 mL of tetrahydrofuran cooled in an ice bath was added 7.27 mL (29.2 mmol) of tri-*n*-butylphosphine in 50 mL of tetrahydrofuran over a 10-min period. The mixture was warmed to room temperature, stirred for 1 h, and cooled in an ice bath, and 13.8 g (104 mmol) of anhydrous disodium hydrogen phosphate was added. The mixture was stirred for 10 min, and 37.0 mL (362 mmol) of 30% aqueous hydrogen peroxide was added over a 10-min period. The mixture was warmed to room temperature, stirred for 4 h, and diluted with 300 mL of dichloromethane. The solution was washed with 300 mL of saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with 150 mL of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed over 200 g of silica gel (ethyl acetate–hexane, 1:4) to give 5.43 g (76%) of **30** as a yellow oil: IR ($CHCl_3$) 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.69 (dd, J = 14.3, 13.0 Hz, 1 H, $C_6'H$), 2.00 (dd, J = 14.3, 6.2 Hz, 1 H, $C_6'H$), 2.06 (dd, J = 14.6, 5.2, 1 H, $C_4'H$), 2.48 (dd, J = 14.6, 4.3 Hz, 1 H, $C_4'H$), 2.74 (m, 1 H, $C_7'H$), 2.92 (s, 3 H, NCH_3), 3.00 (m, 2 H, $C_{3'a}H$ and $C_{7'a}H$), 3.29 (d, J = 11.5 Hz, 1 H, OCH_2), 3.39 (d, J = 11.5 Hz, 1 H, OCH_2),

3.48 (d, J = 11.5 Hz, 1 H, OCH_2), 3.54 (d, J = 11.5 Hz, 1 H, OCH_2), 5.12 (m, 2 H, $=CH_2$), 6.29 (ddd, J = 17.0, 10.2, 7.9 Hz, 1 H, =CH); exact mass calcd for $C_{16}H_{23}NO_4$ m/e 293.1627, found 293.1621.

(3′α,3′aα,7′β,7′aα)-(±)-7′-Ethenyl-3′-ethoxyhexahydro-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5*H*]isoindol]-1′-(4′*H*)-one (31). To a solution of 3.10 g (10.2 mmol) of **30** in 100 mL of methanol cooled in a dry ice–carbon tetrachloride bath was added 1.16 g (30.6 mmol) of sodium borohydride portionwise over a 5-min period. The mixture was stirred for 30 min at −23 °C, warmed to room temperature, and diluted with 300 mL of dichloromethane. The solution was washed with 300 mL of saturated aqueous sodium bicarbonate, and the aqueous layer was extracted twice with 150-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 3.17 g of the crude hydroxy lactam as a yellow foam. The residue was dissolved in 70 mL of absolute ethanol, and Dowex 50X8-100 ion-exchange resin (3.0 g) and 4A molecular sieves (10 g) were added. The mixture was stirred for 3 h at room temperature. The mixture was filtered and concentrated in vacuo, and the residue was chromatographed over 200 g of silica gel (ethyl acetate–hexane, 1:3) to give 2.70 g (82%) of impure **31** as a colorless oil, which was used in the next reaction without further purification: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 0.88 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.19 (dd, J = 13.4, 5.7 Hz, 1 H, C_6′H), 1.21 (t, J = 7.0 Hz, 3 H, CH_3), 1.31 (t, J = 13.4 Hz, 1 H, C_6′H), 2.19 (ddd, J = 13.5, 5.8, 2.8 Hz, 1 H, C_4′H), 2.30 (dt, J = 13.5, 3.0 Hz, 1 H, C_4′H), 2.48 (qu, J = 6.0 Hz, 1 H, $C_{3'a}$H), 2.58 (m, 1 H, C_7H), 2.86 (s, 3 H, NCH_3), 2.91 (t, J = 6.0 Hz, 1 H, $C_{7'a}$H), 3.39–3.62 (m, 6 H, OCH_2 manifold), 4.24 (s, 1 H, C_3′H), 5.06 (m, 2 H, $=CH_2$), 6.56 (ddd, J = 17.4, 10.1, 8.0 Hz, 1 H, =CH). Weak signals at δ 1.39 (t), 1.95 (dt), 2.12 (ddd), 2.43 (qu), and 4.23 (s) in the ^1H NMR spectrum of this material were attributed to a diastereomer of this ethoxy lactam; exact mass calcd for $C_{18}H_{29}NO_4$ m/e 323.2096, found 323.2086.

(3′α,3′aα,7′β,7′aα)-(±)-7′-Ethenyl-3′-ethoxyhexahydro-7′a-(methoxymethyl)-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5*H*]isoindol]-1′(4′*H*)-one (32). To a solution of 1.75 mL (12.5 mmol) of diisopropylamine in 80 mL of tetrahydrofuran cooled in a dry ice–acetone bath was added 7.80 mL (12.5 mmol) of 1.60 M n-butyllithium in hexane over a 5-min period. The mixture was stirred for 30 min, and 3.11 g (9.63 mmol) of **31** in 20 mL of tetrahydrofuran was added over a 5-min period. The mixture was stirred for 30 min at −78 °C, warmed to −20 °C, and stirred for 10 min in a dry ice–carbon tetrachloride bath. The mixture was cooled in a dry ice–acetone bath, and 1.65 mL (21.7 mmol) of chloromethyl methyl ether was added over a 5-min period. The mixture was stirred for 30 min at −78 °C, warmed to room temperature, stirred for 30 min, and diluted with 300 mL of dichloromethane. The solution was washed with 300 mL of brine, and the aqueous layer was extracted with 150 mL of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed over 150 g of silica gel (ethyl acetate–hexane, 1:3) to give 2.97 g (84%) of impure **32** as a colorless oil, which was used in the next reaction without further purification: IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 0.87 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.23 (t, J = 7.4 Hz, 3 H, CH_3), 1.38 (dd, J = 14.0, 13.0 Hz, 1 H, C_6′H) 1.84 (dd, J = 14.3, 6.7 Hz, 1 H, C_4′H), 1.97 (ddd, J = 14.3, 5.9, 0.8 Hz, 1 H, C_4′H), 2.12 (dd, J = 14.0, 3.1 Hz, 1 H, C_6′H), 2.58 (m, 2 H, $C_{3'a}$H and C_7H), 2.82 (s, 3 H, NCH_3), 3.30 (s, 3 H, OCH_3), 3.41–3.59 (m, 8 H, OCH_2 manifold), 4.59 (d, J = 2.4 Hz, 1 H, C_3′H), 5.06 (m, 2 H, $=CH_2$), 6.21 (m, 1 H, =CH); exact mass calcd for $C_{20}H_{33}NO_5$ m/e 367.2359, found 367.2366.

(3′α,3′aα,7′β,7′aα)-(±)-3′-Ethoxy-7′-formylhexahydro-7′a-(methoxymethyl)-2′,5,5-trimethylspiro[1,3-dioxane-2,5′-[5*H*]isoindol]-1′(4′*H*)-one (33). To a solution of 2.60 g (7.08 mmol) of **32** in 60 mL of *tert*-butyl alcohol, 30 mL of tetrahydrofuran, and 9 mL of water cooled in an ice bath were added 9 mL of 1% aqueous osmium tetraoxide and 3.80 g (17.8 mmol) of sodium periodate. The mixture was warmed to room temperature, stirred for 2 h, diluted with 300 mL of dichloromethane, and washed with 400 mL of water. The aqueous layer was extracted with two 150-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was flash chromatographed over 150 g of silica gel (ethyl acetate–hexane, 2:3) to give 1.90 g (73%) of impure **33** as a colorless oil which was used in the next reaction without further purification: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 0.82 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.15 (dt, J = 12.5, 7.1, 1 H, C_4′H), 1.24 (t, J = 7.0 Hz, 3 H, CH_3), 1.37 (dd, J = 13.8, 10.2 Hz, 1 H, C_6′H), 2.10 (ddd, J = 13.8, 6.7, 2.4 Hz, 1 H, C_6′H), 2.58 (dd, J = 10.2, 6.7 Hz, 1 H, C_7H), 2.65 (m, 1 H, $C_{3'a}$H), 2.78 (dd, J = 12.5, 4.2 Hz, 1 H, C_4′H), 2.86 (s, 3 H, NCH_3), 3.36 (s, 3 H, OCH_3), 3.38–3.90 (m, 8 H, OCH_2 manifold), 4.35 (d, J = 0.8 Hz, 1 H, C_3′H), 10.2 (s, 1 H, CHO). Weak signals at δ 1.59 (dd), 1.73 (dd), 2.23 (ddd), and 2.51 (dd) in the ^1H NMR spectrum of this material were attributed to a diastereomer of the ethoxy lactam; exact mass calcd for $C_{19}H_{31}NO_6$ m/e 369.2152, found 369.2125.

(3′α,3′aα,7′β(*E*),7′aα)-(±)-Ethyl 3-[3′-Ethoxyoctahydro-7′a-(methoxymethyl)-2′,5,5-trimethyl-1′-oxospiro[1,3-dioxane-2,5′-[5*H*]isoindol]-7′-yl]-2-propenoate (34). A mixture of 1.19 g (3.22 mmol) of **33** and 2.44 g (6.44 mmol) of (carbethoxymethylidene)triphenylphosphorane in 15 mL of dichloromethane was heated at reflux for 3 days. The mixture was chromatographed over 100 g of silica gel (ethyl acetate–hexane, 1:2) to give 1.28 g (91%) of impure **34** as a colorless oil, which was used in the next reaction without further purification: IR ($CDCl_3$) 1690 cm^{-1}; ^1H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 0.85 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.23 (t, J = 7.0 Hz, 3 H, CH_3), 1.29 (t, J = 7.1 Hz, 3 H, CH_3), 1.41 (t, J = 14.2 Hz, 1 H, C_6′H), 1.69 (dd, J = 14.2, 7.7 Hz, 1 H, C_6′H), 2.05 (ddd, J = 14.2, 6.3, 1.3 Hz, 1 H, C_4′H), 2.17 (ddd, J = 14.2, 4.3, 1.1 Hz, 1 H, C_4′H), 2.61 (m, 1 H, $C_{3'a}$H), 2.82 (s, 3 H, NCH_3), 3.30 (s, 3 H, OCH_3), 3.39–3.60 (m, 9 H, OCH_2 manifold and C_7H), 4.19 (m, 2 H, CO_2CH_2), 4.50 (d, J = 1.9 Hz, 1 H, C_3′H), 5.82 (dd, J = 15.7, 0.8 Hz, 1 H, $=CHCO_2Et$), 7.41 (dd, J = 15.7, 9.5 Hz, 1 H, =CH); exact mass calcd for $C_{23}H_{37}NO_7$ m/e 439.2570, found 439.2572.

(3′α,3′aα,7′β(*E*),7′aα)-(±)-Ethyl 3-[Octahydro-7′a-(methoxymethyl)-2′,5,5-trimethyl-1′-oxo-3′-(phenylthio)spiro[1,3-dioxane-2,5′-[5*H*]isoindol]-7′-yl]-2-propenoate (35) and (1α,3aα,4β(*E*),7′aα)-(±)-Ethyl 3-[Octahydro-3a-(methoxymethyl)-2-methyl-1-(phenylthio)-3,6-dioxo-[1*H*]isoindol-4-yl]-2-propenoate (38). A mixture of 445 mg (1.01 mmol) of **34**, 0.114 mL (1.11 mmol) of thiophenol, and 0.40 g of Dowex 50X8-100 ion-exchange resin in 5 mL of dichloromethane was stirred for 12 h at room temperature. The mixture was filtered, and the residual resin was washed with 10 mL of dichloromethane. The filtrate was concentrated in vacuo, and the residue was chromatographed over 30 g of silica gel (ethyl acetate–hexane, 1:3) to give 420 mg (83%) of impure **35** as a colorless oil. This material partially hydrolyzed after standing for 5 h in a silica gel column. Elution with ethyl acetate gave **38** as a slightly yellow oil (one isomer by ^1H NMR). Lactam **35**: IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 0.90 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.27 (t, J = 7.0 Hz, 3 H, CH_3), 1.53 (dd, J = 14.8, 12.1 Hz, 1 H, C_6′H), 1.82 (dd, J = 14.8, 5.7 Hz, 1 H, C_6′H), 2.05 (dd, J = 14.2, 3.3 Hz, 1 H, C_4′H), 2.34 (dd, J = 14.2, 3.7 Hz, 1 H, C_4′H), 2.66 (m, 1 H, $C_{3'a}$H), 2.76 (d, J = 9.4 Hz, 1 H, CH_2OMe), 2.89 (s, 3 H, NCH_3), 3.13 (s, 3 H, OCH_3), 3.29 (d, J = 9.4 Hz, 1 H, CH_2OMe), 3.41–3.46 (m, 5 H, OCH_2CMe_2 and C_7H), 4.17 (dq, J = 7.1, 1.9 Hz, 2 H, CO_2CH_2), 4.80 (d, J = 5.8 Hz, 1 H, C_3′H), 5.76 (d, J = 15.6 Hz, 1 H, $=CHCO_2Et$), 7.11 (dd, J = 15.6, 9.0 Hz, 1 H, =CH), 7.30–7.42 (m, 5 H, Ar H); mass spectrum, m/e (relative intensity) 394 (13), 348 (6), 262 (11), 239 (44), 153 (10), 122 (30), 110 (100); exact mass calcd for $C_{27}H_{37}NO_6S - C_6H_5S$ m/e 394.2230, found 394.2230. This material was contaminated by substances that displayed weak signals at δ 0.93 (s), 0.97 (s), 2.95 (s), 2.96 (s), 3.12 (s), 3.15 (s), and 5.00 (d, J = 6 Hz). Lactam **38**: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3 H, CH_3), 2.08 (dd, J = 18.9, 13.3 Hz, 1 H, C_5H), 2.39 (dd, J = 18.9, 4.0 Hz, 1 H, C_5H), 2.57 (dd, J = 16.0, 2.4 Hz, 1 H, C_7H), 2.74 (dd, J = 16.0, 6.6 Hz, 1 H, C_7H), 2.91 (m, 1 H, C_{7a}H), 2.96 (s, 3 H, NCH_3), 3.13 (s, 3 H, OCH_3), 3.16 (m, 1 H, C_4H), 3.27 (d, J = 9.1 Hz, 1 H, CH_2OMe), 3.35 (d, J = 9.1 Hz, 1 H, CH_2OMe), 4.18 (dq, J = 7.1, 1.8 Hz, 2 H, CO_2CH_2), 4.18 (d, J = 5.1 Hz, 1 H, CHS), 5.77 (dd, J = 15.6, 0.8 Hz, 1 H, $=CHCO_2Et$), 7.07 (dd, J = 15.6, 9.0 Hz, 1 H, =CH), 7.35 (m, 5 H, Ar H); mass spectrum, m/e (relative intensity) 372 (7), 308 (85), 262 (53), 230 (32), 202 (19), 122 (78), 45 (100); exact mass calcd for $C_{22}H_{27}NO_5S - C_6H_5S$ m/e 308.1498, found 308.1552.

(1′α,3′aβ,4′α,7′aβ,8′R*)-(±)-Ethyl [Hexahydro-3′a-(methoxymethyl)-2′,5,5-trimethyl-3′-oxospiro[1,3-dioxane-2,6′-(2′H)-[1,4]methano[1H]isoindol]-8′-yl]acetate (37). To a solution of 920 mg (1.83 mmol) of **35** in 80 mL of benzene heated at reflux was added a mixture of 0.650 ml (3.68 mmol) of tri-*n*-butyltin hydride and 10 mg of AIBN in 10 mL of benzene over a 15-h period using syringe pump. The mixture was concentrated in vacuo, and the residue was chromatographed over 60 g of silica gel (ethyl acetate–hexane, 2:1; ethyl acetate) to give 652 mg (90%) of **37** as a colorless oil, which was used in the next reaction without further purification: IR ($CHCl_3$) 1720, 1685 cm^{-1}; ^1H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 0.85 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.45 (t, J = 7.1 Hz, 3 H, CH_3), 1.63 (m, 1 H, C_4H), 1.84 (dd, J = 14.5, 2.8 Hz, 1 H, C_5H), 2.09 (d, J = 8.2 Hz, 1 H, CH_2CO_2), 2.10 (d, J = 4.7 Hz, 1 H, CH_2CO_2), 2.16 (dd, J = 16.6, 9.4 Hz, 1 H, C_7H), 2.33 (dd, J = 16.6, 6.1 Hz, 1 H, C_7H), 2.39 (m, 1 H, C_{7a}H), 2.66 (dd, J = 14.5, 3.9 Hz, 1 H, C_5H), 2.87 (s, 3 H, NCH_3), 3.12 (octet, J = 3.2 Hz, 1 H, C_8H), 3.35–3.43 (m, 2 H, OCH_2), 3.40 (s, 3 H, OCH_3), 3.49 (d, J = 11.6 Hz, 1 H, OCH_2), 3.51 (t, J = 2.5 Hz, 1 H, C_1H), 3.64 (d, J = 9.6 Hz, 1 H, CH_2OMe), 3.69 (d, J = 11.6 Hz, 1 H, OCH_2), 3.82 (d, J = 9.6 Hz, 1 H, CH_2OMe), 4.12 (dq, J = 7.1, 1.3 Hz, 2 H, CH_2CO_2Et); exact mass calcd for $C_{21}H_{33}NO_6$ m/e 395.2308, found 395.2310.

(1α,3aβ,4α,7aβ,8R*)-(±)-Ethyl Octahydro-3a-(methoxymethyl)-2-methyl-3,6-dioxo-1,4-methano-[1H]isoindole-8-acetate (39). A. From 37. A mixture of 652 mg (1.65 mmol) of **37** and 1.0 g of Dowex 50X8-100 ion-exchange resin in 25 mL of acetone was stirred at room temperature for 90 min. The mixture was filtered, and the residual resin was washed with 30 mL of acetone. The filtrate was concentrated in vacuo, and the residue was chromatographed over 50 g of silica gel (ethyl acetate; ethyl acetate–methanol, 10:1) to give 445 mg (87%) of **39** as a white solid: mp 77–82 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.86 (qu, J = 2.6 Hz, 1 H, C_4H), 2.32 (dd, J = 21.9, 3.2 Hz, 1 H, C_5H), 2.32 (m, 1 H, C_7H), 2.39 (d, J = 7.0 Hz, 1 H, CH_2CO_2Et), 2.39 (d, J = 8.2 Hz, 1 H, CH_2CO_2Et), 2.63 (m, 1 H, C_8H), 2.63 (dd, J = 21.9, 7.0 Hz, 1 H, C_5H), 2.67 (t, J = 2.7 Hz, 2 H, C_7H), 2.92 (s, 3 H, NCH_3), 3.36 (s, 3 H, OCH_3), 3.66 (t, J = 2.2 Hz, 1 H, C_1H), 3.73 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.92 (d, J = 10.0 Hz, 1 H, CH_2OMe), 4.14 (q, J = 7.1 Hz, 2 H, CO_2CH_2); ^{13}C NMR ($CDCl_3$) δ 14.01 (q), 30.12 (q), 35.42 (t), 39.15 (t), 39.61 (d), 43.01 (t), 46.10 (d), 49.04 (d), 54.42 (s), 59.31 (q), 60.64 (t), 65.71 (d), 69.03 (t), 171.50 (s), 175.30 (s), 208.52 (s); exact mass calcd for $C_{16}H_{23}NO_5$ m/e 309.1576, found 309.1576.

B. From 38: To a solution of 139 mg (0.333 mmol) of **38** in 12 mL of benzene heated at reflux was added a mixture of 0.118 mL (0.668 mmol) of tri-*n*-butyltin hydride and 10 mg of AIBN in 3 mL of benzene over a 10-h period. The mixture was concentrated in vacuo and chromatographed over 15 g of silica gel (ethyl acetate–hexane, 2:1; ethyl acetate) to give 86 mg (83%) of **39**.

(1α,3aβ,4α,7aβ,8R*)-(±)-8-(2,2-Diphenylethenyl)hexahydro-3a-(methoxymethyl)-2-methyl-1,4-methano-1H-isoindole-3,6(2H)-dione (40). To a solution of 150 mg (0.38 mmol) of ketal **37** in 30 mL of tetrahydrofuran cooled in a dry ice–acetone bath was added 2.3 mL (1.50 mmol) of 0.65 M phenylmagnesium bromide in tetrahydrofuran over a 4-min period. The mixture was warmed to room temperature and stirred for 30 min. The resulting solution was concentrated in vacuo. The residue was diluted with 50 mL of dichloromethane and washed with 30 mL of saturated aqueous ammonium chloride. The aqueous washes were extracted with three 20-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (ethyl acetate) to give 142 mg (78%) of Grignard adduct as a clear oil. This material was dissolved in 30 mL of benzene, and 50 mg (0.26 mmol) of *p*-toluenesulfonic acid was added. The mixture was warmed under reflux for 1.5 h and concentrated in vacuo, and the residue was chromatographed over 6 g of silica gel (ethyl acetate) to give 115 mg (76% from **37**) of ketone **40** as clear oil: IR (CH_2Cl_2) 1705, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.05 (d, J = 19 Hz, 1 H, C_5H), 2.09 (m, 1 H, C_{7a}H), 2.32 (dd, J = 18.6, 2.9 Hz, 1 H, C_7H), 2.51 (dd, J = 19, 6.9 Hz, 1 H, C_5H), 2.58–2.65 (m, 3 H, C_4H, C_7H, and C_8H), 3.01 (s, 3 H, NCH_3), 3.35 (s, 3 H, OCH_3), 3.44 (t, J = 2.5 Hz, 1 H, C_1H), 3.74 (d, J = 10.3 Hz, CH_2OMe), 3.96 (d, J = 10.3 Hz, 1 H, CH_2OMe), 5.82 (d, J = 9.4 Hz, 1 H, =CH), 7.1–7.4 (m, 10 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 30.5 (q), 39.1 (t), 41.5 (d), 42.5 (t), 49.0 (d), 50.2 (d), 55.0 (s), 59.4 (q), 68.0 (d), 69.4 (t), 126.5 (d), 126.8 (d), 127.6 (d), 127.7 (d), 128.2 (d), 128.6 (d), 129.1 (d), 139.2 (s), 140.9 (s), 144.4 (s), 175.6 (s), 208.0 (s); exact mass calcd for $C_{26}H_{27}NO_3$ m/e 401.1992, found 401.1966.

(1α,3aβ,4α,6α,7aβ,8R*)-(±)-8-(2,2-Diphenylethenyl)hexahydro-6-hydroxy-3a-(methoxymethyl)-2-methyl-1,4-methano-1H-isoindole-3,6(2H)-dione (41). To a solution of 110 mg (0.27 mmol) of ketone **40** in 5 mL of methanol cooled in an ice bath was added 26 mg (0.69 mmol) of sodium borohydride in one portion. The mixture was stirred for 30 min at 0 °C and 1 h at room temperature. The resulting solution was concentrated in vacuo. The residue was diluted with 50 mL of dichloromethane and washed with 30 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (ethyl acetate–methanol, 15:1) to give 89 mg (81%) of alcohol **41** as white solid and 6.4 mg (7%) of an impure material suspected to be epimeric to **41** at C_6: mp 171–173 °C; IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (dd, J = 15.6, 4.4 Hz, 1 H, C_5H), 1.49 (br s, 1 H, OH), 1.50 (dt, J = 14.9, 2.8 Hz, 1 H, C_7H), 1.79 (m, 1 H, C_4H), 2.13 (m, 2 H, C_5H and C_7H), 2.35 (m, 1 H, C_{7a}H), 2.98 (s, 3 H, NCH_3), 3.33 (t, J = 2.5 Hz, 1 H, C_1H), 3.38 (s, 3 H, OCH_3), 3.45 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.48 (dt, J = 9.9, 2.5 Hz, 1 H, C_8H), 3.88 (d, J = 10.0 Hz, 1 H, CH_2OMe), 4.00 (m, 1 H, C_6H), 5.77 (d, J = 9.9 Hz, 1 H, =CH), 7.15–7.45 (m, 10 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 30.6 (q), 31.6 (t), 35.8 (t), 41.3 (d), 47.3 (d), 48.1 (d), 55.5 (s), 59.6 (q), 62.2 (d), 67.1 (d), 68.8 (t), 126.8 (d), 127.2 (d), 128.2 (d), 128.3 (d), 128.7 (d), 129.7 (d), 140.0 (s), 141.3 (s), 143.1 (s), 176.7 (s); exact mass calcd for $C_{26}H_{29}NO_3$ m/e 403.2147, found 403.2124.

(1α,3aβ,4α,6α,7aβ,8R*)-(±)-8-Formylhexahydro-3a-(methoxymethyl)-6-hydroxy-2-methyl-1,4-methano-1H-isoindole-3,6(2H)-dione (42) and (1aβ,3α,4aβ,5β,8α,8aβ,9R*)-(±)-Octahydro-1-hydroxy-5-(methoxymethyl)-7-methyl-3,5,8-ethanylylidene-6H-pyrano[3,4-c]pyridin-6-one (43). To a solution of 90 mg (0.20 mmol) of **41** in 20 mL of methanol cooled in a dry ice–acetone bath was passed ozone (Welsbach ozone generator) until a pale blue color persisted. The mixture was stirred for 15 min, and 1 mL of dimethyl sulfide was added in one portion. The cold bath was removed, and the mixture was warmed to room temperature and stirred for 18 h. The mixture was concentrated in vacuo, and the residue was chromatographed over 6 g of silica gel (ethyl acetate–methanol, 15:1) to give 35.4 mg (63%) of aldehyde **42** as colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.66 (br d, J = 16 Hz, 1 H, C_5 or C_7H), 1.80 (br d, J = 15.6 Hz, 1 H, C_5 or C_7H), 2.19 (br, 1 H, OH), 2.23–2.32 (m, 2 H, C_5H and C_7H), 2.48 (m, 1 H, C_4H), 2.53 (m, 1 H, C_{7a}H), 2.77 (s, 3 H, NCH_3), 3.38 (s, 3 H, OCH_3), 3.54 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.87 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.95–4.01 (m, 2 H, C_1H and C_8H), 4.14 (m, 1 H, C_6H), 9.72 (d, J = 1.05 Hz, 1 H, CHO). This material was used directly in subsequent reactions although the ^1H NMR spectrum indicated the presence of minor impurities.

To a solution of 30 mg (0.12 mmol) of the aldehyde **42** in 5 mL of dichloromethane was added 0.018 mL (0.12 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was warmed under reflux for 18 h and concentrated in vacuo, and the residue was chromatographed over 4 g of silica gel (ethyl acetate–methanol, 10:1) to give 25 mg (83%) of **43** as a white solid: mp 151–157 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75–1.85 (m, 3 H), 2.19–2.28 (m, 4 H), 2.65 (dqu, J = 14.4, 2.5 Hz, 1 H, C_4H), 2.77 (s, 3 H, NCH_3), 3.41 (s, 3 H, OCH_3), 3.53 (d, J = 1.5 Hz, 1 H, C_8H), 3.74 (d, J = 9.9 Hz, 1 H, CH_2OMe), 3.93 (d, J = 9.9 Hz, 1 H, CH_2OMe), 4.0 (m, 1 H, C_3H), 5.39 (d, J = 2 Hz, 1 H, C_1H). Weak signals at δ 2.79 (s), 3.41 (s), 3.69 (d), 3.99 (d), and 5.25 (d) in the ^1H NMR of this material were attributed to the minor diastereomer of the hemiacetal; exact mass calcd for $C_{13}H_{19}NO_4$ m/e 253.1314, found 253.1323.

(3α,4aβ,5β,8α,8aβ,9R*)-(±)-Octahydro-5-(methoxymethyl)-7-methyl-3,5,8-ethanylylidene-6H-pyrano[3,4-c]-pyridin-6-one (3). To a solution of 25 mg (0.10 mmol) of the hemiacetal **43** and 0.1 mL of triethylsilane in 5 mL of dichloro-

methane was added 0.1 mL of trifluoroacetic acid. The mixture was stirred for 1 h at room temperature, diluted with 30 mL of dichloromethane, and washed with 20 mL of saturated aqueous sodium bicarbonate. The aqueous wash was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the residue was chromatography over 4 g of silica gel (ethyl acetate–methanol, 10:1) to give 18 mg (78%) of **3** as a white solid: mp 62–68 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (ddd, J = 15.0, 4.8, 2.3 Hz, 1 H, $C_{10}H$), 1.81 (dd, J = 14.4, 3.0 Hz, 1 H, C_4H), 1.84 (dt, J = 15.0, 3.3 Hz, 1 H, $C_{10}H$), 2.05 (br s, 2 H, $C_{4a}H$ and C_9H), 2.10 (dqu, J = 14.4, 2.3 Hz, 1 H, C_4H), 2.26 (br s, 1 H, $C_{8a}H$), 2.78 (s, 3 H, NCH_3), 3.42 (s, 3 H, OCH_3), 3.61 (br s, 1 H, C_8H), 3.68 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.78 (d, J = 11.7 Hz, 1 H, OC_1H), 3.89 (d, J = 10.0 Hz, 1 H, CH_2OMe), 3.95 (d, J = 11.7 Hz, 1 H, OC_1H), 4.0 (br s, 1 H, C_3H); ^{13}C NMR ($CDCl_3$) δ 24.5 (t), 27.4 (q, NCH_3), 31.0 (t), 32.5 (d), 43.2 (d), 44.1 (d), 57.2 (s, C_5), 59.7 (q, OCH_3), 60.8 (t, CH_2OMe), 66.4 (d, C_8), 67.5 (t, C_1), 68.6 (d, C_3), 177.8 (s, C_6); exact mass calcd for $C_{13}H_{19}NO_3$ m/e 237.1365, found 237.1347.

(1α,3aβ,4α,7aβ,8R*)-(±)-Ethyl 2,3,3a,4,5,7a-Hexahydro-6-methoxy-3a-(methoxymethyl)-2-methyl-3-oxo-1,4-methano-1H-isoindole-8-acetate (44). A mixture of 24 mg (0.080 mmol) of the ketone **39** and 300 mg (1.58 mmol) of *p*-toluenesulfonic acid in 4 mL of trimethyl orthoformate and 1 mL of methanol was warmed at reflux for 60 h. The resulting solution was concentrated in vacuo. The residue was diluted with 20 mL of dichloromethane and washed with three 10-mL portions of saturated sodium bicarbonate followed by 10 mL of brine. The organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed over 2 g of silica gel (ethyl acetate) to yield 19 mg (72%) of **44** as a clear oil: IR (CH_2Cl_2) 1730, 1690, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H, OCH_3), 1.72 (qu, J = 2.6 Hz, 1 H, $C_{7a}H$), 2.20 (dd, J = 17, 2.7 Hz, 1 H, C_7H), 2.31 (m, 2 H, CH_2CO_2Et), 2.41 (dd, J = 17.5, 2.3 Hz, 1 H, C_7H), 2.50 (m, 1 H, C_8H), 2.70 (dt, J = 6.8, 1.8 Hz, 1 H, C_4H), 2.89 (s, 3 H, NCH_3), 3.39 (s, 3 H, OCH_3), 3.47 (d, J = 9.5 Hz, 1 H, CH_2OMe), 3.53 (s, 3 H, $=COCH_3$), 3.68 (t, J = 2.3 Hz, 1 H, C_1H), 3.69 (d, J = 9.5 Hz, 1 H, CH_2OMe), 4.13 (q, J = 7 Hz, 2 H, OCH_2), 4.53 (d, J = 6.8 Hz, 1 H, C_5H); exact mass calcd for $C_{17}H_{25}NO_5$ m/e 323.1734, found 323.1724.

Acknowledgment. We thank the National Institutes of Health for their generous support of this research (Grant GM-27647). One of us (D.J.H.) thanks Professor Leo A. Paquette for a stimulating discussion.

Supplementary Material Available: Experimental procedures for the preparation of compounds i–iv and crystallographic details for compound **39** (9 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Butenolide and Tetronic Acid Analogues of Thiolactomycin[1,2]

Ian W. J. Still* and Michael J. Drewery

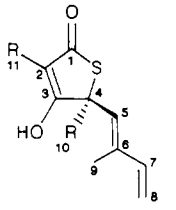
J. Tuzo Wilson Research Laboratories, Erindale Campus, University of Toronto in Mississauga, Mississauga, Ontario, Canada L5L 1C6

Received July 25, 1988

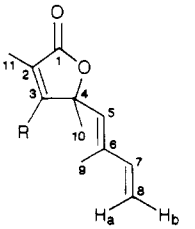
A synthetic route to the three lactone analogues **2a–c** of the interesting antibiotic thiolactomycin (**1a**) is described. The synthetic strategy used is flexible in that it allows in principle for variation in the nature of the substituents introduced at C-2, C-3, or C-4 of the 2-butenolide nucleus. Of the three synthetic analogues of thiolactomycin that we describe, **2a** lacks the acidic C-3 hydroxyl group while **2b** and **2c** are tetronic acid analogues of the antibiotic.

Introduction

In 1982, the structure and antibiotic properties of thiolactomycin (**1a**), isolated from a soil sample containing an organism of the genus *Nocardia*, were first reported by Oishi et al.[3] This is the first example of a naturally occurring thiolactone to exhibit antibiotic activity. The compound displayed only moderate in vitro activity against a broad spectrum of pathogens, including Gram-positive cocci and enteric bacteria, but revealed a unique synergistic effect, in combination with β-lactam antibiotics, in inhibiting inducible β-lactamase-producing microorganisms.[4] Thiolactomycin was also found to display effective in vivo activity against *S. marcescens* and *K. pneumoniae* in mice and showed only moderate toxicity.[5] More recently, interest in the biological activity of thiolactomycin has focused on its inhibition of fatty acid synthetases.[6] The isolation and structure determination of the closely related antibiotic thiotetromycin (**1b**) have been reported by Omura et al.[7] In contrast to thiolactomycin, the absolute configuration of **1b** does not appear to have been determined.



1a, R = CH_3
b, R = CH_2CH_3



2a, R = H
b, R = OMe
c, R = OH

Despite the obvious interest in these compounds, only one synthesis of racemic thiolactomycin has been reported

(1) The formal name is (4*S*)-(2*E*,5*E*)-2,4,6-trimethyl-3-hydroxy-2,5,7-octatriene-4-thiolide.

(2) (a) Abstracted in part from the Ph.D. Thesis of M. J. Drewery, University of Toronto, 1988. (b) These results have been presented in part at the 3rd Chemical Congress of North America (Abstract Number ORG-471), Toronto, Ontario, Canada, June 5–10, 1988.

(3) (a) Oishi, H.; Noto, T.; Sasaki, H.; Suzuki, K.; Hayashi, T.; Okazaki, H.; Ando, K.; Sawada, M. *J. Antibiot.* **1982**, *35*, 391. (b) Sakai, H.; Oishi, H.; Hayashi, T.; Matsuura, I.; Ando, K.; Sawada, M. *J. Antibiot.* **1982**, *35*, 396.

(4) Noto, T.; Miyakawa, S.; Oishi, H.; Endo, H.; Okazaki, H. *J. Antibiot.* **1982**, *35*, 401.

(5) Miyakawa, S.; Suzuki, K.; Noto, T.; Harada, Y.; Okazaki, H. *J. Antibiot.* **1982**, *35*, 411.

(6) Nishida, I.; Kawaguchi, A.; Yamada, M. *J. Biochem. (Tokyo)* **1986**, *99*, 1447.

(7) (a) Omura, S.; Iwai, Y.; Nakagawa, A.; Iwata, R.; Takahashi, Y.; Shimizu, H.; Tanaka, H. *J. Antibiot.* **1983**, *36*, 109. (b) Omura, S.; Nakagawa, A.; Iwata, R.; Hatano, A. *J. Antibiot.* **1983**, *36*, 1781.

0022-3263/89/1954-0290$01.50/0