(m, 2, NCH_2), 6.9–7.2 (m, 3, Ar H), 7.3–7.6 (m, 1, Ar H); ^{13}C NMR 19.4, 24.7, 25.2, 26.3, 28.2, 32.4, 33.0, 36.4, 38.4, 43.8 (NCH_2), 51.8 (OCH_3), 104.5 (C12b), 109.0 (C9), 117.9, 119.1, 120.3 (C9*, C10*, C11*), 127.9 (C12a), 133.8, 137.3 (C8a*, C12c*), 175.6 (C=O).

2,3,3a,4,5,6-Hexahydro-1-oxo-1*H*-pyrido[3,2,1-*jk*]carbazole-5-carboxylic Acid Methyl Ester (3e) and 2,3-Dihydro-1-oxo-1*H*-pyrido[3,2,1-*jk*]carbazole-5-carboxylic Acid Methyl Ester (6b). The precursor **2e** was heated under nitrogen to 300 °C for 5 min. The crude product was chromatographed on silica gel with toluene. Two products were isolated. The first one to elute was 0.2 g of **6b**. This was recrystallized from ether/hexane to give 0.1 g of pure **6b**: yield, 5%; mp 160–162 °C; MS, *m/e* 279 [M^+]; NMR 3.05 (t, 2, J = 7.7 Hz, CH_2), 3.3 (t, 2, J = 7.5 Hz, CH_2), 3.93 (s, 3, OCH_3), 7.42 (t, 1, J = 7.3 Hz, Ar H), 7.52 (t, 1, J = 7.6 Hz, Ar H), 7.9–8.0 (m, 2, Ar H), 8.4–8.5 (m, 2, Ar H). The second product to elute was 0.7 g of **3e**. This was recrystallized from ether/hexane to give 0.3 g of **3e** as a mixture of diastereoisomers: yield, 15%; mp 138–140 °C; *m/e* 283 [M^+]; NMR 1.5–1.7 (m, 2, CH_2), 2.1–3.3 (m, 8, 3 CH_2 + 2 CH), 3.69 and 3.78 (2 s, 3, OCH_3), 7.2–7.5 (m, 3, Ar H), 8.3–8.4 (m, 1, Ar H); IR 1710, 1735 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_3$ (283.3): C, 72.1; H, 6.1. Found: C, 72.0; H, 5.5.

1,2,2a,3,4,5,5a,5b,6,7-Decahydro-1-oxoisoquino[2,1,8-*lma*]carbazole-6-carboxylic Acid Methyl Ester (3f). After 3.0 g (0.01 mol) of **2f** was heated to 300 °C for 10 min, the crude product was chromatographed on silica gel to give 0.4 g of the crystalline product: yield, 13%; mp 180–182 °C; MS, *m/e* 323; NMR 0.6–3.2 (m, 12, 4 CH_2 + 4 CH), 3.77 (s, 3, OCH_3), 4.0–4.4 (m, 2, O=CCH_2), 6.9–7.4 (m, 3, Ar H), 8.0–8.2 (m, 1, Ar H). Additional fractions (1.0 g; 33% yield) with lower melting points were also collected.

2,3,3a,4,5,6-Hexahydro-1*H*-pyrido[3,2,1-*jk*]carbazole-5-carboxylic Acid (3g). A solution of 2.7 g (0.01 mol) of the ester $\mathbf{3a}_1$ and 1 g (0.02 mol) of KOH in 100 mL of 20% aqueous methanol was heated to reflux for 2 h. After acidification with 2 N HCl extraction with CH_2Cl_2/ethyl acetate gave 1.97 g of the product: yield, 77%; mp 210–212 °C. Anal. Calcd for $C_{16}H_{17}NO_2$ (255.3): C, 75.3; H, 6.7; N, 5.5. Found: C, 75.1; H, 6.7; N, 5.3.

1,2,2a,3,4,5,5a,5b,6,7-Decahydroisoquino[2,1,8-*ml*]carbazole-6-carboxylic Acid (3h). A mixture of 0.5 g (0.002 mol) of ester **3d** and 0.2 g (0.004 mol) of KOH in 10 mL of 80% aqueous methanol was heated to reflux for 2 h, acidified, and extracted with methylene chloride to give 0.27 g of crude acid: mp 210–213 °C [after recrystallization from methylene chloride/hexane the mp was 229–231 °C]; MS, *m/e* 309 [M^+]; IR (Nujol) 1700 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$ (295.4): C, 77.2; H, 7.2; N, 4.7. Found: C, 76.7; H, 7.5; N, 4.7.

1-(4-Pentynyl)-1*H*-indole-3-carboxaldehyde (4). Prepared from 53 g (0.36 mol) of indole-3-carboxaldehyde, 10 g (0.42 mol) of sodium hydride, and 43 g (0.43 mol) of 5-chloropentyne[6] in DMF as described above, 25.4 g of the product was obtained: yield, 33%; mp 53–54 °C; MS, *m/e* 211 [M^+]; NMR 1.8–2.2 (m, 5, 2 CH_2 + CH), 4.27 (t, 2, J = 6 Hz, NCH_2), 7.1–7.5 (m, 3, Ar H), 7.67 (s, 1, NCH=), 8.1–8.5 (m, 1, Ar H), 9.9 (s, 1, CHO); IR 1540, 1665 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO$ (211.3): C, 80.0; H, 6.2; N, 6.6. Found: C, 79.7; H, 6.4; N, 6.5.

1-(4-Pentynyl)-1*H*-indole-3-acrylic Acid Methyl Ester (5). Prepared from 21 g (0.1 mol) of **4** and 33.4 g (0.1 mol) methyl (triphenylphosphoranylidene)acetate[5] in 300 mL of toluene as described above to give 19.7 g of the product: yield, 74%; mp 78–79 °C; MS, *m/e* 267 [M^+]; NMR 1.7–2.2 (m, 5, 2 CH_2 + CH), 3.78 (s, 3, OCH_3), 4.2 (t, 2, NCH_2), 6.33 (d, 1, J = 16 Hz, =CH), 7.0–7.4 (m, 4, Ar H), 7.7–8.0 (m, 1, Ar H), 7.83 (d, 1, J = 16 Hz, =CH); IR 1540, 1630, 1705 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$ (267.3): N, 5.2. Found: N, 5.2.

2,3-Dihydro-1*H*-pyrido[3,2,1-*jk*]carbazole-5-carboxylic Acid Methyl Ester (6a). Under an atmosphere of nitrogen, 11.6 g (0.43 mol) of **5** was heated to 300 °C for 10 min. The residue was chromatographed on silica gel with toluene to give 4.2 g of the product: yield, 36%; mp 108–109 °C; MS, *m/e* 265 [M^+]; NMR 1.8–2.3 (m, 2, CH_2), 2.8 (t, 2, J = 6 Hz, $PhCH_2$), 3.85 (t, 2, NCH_2), 3.9 (s, 3, OCH_3), 7.0–7.5 (m, 3, Ar H), 7.7–7.8 (m, 1, Ar H), 7.9–8.1 (m, 1, Ar H), 8.5–8.6 (m, 1, Ar H); IR 1709 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO_2$ (265.3): C, 77.0; H, 5.7; N, 5.3. Found: C, 77.2; H, 5.9; N, 5.2.

2,3-Dihydro-1-oxo-1*H*-pyrido[3,2,1-*jk*]carbazole-5-carboxylic Acid (6b). For analytical data see under **3e**.

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Registry No. **1a**, 110206-12-7; **1b**, 110206-13-8; **1c**, 110206-14-9; **1d**, 110206-15-0; **1e**, 110206-16-1; **1f**, 110206-17-2; **2a**, 110206-18-3; **2b**, 110206-19-4; **2c**, 110206-20-7; **2d**, 110206-21-8; **2e**, 110206-22-9; **2f**, 110206-23-0; $\mathbf{3a}_1$, 110206-24-1; $\mathbf{3a}_2$, 110206-25-2; **3b** (isomer 1), 110206-26-3; **3b** (isomer 2), 110206-27-4; **3c**, 110269-33-5; **3d**, 110206-28-5; **3e** (isomer 1), 110206-29-6; **3e** (isomer 2), 110206-30-9; **3f**, 110269-34-6; **3g** (isomer 1), 110206-31-0; **3g** (isomer 2), 110206-32-1; **3h**, 110206-33-2; **4**, 110206-34-3; **5**, 110206-35-4; **6a**, 110222-95-2; **6b**, 110206-36-5; indole-3-carboxaldehyde, 487-89-8; 5-bromopentene, 1119-51-3; 6-bromohexene, 2695-47-8; 3-(2-chloroethyl)cyclopentene, 21298-00-0; 3-(2-chloroethyl)cyclohexene, 19509-51-4; 4-pentenoyl chloride, 39716-58-0; 2-(2-cyclohexen-1-yl)acetyl chloride, 3514-86-1; methyl (triphenylphosphoranylidene)acetate, 2605-67-6; 5-chloropentyne, 14267-92-6.

Total Synthesis of (±)-Lythrancepine II and (±)-Lythrancepine III

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Total syntheses of the Lythraceae alkaloids (±)-lythrancepine II (**2**) and (±)-lythrancepine III (**3**) are described. The syntheses feature a stereoselective *N*-acyliminium ion cyclization (**26** → **27–31**), a mechanistically interesting Eschenmoser sulfide contraction (**16** → **19** and **41** → **42**), and construction of a 13-membered ring by using the Semmelhack–Ullmann procedure.

The Lythraceae alkaloids are a large family of natural products, most of which contain 4-arylquinolizidine substructures.[3,4] Over 10 of these alkaloids are quinolizidine metacyclophanes, exemplified in Figure 1 by lythrancepines I–III (**1–3**) and lythrancine II (**4**). The structure assignments for these natural products are based on several X-ray crystallographic studies, spectral data, and a number of chemical correlations. For example, the structures of **1–3** were assigned on the basis of chemical studies,[5] which

(1) Alfred P. Sloan Foundation Fellow, 1983–1987.

(2) Author to whom correspondence regarding crystal structures should be addressed.

(3) Fujita, E.; Fuji, K. *International Review of Science, Organic Chemistry Series Two*; Wiesner, K., Ed.; Butterworths: London, 1976; p 119.

(4) Golebiewski, W. M.; Wrobel, J. T. *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic: New York, 1981; Vol. 18, pp 263–322.

0022-3263/87/1952-4665$01.50/0

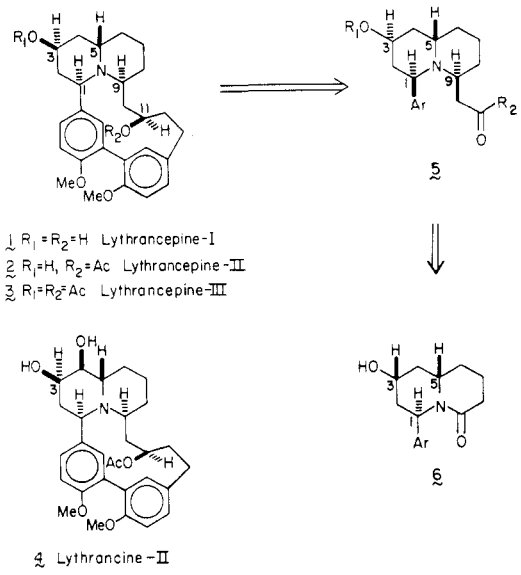


Figure 1.

connected these compounds with the 3-*O*-*p*-bromobenzenesulfonate of lythrancine II (**4**).[6]

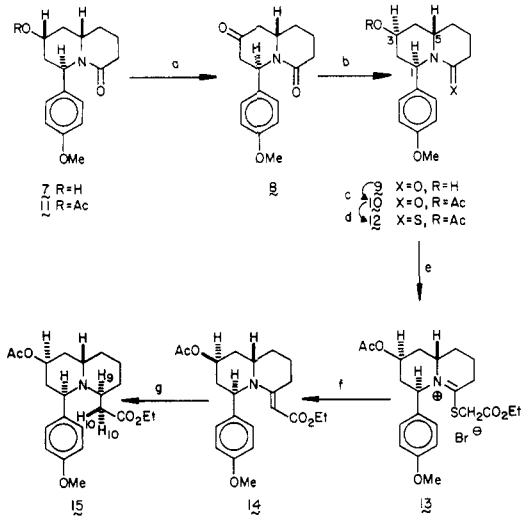
Several years ago, we showed that *N*-acyliminium ion cyclizations[7] provided a route to 4-arylquinolizidinones, which might be used to prepare a variety of Lythraceae alkaloids including metacyclophanes of type **1**–**3**.[8] This paper presents an application of these early observations to syntheses of (±)-lythrancepine II (**2**) and (±)-lythrancepine III (**3**), which confirm the structures assigned to these interesting alkaloids.[9]

Preliminary Studies

A brief retrosynthetic analysis for lythrancepine-II (**2**) is presented in Figure 1. It was projected that a synthesis of **2** would be completed from an appropriately substituted quinolizidine **5** by routes involving either intramolecular construction of the biphenyl unit or macrocyclization of compounds already carrying an appropriately substituted biphenyl. Quinolizidines of type **5** would be prepared from quinolizidinones of type **6**, available from procedures developed in early model studies[8] and during the course of a synthesis of the macrocyclic lactonic Lythraceae alkaloid (±)-vertaline.[10]

The conversion of generic quinolizidinone **6** to quinolizidine **5** requires inversion of stereochemistry at C(3) and attachment of the C(9) side chain with stereochemical control. Prior to embarking on a synthesis of **2**, these operations were examined with the model system described in Scheme I. Alcohol **7** was prepared in four steps from *p*-anisaldehyde with a straightforward procedure.[11] Treatment of **7** with Jones reagent gave quinolizidinedione **8** in 74% yield. Reduction of **8** with lithium triethylborohydride followed by acetylation of the resulting mixture of diastereomeric alcohols afforded acetates **10** (79%) and **11** (8%) after chromatographic separation. The C(3) proton in **10** appeared as a quintet (J = 3.5 Hz) centered at δ 5.1 while the C(3) proton in **11** appeared as a broad triplet of triplets (J = 14, 4 Hz) at δ 5.0. In addition, the

Scheme I[a]



[a] (a) Jones oxidation; (b) $LiEt_3BH$; (c) Ac_2O, 4-DMAP, Et_3N; (d) [*p*-MeOPhP(S)S]$_2$; (e) $BrCH_2CO_2Et$; (f) DABCO, Ph_3P Δ; (g) $NaBH_3CN$.

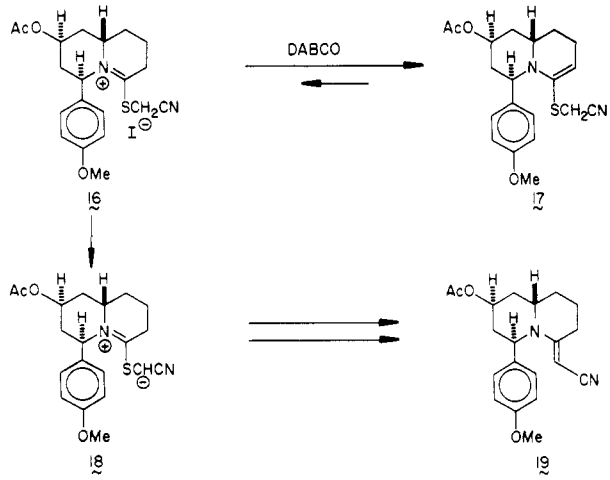
C(1) protons in both **10** and **11** appeared as broad doublets (J = 5 Hz) at δ 6.08 and 6.25, respectively.[12] These data suggest that both the aryl and acetoxy groups in **10** occupy axial sites on the quinolizidine framework.

The C(9) side chain was next introduced by using the Eschenmoser sulfide contraction procedure.[13] Thus, treatment of lactam **10** with Lawesson's reagent[14] gave thiolactam **12** (99%). Treatment of **12** with ethyl bromoacetate followed by warming a chloroform solution of the resulting iminium salt **13** under reflux in the presence of 1,4-diazabicyclo[2.2.2]octane and triphenylphosphine gave vinylogous urethane **14** in 65% yield. Reduction of **14** with sodium cyanoborohydride under the Borch conditions[15] gave quinolizidine **15** (77%). The C(9) stereoisomer of **15** was not observed.

The stereochemistry of **15** was initially assigned on the basis of the following NMR arguments. The ^{1}H NMR spectrum of **15** displayed a triplet of triplets (J = 11, 5 Hz) at δ 4.95 and a doublet of doublets (J = 11, 3 Hz) at δ 4.02, assigned to H(3) and H(1), respectively. This suggests that **15** adopts a cis-fused chair–chair conformation in which the aryl and acetoxy groups occupy equatorial sites. A series of decoupling experiments identified H(9) as a multiplet at δ 3.20. Independent irradiation of the diastereotopic C(10) protons [δ 2.28 (dd, J = 14, 5 Hz) and δ 2.75 (dd, J = 14, 9 Hz)] caused H(9) to collapse to a broad doublet (J = 9 Hz) and broad singlet ($W_{1/2}$ = 10 Hz), respectively. Since a large coupling to the axial C(8) hydrogen was not observed, this suggested that H(9) was equatorially disposed and established the structure of **15**.[16] This assignment was confirmed by X-ray crystallographic analysis.[17]

(5) Fujita, E.; Saeki, Y. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2141.
(6) Barrow, M. J.; Cradwick, P. D.; Simm, G. A. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1812.
(7) Speckamp, W. N., Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(8) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.
(9) For a preliminary account of a portion of this work see: Hart, D. J.; Hong, W.-P. *J. Org. Chem.* **1985**, *50*, 3670.
(10) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.
(11) The preparation of **7** is described in the supplementary material.
(12) This C(1) coupling pattern is typical of quinolizidines having the C(1)–C(5) stereochemical relationship and conformational preferences expressed by **10** and **11**. For examples, see: ref 10. Quick, J.; Oterson, R. *Tetrahedron Lett.* **1977**, 603. Quick, J.; Meltz, C. *J. Org. Chem.* **1979**, *44*, 573.
(13) Roth, M.; Dubs, P.; Göschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(14) Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.
(15) Borch, R. F.; Bernstein, M. D., Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(16) Base-catalyzed exchange of the C(10) hydrogens of **15** [(i) NaOEt, EtOD; (ii) Ac_2O, 4-DMAP, Et_3N] aided in the assignment of ^{1}H NMR signals. Spectra of the dideuterio compound confirmed the equatorial disposition of H(9).

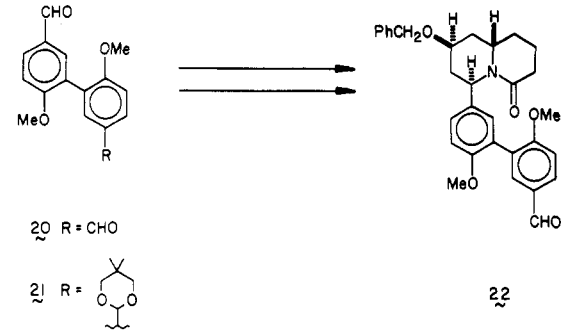
Scheme II



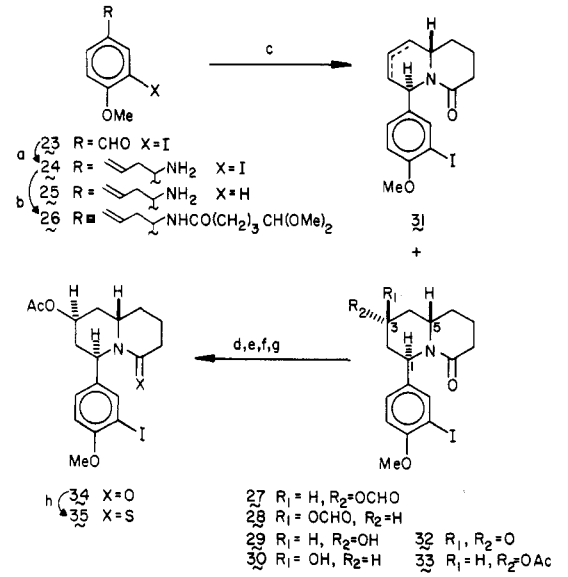
Several aspects of Scheme I are notable. First, the conversion of **13** to **14** was initially problematic. For example, treatment of **13** with 1,4-diazabicyclo[2.2.2]octane and triphenylphosphine in chloroform at room temperature followed by direct chromatography over silica gel gave only 12% of **14** in addition to lactam **10** (74%). Variations of solvent and base led to no improvement in yield. Only after performing the experiment outlined in Scheme II did it become apparent that warming the reaction mixture might afford **14** in a satisfactory yield. Iminium salt **16** was prepared from **12** and iodoacetonitrile in 93% yield.[18] A sample of **16** was dissolved in deuteriochloroform and placed in an NMR tube. The addition of 1.2 equiv of triphenylphosphine had no effect on the NMR spectrum of **16**. The addition of 1.2 equiv of DABCO, however, caused an immediate change. The NMR spectrum showed disappearance of doublets at δ 4.35 (J = 19 Hz) and δ 5.10 (J = 19 Hz) due to the C(10) methylene of salt **16**. No formation of the thiolactam **12**, lactam **10**, or unsaturated nitrile **19** was observed. The appearance of a two proton singlet at δ 3.20, presumably due to a new side-chain methylene, indicated that **16** had probably been converted to ketene *N,S*-acetal **17**.[19] Finally, an aqueous workup of this mixture afforded lactam **10** while warming the sample led to the production of unsaturated nitrile **19**. Therefore, it appeared that base kinetically deprotonated **16** at C(8) rather than C(10). The pK_a's of these protons, as well as the hydrogen iodide salt of 1,4-diazabicyclo[2.2.2]octane, are apparently, and fortunately, balanced such that warming the sample eventually leads to occasional deprotonation at C(10) to afford **18** with subsequent production of **19**. We imagine that a similar sequence of events takes place during the conversion of **13** to **14**. Although the conversion of thioalkyliminium salts to ketene *N,S*-acetals under Eschenmoser sulfide contraction conditions is known,[20,21] this example demonstrates that such an event is reversible and does not preclude ultimate carbon–carbon bond formation.

The second notable feature of Scheme I is the stereoselective reduction of **14** to **15**. An examination of steric interactions in **15** and its C(9) isomer suggests that **15** would be the thermodynamically more stable diastereomer. Prior results in related systems, however, suggested that the stereochemical course of the reduction was kinetically controlled.[22] Although evidence was not gathered during model studies, experiments conducted during the synthesis of **2** (vide infra) indicate that this is the case.

Scheme III



Scheme IV[a]



[a] (a) $LiN(SiMe_3)_2$, $CH_2{=}CHCH_2MgBr$; (b) $AlMe_3$, $(MeO)_2CHCH_2CH_2CH_2CO_2Me$; (c) HCOOH; (d) NaOH, H_2O, MeOH; (e) DMSO, $(COCl)_2$, Et_3N; (f) $LiEt_3BH$; (g) Ac_2O, 4-DMAP, Et_3N; (h) [*p*-MeOPhP(S)S]$_2$.

Synthesis of (±)-Lythrancepines II and III

Encouraged by the model studies, we examined two routes to the lythrancepines. Early studies focused on the preparation of a quinolizidinone carrying a substituted biphenyl at C(1). Lactam **22** was eventually prepared from symmetrical biaryl **20** via the intermediacy of **21** (Scheme III). Protecting group problems and success with alternate routes, however, led us to abandon this approach.[23]

The second route focused on construction of the biphenyl unit by an intramolecular Ullmann reaction.[24,25] Although such an approach was regarded as a high-risk

(17) X-ray crystallographic analyses were performed by Dr. L.-Y. Hsu at The Ohio State University Department of Chemistry Crystallographic Facility. Details appear in the supplementary material.

(18) Iminium salt **16** was selected for detailed studies due to the ease with which this system could be monitored by ^{1}H NMR.

(19) Gompper, R.; Elser, W. *Justus Liebigs Ann. Chem.* **1969**, *725*, 64.

(20) Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868.

(21) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.

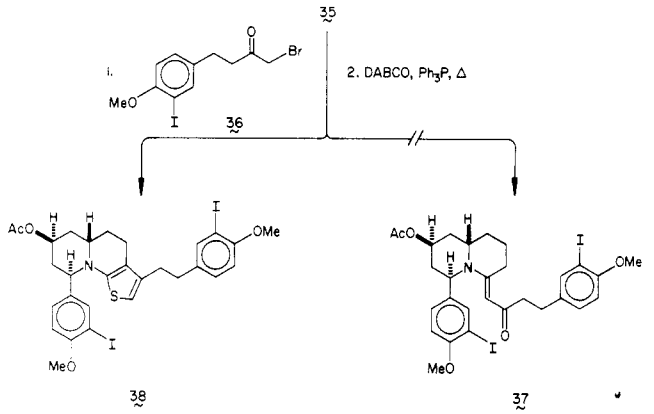
(22) (a) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (b) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403.

(23) For details see: Hong, W.-P. Ph.D. Thesis, The Ohio State University, 1985.

(24) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327.

(25) Semmelhack, M. F.; Ryono, L. S. *J. Am. Chem. Soc.* **1975**, *97*, 3873. Semmelhack, M. F.; Helquist, P. M.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460.

Scheme V



venture,[26] the convergent nature of the initial synthetic plan was appealing.

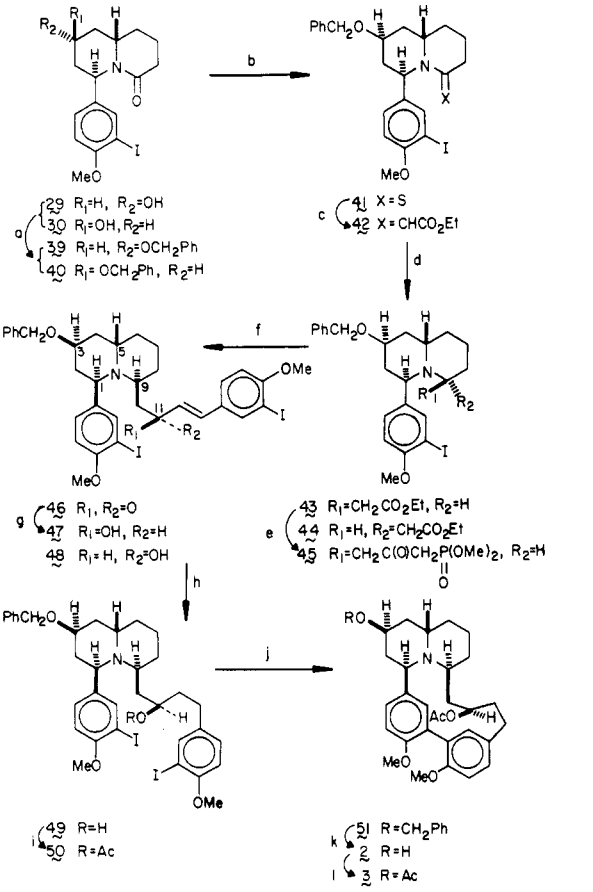
Studies began with the preparation of thiolactam **35** with now familiar procedures (Scheme IV). Thus, sequential treatment of *m*-iodoanisaldehyde[27] (**23**) with lithium hexamethyldisilazide and allylmagnesium bromide gave separable homoallylic amines **24** (76%) and **25** (9%).[28,29] Amine **24** was converted to **26** (96%) by using Weinreb's procedure.[30]

Treatment of amide **26** with formic acid in dichloromethane gave formate **27** (48%), isomeric formate **28** (5%), inseparable alcohols **29** and **30** (22%), olefins **31** (9%),[31] and *m*-iodoanisaldehyde (11%). Both formates (**27** and **28**) and both alcohols (**29** and **30**) were useful synthetic intermediates. Hydrolysis of **27** and **28** gave **29** and **30** (95%), both of which were oxidized to ketone **32** with Swern's procedure.[32] Reduction of **32** with lithium triethylborohydride[33] followed by acetylaton[34] of the resulting diastereomeric alcohols gave acetates **33** (8%) and **34** (84%). Treatment of **34** with Lawesson's reagent completed the synthesis of **35** (98%).

Our original plan called for the coupling of thiolactam **35** and α-bromo ketone **36**.[35] Unfortunately, none of the desired vinylogous amide **37** was obtained as thiophene **38** was produced in 68% yield.[36] Apparently, deprotonation occurs at C(8) followed by attack of the intermediate ketene *N,S*-acetal on the ketone carbonyl group. One can attribute the difference in behavior observed in Scheme I and Scheme V to the differing electrophilicities of ketone and ester carbonyl groups.

The observation presented in Scheme V required that we introduce the C(9) side chain in a stepwise manner and called for a different protecting group at C(3). This was accomplished as shown in Scheme VI. Thus, the aforementioned mixture of alcohols **29** and **30** was treated with sodium hydride and benzyl bromide to give **40** (66%) and **39** (10%) after separation by column chromatography. Lactam **40** was then converted to thiolactam **41** (98%) and vinylogous urethane **42** (92%) with the protocol established during the model studies. Reduction of **42** with sodium cyanoborohydride gave stereoisomeric esters **43** (88%) and **44** (10%). It was demonstrated that **43** and **44** did not interconvert under the acidic reaction conditions. Therefore, the partitioning of **42** between **43** and **44** is kinetically controlled. The application of stereoelectronic arguments advanced to rationalize the course of a variety of iminium ion reactions does not provide a definitive explanation of the observed stereochemical results.[37] It is probable, however, that steric effects due to the axial C(1)-aryl group in the presumed intermediate iminium ion influence the course of the reduction.[38] Continuing with the synthesis, ester **43** was treated with dimethyl (lithiomethyl)phosphonate to afford β-keto phosphonate **45** (99%),[39] and a Horner–Wadsworth–Emmons reaction gave α,β-unsaturated ketone **46** (81%).[40] Reduction of **46** with

Scheme VI[a]



[a] (a) NaH, $PhCH_2Br$; (b) $[p\text{-MeOPhP(S)S}]_2$; (c) $BrCH_2CO_2Et$, DABCO, Ph_3P, Δ; (d) $NaBH_3CN$, pH 4; (e) $(MeO)_2P(O)CH_2Li$; (f) NaH, **23**; (g) $LiEt_3BH$; (h) $TsNHNH_2$, NaOAc; (i) Ac_2O, 4-DMAP, Et_3N; (j) $Ni(PPh_3)_4$, DMF, Δ; (k) BBr_3, CH_2Cl_2; (l) Ac_2O, Pyr.

(26) For prior use of the Semmelhack modification of the Ullmann reaction in alkaloid synthesis see: Brandt, S.; Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1979**, 2193.
(27) Fujita, E.; Fuji, K.; Tanaka, K. *J. Chem. Soc. C* **1971**, 205.
(28) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289.
(29) The use of excess allylmagnesium bromide gave substantial amounts of **25**. The source of **25** is most likely Grignard exchange followed by protonation during workup.
(30) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(31) The $\Delta^{2,3}$-olefin was isolated in pure form by crystallization.
(32) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(33) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669. Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
(34) Steglich, W.; Holfe, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(35) The preparation of **36** is described in the supplementary material.
(36) This type of thiophene formation has previously been observed (ref 20), but does not always occur upon application of the Eschenmoser procedure to *N*-alkyl lactams and α-halo ketones (ref 22b).
(37) For an appropriate discussion see: Delongschamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 211–221.
(38) The ^1H NMR spectra of iminium salts **13** and **18** indicate that the aryl groups are axially disposed. This suggests that the aryl group in the iminium ion generated by protonation of **42** will also occupy an axial site.
(39) Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4973.
(40) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. Horner, L.; Hoffman, H.; wippel, H. F.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499.

lithium triethylborohydride afforded a mixture of **47** (71%) and **48** (25%), which was easily separated by column chromatography. Reduction of **47** with diimide gave amino alcohol **49** (92%), and acetylation afforded acetate **50** (85%). The stereochemical assignment at C(11) was confirmed by X-ray crystallographic analysis of alcohol **49**.[17] The crystal structure revealed that **49** crystallized as quinolizidine in a chair–chair conformation. The C-(1)-aryl and C(3)-benzyloxy groups were equatorially disposed, and the C(9) side chain was axially disposed with hydrogen bonding between the C(11) hydroxyl group and nitrogen lone pair.

With diiodide **50** in hand, we were set to attempt the crucial intramolecular Ullmann reaction. On the basis of detailed studies of Semmelhack, **50** was treated with an excess of tetrakis(triphenylphosphine)nickel(0) in *N,N*-dimethylformamide to afford biaryl **51** in **20**% yield.

The synthesis of (±)-lythrancepine II (**2**) was completed by removing the C(3)-*O*-benzyl protecting group. Model studies suggested that reduction of the C(1)-benzylic nitrogen bond would complicate attempts to effect the required transformation by hydrogenolysis procedures.[41] Brief exposure of **51** to boron tribromide in dichloromethane,[42] however, did give (±)-lythrancepine II (**2**) in 54% yield. Finally, acetylation of **2** afforded (±)-lythrancepine II (**3**) in 64% yield. Both **2** and **3** were identical (500-MHz ^{1}H NMR, IR, MS, and TLC) with authentic samples of the natural products.[43]

Experimental Section[44]

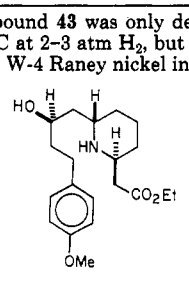
All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance spectra were recorded on Varian Associates EM-360 (60 MHz), Brucker NR-80 (80 MHz), Varian Associates EM-390 (90 MHz), Bruker WP-200 (200 MHz), or Bruker AM-500 (500 MHz) spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants (in hertz), integration, interpretation]. ^{13}C nuclear magnetic resonance spectra were recorded on Bruker WP-80 (20.11 MHz), Bruker WP-200 (50.28 MHz), Nicolet NT-300 (75.42 MHz), or Bruker AM-500 (125.69 MHz) spectrometers and are reported in parts per million from internal tetramethylsilane. Multiplicities are reported when appropriate data was collected. Magnetically equivalent aryl carbons were encountered on numerous occasions. Infrared spectra were taken with Perkin-Elmer 457, Perkin-Elmer 283B, or Mattson Cygnus 25 FT-IR instruments. Mass spectra were recorded on AEI-MS9, Kratos DS-55, or Kratos MS-30 instruments 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. Laser desorption Fourier transform mass spectrometry was performed for compound **46** with a Nicolet FT/MS-1000 and Tachisto 215 G TEA CO_2 laser doped with KBr to supply K^+ without calibration. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: acetic anhydride (distilled from P_2O_5); tetrahydrofuran and diethyl ether (distilled from sodium metal); dichloromethane and chloroform (passed through activity I alumina or distilled from CaH_2); benzene, dimethoxyethane, dimethylformamide, toluene, and triethylamine (distilled from CaH_2); methanol (distilled from magnesium methoxide); dimethyl sulfoxide (distilled from CaH_2 at reduced pressure). All reaction temperatures refer to those of the reaction mixture unless indicated otherwise. Reactions requiring an inert atmosphere were run under a blanket of argon or nitrogen. Most reactions were followed by thin-layer chromatography over silica gel or alumina using EM Laboratories glass-backed 0.25-mm-thick precoated silica gel 60 F-254 plates or EM Laboratories glass-backed 0.25-mm-thick precoated aluminum oxide 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel 60 (70–230 mesh) or Woelm neutral alumina. Preparative thin-layer chromatography was performed over EM Laboratories glass-backed 2.0-mm-thick precoated silica gel 60 F-254 plates or EM Laboratories glass-backed 0.5-mm-thick precoated silica gel 60 F-254 plates. Medium-pressure liquid chromatography (MPLC) was performed over EM Laboratories Lobar columns by using an FMI RPSY lab pump. Rotary disk chromatography was performed over EM Laboratories silica gel PF-254 with $CaSO_4 \cdot {}^1/_2H_2O$ type 60 plates by using an FMI RP G-150 lab pump. Ethyl acetate and *n*-hexane, used as eluents in column chromatography, were distilled prior to use.

4-Amino-4-(3-iodo-4-methoxyphenyl)-1-butene (24) and 4-Amino-4-(4-methoxyphenyl)-1-butene (25). To a solution of 21.1 mL (100.2 mmol) of 1,1,1,3,3,3,-hexamethyldisilazane in 20 mL of tetrahydrofuran was added 70.6 mL (100.2 mmol) of 1.42 M *n*-butyllithium in hexane with cooling in an ice bath. The solution was stirred for 10 min and a solution of 25.0 g (95.4 mmol) of 3-iodo-4-methoxybenzaldehyde (**23**)[27] in 100 mL of tetrahydrofuran was added via syringe with cooling in an ice bath. The mixture was stirred at room temperature for 1 h followed by addition of 139 mL (100.2 mmol) of 0.72 M ethereal allylmagnesium bromide with cooling in an ice bath. The resulting mixture was stirred for 10 min, carefully poured into 200 mL of saturated aqueous ammonium chloride, and extracted with two 150-mL portions of dichloromethane. The combined organic phases were washed with 100 mL of saturated aqueous ammonium chloride and two 100-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The residual pale red oil was chromatographed over 500 g of silica gel (eluted with 10% ammonium hydroxide in methanol–chloroform, 1:30) to give 21.4 g (74%) of amine **24** as a yellow oil and 1.52 g (9%) of reduced amine **25** as a yellow oil. Iodo amine **24**: IR (CCl_4) 3390, 3320, 1595 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.32 (s, 2 H, NH_2), 2.15–2.40 (m, 2 H, CH_2), 3.70–3.90 (m with s at 3.82, 4 H, OCH_3 and Ar CHN), 4.85–5.20 (m, 2 H, $=CH_2$), 5.45–5.95 (br m, 1 H, =CH), 6.70 (d, J = 9 Hz, 1 H, Ar H_5), 7.39 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.78 (d, J = 2 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 302 (M^+ – H, 3), 287 (2), 262 (100), 247 (9), 219 (3); exact mass calcd for $C_{11}H_{13}ONI$ (M^+ – H) m/e 302.0042, found m/e 302.0032.

***N*-[1-(3-Iodo-4-methoxyphenyl)but-3-en-1-yl]-5,5-dimethoxypentanamide (26).** To a solution of 18.3 g (60.4 mmol) of amine **24** in 60 mL of dichloromethane at room temperature was added 38.5 mL (90.6 mmol) of 2.36 M trimethylaluminum in heptane under nitrogen. The solution was stirred for 30 min followed by addition of 11.7 g (66.4 mmol) of methyl 5,5-dimethoxypentanoate.[45] The resulting solution was warmed under reflux for 20 h, cooled to room temperature, poured into 50 mL of 1 N aqueous sodium hydroxide, and extracted with two 200-mL portions of dichloromethane. The combined organic extracts were washed with two 200-mL portions of 1 N aqueous hydrochloric acid and two 200-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to give 26 g (96%) of amide **26** as a yellow

(41) For example, compound **43** was only deiodinated upon hydrogenation over 10% Pd on C at 2–3 atm H_2, but afforded amino alcohol **i** upon hydrogenolysis over W-4 Raney nickel in ethanol at 2–3 atm H_2.



i

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

(43) We thank Professor Eiichi Fujita for graciously supplying samples of (+)-**2** and (+)-**3**.

(44) Compounds throughout the text have been numbered with the accepted numbering scheme for the Lythraceae alkaloid targets (ref 3). Compounds in the experimental section have been named and numbered as they appear in *Chemical Abstracts*.

(45) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

oil, homogeneous by TLC (silica gel; chloroform–10% ammonium hydroxide in methanol, 7:1). This material was used in subsequent reactions without purification: IR (CCl_4) 3300, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–1.85 (m, 4 H, $CH_2CH_2C(OMe)_2$), 2.15–2.35 (m, 2 H, $COCH_2$), 2.55 (t, J = 6 Hz, 2 H, $=CCH_2$), 3.32 (s, 6 H $(OCH_3)_2$), 3.83 (s, 3 H, Ar OCH_3), 4.25–4.45 (m, 1 H, $HC(OMe)_2$), 5.03 (m, 1 H, Ar CHN), 5.10–5.25 (m, 2 H, $=CH_2$), 5.45–5.90 (m, 1 H, =CH), 6.38 (d, 1 H, NH), 6.80 (d, J = 9 Hz, 1 H, Ar H_2), 7.25 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.70 (d, J = 2 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 416 (M^+ – OMe, 5), 415 (9), 406 (16), 375 (12), 374 (73), 330 (2), 302 (6), 261 (3), 214 (3), 145 (32), 113 (29), 106 (7), 91 (5), 75 (26), 71 (100), 63 (3); exact mass calcd for $C_{17}H_{23}O_3NI$ (M^+ – OMe) m/e 416.0723, found m/e 416.0660.

***cis*-(±)-1,2,3,6,9,9a-Hexahydro-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (31), (6α,8β,9aα)-(±)-Octahydro-8-(formyloxy)-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (27), (6α,8α,9aα)-(±)-Octahydro-8-(formyloxy)-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (28), and (6α,8β,9aα)- and (6α,8α,9aα)-(±)-Octahydro-8-hydroxy-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (29 and 30).** To a solution of 26 g (58.2 mmol) of amide **26** in 100 mL of dichloromethane at room temperature was added 300 mL of 98% formic acid. The solution was stirred at room temperature for 2 h and concentrated in vacuo. The residual dark oil was diluted with 200 mL of dichloromethane, washed with three 100-mL portions of saturated aqueous sodium bicarbonate and two 100-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The resulting mixture was crystallized from methanol to give 9.4 g (38%) of formate **27** as a white solid. The residue was chromatographed over a Lobar size C column (eluted with ethyl acetate–hexane, 1:1) to give 1.65 g (11%) of 3-iodo-4-methoxybenzaldehyde (**23**) as a yellow solid, 2.05 g (9.2%) of a mixture of isomeric olefins **31** as a white solid, 1.70 g (10%) of additional formate **27** as a pale yellow foam, 1.15 g (4.6%) of isomeric formate **28** as a yellow foam, and 5.06 g (22%) of a mixture of isomeric alcohols **29** and **30** as a white solid. $\Delta^{7,8}$ olefin **31**: mp 136.5–138.5 °C (EtOAc); IR ($CHCl_3$) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.60 (m, 8 H, CH_2), 3.50–3.80 (m, 1 H, NCH), 3.88 (s, 3 H, OCH_3), 5.65–6.10 (m, 2 H, CH=CH), 6.22 (br s, 1 H, Ar CHN), 6.78 (d, J = 9 Hz, 1 H, Ar H_5), 7.45 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.82 (d, J = 2 Hz, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 17.2, 28.1, 32.4, 32.9, 47.8, 51.5, 56.3, 85.7, 110.7, 126.4, 126.1, 129.9, 135.0, 139.0, 157.4, 168.7; mass spectrum, m/e (relative intensity) 383 (M^+, 100), 368 (6), 354 (2), 340 (2), 326 (3), 312 (4), 150 (6). Anal. Calcd for $C_{16}H_{18}NO_2I$: C, 50.13; H, 4.74. Found: C, 50.47; H, 4.70.

Formate **27**: mp 162–163 °C; IR ($CHCl_3$) 1730, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.85 (m, 10 H, CH_2), 3.25–3.60 (m, 1 H, NCH), 3.84 (s, 3 H, OCH_3), 4.90–5.30 (br m, 1 H, CO_2CH), 6.25 (br d, J = 4.5 Hz, 1 H, Ar CHN), 6.78 (d, J = 9 Hz, 1 H, Ar H_5), 7.25 (d, J = 9 Hz, 1 H, Ar H_6), 7.60 (br s, 1 H, Ar H_2), 8.08 (s, 1 H, HCO_2); mass spectrum, m/e (relative intensity) 429 (M^+, 100), 414 (1), 385 (1), 384 (9), 383 (9), 356 (3), 328 (4), 302 (3), 256 (14). Anal. Calcd for $C_{17}H_{20}NO_4I$: C, 47.57; H, 4.70. Found: C, 47.12; H, 4.28.

Isomeric formate **28**: mp 48–50 °C; IR ($CHCl_3$) 1725, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.90 (m, 10 H, CH_2), 3.60–3.90 (m with s at 3.80, 4 H, NCH and OCH_3), 5.00–5.30 (qu, J = 3 Hz, 1 H, CO_2CH), 5.90 (dd, J = 6, 3 Hz, 1 H, Ar CHN), 6.70 (d, J = 9 Hz, 1 H, Ar H_5), 7.05 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.48 (d, J = 2 Hz, 1 H, Ar H_2), 7.68 (s, 1 H, HCO_2); mass spectrum, m/e (relative intensity) 429 (M^+, 100), 383 (35); exact mass calcd for $C_{17}H_{20}NO_4I$ 429.0438, found m/e 429.0444.

(6α,8β,9aα)-(±)-Octahydro-8-hydroxy-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (29). To a solution of 10.55 g (24.6 mmol) of formate **27** in 70 mL of methanol at room temperature was added 4 mL of 3 N aqueous sodium hydroxide. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo, diluted with 200 mL of dichloromethane, washed with two 100-mL portions of 1 N aqueous hydrochloric acid and two 200-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The residual solid was recrystallized from ethyl acetate–dichloromethane to give 9.4 g (95%) of alcohol **29** as a white solid: mp 158–160 °C; IR (CH_2Cl_2) 3600 (sharp), 3390 (br), 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–2.70 (m, 10 H, CH_2), 3.05–3.50 (m, 1 H, OCH), 3.55–3.95 (m with s at 3.75, 5 H, OH, CHN, and OCH_3), 6.10 (br d, J = 4 Hz, 1 H, Ar CHN), 6.68 (d, J = 9 Hz, 1 H, Ar H_5), 7.05 (br d, J = 9 Hz, 1 H, Ar H_6), 7.60 (br s, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 401 (M^+, 100), 400 (39), 384 (7), 383 (3), 356 (6), 328 (10), 274 (48). Anal. Calcd for $C_{16}H_{20}NO_3I$: C, 47.90; H, 5.02. Found: C, 48.15; H, 4.68.

***cis*-(±)-Hexahydro-4-(3-iodo-4-methoxyphenyl)-2*H*-quinolizine-2,6-dione (32).** To a stirred solution of 60 mL of dichloromethane and 2.4 mL (27.5 mmol) of oxalyl chloride was added a solution of 3.9 mL (54.9 mmol) of dimethyl sulfoxide in 15 mL of dichloromethane at –50 to –60 °C under nitrogen. The reaction mixture was stirred for 2 min, and a solution of 10 g (25.0 mmol) of alcohol **29** in 30 mL of dichloromethane was added over a 5 min period. Stirring was continued for an additional 30 min, and 17.4 mL (125 mmol) of triethylamine was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (50 mL) was added, and the aqueous layer was extracted with three 100-mL portions of dichloromethane. The organic layers were combined, washed with three 100-mL portions of brine and 100 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give white solid, which was recrystallized from ethyl acetate to give 9.9 g (100%) of ketone **32** as a white solid: mp 136–137 °C; IR (CH_2Cl_2) 1725, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–3.10 (m, 10 H, CH_2), 3.38–3.80 (m, 1 H, NCH), 3.85 (s, 3 H, OCH_3), 6.45 (dd, J = 6, 3 Hz, 1 H, Ar CHN), 6.78 (d, J = 9 Hz, 1 H, Ar H_5), 7.20 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.65 (d, J = 2 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 399 (M^+, 100), 371 (26), 340 (13), 260 (33), 195 (51). Anal. Calcd for $C_{16}H_{18}NO_3I$: C, 48.14; H, 4.54. Found: C, 48.58; H, 4.53.

(6α,8α,9aα)-(±)-Octahydro-8-hydroxy-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (30). To a solution of 11.9 g (30.0 mmol) of ketone **32** in 150 mL of tetrahydrofuran was added 40.0 mL (40.0 mmol) of 1 M lithium triethylborohydride in tetrahydrofuran with cooling in a dry ice bath under nitrogen. The mixture was stirred for 50 min, and 1 mL of water was added. The mixture was allowed to warm to room temperature, and 1 mL of 30% hydrogen peroxide was added followed by stirring at room temperature for 3 h. The aqueous layer was saturated with potassium carbonate, and the organic layer was concentrated in vacuo to give a pale yellow oil. The residual yellow oil was chromatographed over 250 g of silica gel (eluted with ethyl acetate–methanol, 95:5) to give 11.9 g (100%) of a mixture of alcohol **30** and isomeric alcohol **29** as a pale yellow foam. Alcohol **30** (pure sample obtained by additional chromatography): IR ($CHCl_3$) 3595 (sharp), 3400 (br), 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–2.70 (m, 10 H, CH_2), 3.10–3.50 (m, 1 H, OCH), 3.65–4.20 (m with s at 3.80, 5 H, NCH, OH, and OCH_3), 5.75 (br s, 1 H, Ar CHN), 6.75 (d, J = 9 Hz, 1 H, Ar H_5), 7.18 (d, J = 9 Hz, 1 H, Ar H_6), 7.67 (br s, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 17.9, 29.1, 32.7, 34.2, 39.8, 46.5, 48.6, 56.1, 64.0, 85.7, 110.5, 127.1, 135.1, 136.9, 156.3, 169.8; mass spectrum, m/e (relative intensity) 401 (M^+, 100), 400 (38), 384 (13), 383 (6), 356 (11), 328 (13), 274 (16), 260 (7); exact mass calcd for $C_{16}H_{20}NO_3I$ m/e 401.0483, found m/e 401.0486.

(6α,8α,9aα)-(±)-Octahydro-8-acetoxy-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (34) and (6α,8β,9aα)-(±)-Octahydro-8-acetoxy-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizin-4-one (33). To a solution of 3.00 g (7.47 mmol) of alcohols **29** and **30** (from **32**) in 30 mL of dichloromethane were added 14.1 mL (149 mmol) of acetic anhydride, 10.4 mL (74.7 mmol) of triethylamine, and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred vigorously at room temperature for 5 h and diluted with 30 mL of dichloromethane. The excess solvent and reagents were removed in vacuo, and the resulting residue was diluted with 150 mL of dichloromethane, washed with three 100-mL portions of saturated aqueous sodium bicarbonate and two 100-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residual pale yellow foam was chromatographed over a Lobar size C column (eluted with ethyl acetate–hexane, 9:1) to give 2.77 g (84%) of acetate **34** as a white foam and 0.246 g (7.4%) of isomeric acetate **33** as a white solid. Acetate **34**: IR (CCl_4) 1740, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.90 (m with s at 1.68, 13 H, CH_2 and $COCH_3$), 3.65–4.00 (m with s at 3.88, 4 H, NCH and OCH_3), 5.10 (qu, J = 3 Hz, 1 H, AcOCH), 6.00 (br d, J = 5 Hz, 1 H, Ar CHN), 6.75 (d, J = 9 Hz, 1 H, Ar H_5), 7.10 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.55 (d, J =

2 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 443 (M^+, 100), 398 (10), 384 (10), 383 (32), 382 (56), 356 (18), 354 (14), 328 (8), 256 (54); exact mass calcd for $C_{18}H_{22}NO_4I$ m/e 443.0588, found m/e 443.0586.

Acetate **33**: mp 153–154 °C (CCl_4); IR (CH_2Cl_2) 1730, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–2.85 (m with s at 2.08, 13 H, CH_2 and $COCH_3$), 3.20–3.55 (m, 1 H, NCH), 3.88 (s, 3 H, OCH_3), 4.75–5.20 (br m, 1 H, AcOCH), 6.23 (br d, J = 4.5 Hz, 1 H, Ar CHN), 6.78 (d, J = 9 Hz, 1 H, Ar H_5), 7.23 (br d, J = 9 Hz, 1 H, Ar H_6), 7.65 (br s, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 443 (M^+, 100), 398 (8), 384 (9), 383 (27), 382 (48), 356 (17), 354 (16), 328 (8), 256 (83); exact mass calcd for $C_{18}H_{22}NO_4I$ m/e 443.0588, found m/e 443.0577.

(6α,8α,9aα)-(±)-Octahydro-8-acetoxy-6-(3-iodo-4-methoxyphenyl)-4*H*-quinolizine-4-thione (35). A mixture of 0.93 g (2.31 mmol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent)[14] and 2.05 g (4.62 mmol) of lactam **34** in 40 mL of toluene was warmed at 110 °C under nitrogen for 6 min. The mixture was cooled to room temperature, concentrated in vacuo, and chromatographed over 150 g of silica gel (eluted with ethyl acetate–hexane, 1:1) to give 2.10 g (99%) of thiolactam **35** as a yellow foam, which was crystallized from dichloromethane–methanol to give 1.91 g (90%) of **35** as a pale yellow solid: mp 164–164.5 °C; IR (CH_2Cl_2) 1735, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.95 (m with s at 1.85, 11 H, CH_2 and $COCH_3$), 3.20 (t, 2 H, CH_2CS), 3.80–4.10 (m with s at 3.88, 4 H, NCH and OCH_3), 5.15 (qu, J = 3 Hz, 1 H, AcOCH), 6.85 (d, J = 9 Hz, 1 H, Ar H_5), 7.15 (d, J = 9 Hz, 1 H, Ar H_6), 7.30 (m, 1 H, Ar CHN), 7.65 (d, J = 2 Hz, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 17.7, 21.0, 29.2, 29.8, 37.5, 42.5, 50.0, 56.3, 67.1, 85.7, 110.7, 126.7, 132.0, 136.8, 156.8, 169.9, 201.4 (one aromatic quaternary carbon not detected); mass spectrum, m/e (relative intensity) 459 (M^+, 37), 427 (2), 399 (2), 398 (4), 366 (100), 300 (1), 272 (38), 239 (16). Anal. Calcd for $C_{18}H_{22}NO_3SI$: C, 47.07; H, 4.83. Found: C, 46.84; H, 4.69.

(5aα,7α,9aα)-(±)-5,5a,6,7,8,9-Hexahydro-9-(3-iodo-4-methoxyphenyl)-3-[2-(3-iodo-4-methoxyphenyl)ethyl]-4*H*-thieno[3,2-*c*]quinolizin-7-yl Acetate (38). To a solution of 250 mg (0.545 mmol) of thiolactam **35** in 2 mL of chloroform was added 417 mg (1.09 mmol) of 1-bromo-4-(3-iodo-4-methoxyphenyl)-2-butanone (**36**) in a single portion. The mixture was stirred at room temperature under argon for 3 days in the dark. Triphenylphosphine (143 mg, 1.09 mmol) and 122 mg (1.09 mmol) of 1,4-diazabicyclo[2.2.2]octane were added in a single portion at room temperature. The solution was stirred under reflux for 30 min, concentrated in vacuo, and chromatographed directly over 100 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to give 270 mg (68%) of thiophene **38** as a pale green solid: mp 65–78 °C; IR (CH_2Cl_2) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–2.60 (m with s at 1.68, 11 H, CH_2 and $COCH_3$), 2.60–2.85 (m, 4 H, Ar CH_2CH_2), 3.75–3.90 (m with s at 3.85, 7 H, NCH and 2 OCH_3), 4.55 (m, 1 H, Ar CHN), 5.15 (qu, J = 3 Hz, 1 H, AcOCH), 6.05 (s, 1 H, SCH), 6.74 (d, J = 9 Hz, 1 H, Ar H_5 (Ar H_5')), 6.76 (d, J = 9 Hz, 1 H, Ar H_5' (Ar H_5)), 7.13 (d, J = 9, 2 Hz, 1 H, Ar H_6 (Ar H_6')), 7.25 (d, J = 9 Hz, 1 H, Ar H_6' (Ar H_6)), 7.60 (d, J = 2 Hz, 1 H, Ar H_2 (Ar H_2')), 7.75 (d, J = 2 Hz, 1 H, Ar H_2' (Ar H_2)); ^{13}C NMR ($CDCl_3$) δ 20.9 (q), 20.9 (t), 28.0 (t), 31.4 (t), 32.8 (t), 34.1 (t), 34.3 (t), 48.4 (d), 56.4 (q, 2 C), 58.5 (d), 68.0 (d), 85.7 (s), 85.9 (s), 104.8 (d), 110.6 (d), 110.9 (d), 114.6 (s), 128.0 (d), 129.4 (d), 136.3 (s, 2 C), 138.0 (d), 139.3 (d), 139.5 (s), 149.4 (d), 156.5 (s), 156.7 (s), 170.3 (s); mass spectrum, m/e (relative intensity) 745 (M^+ + 2, 6), 743 (M^+, 100), 684 (3), 683 (7), 682 (4), 616 (6), 556 (3), 247 (88); exact mass calcd for $C_{27}H_{28}NO_2I_2S$ ($M^+ - CH_3CO_2$) m/e 683.9932, found m/e 683.9954.

(6α,8α,9aα)-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-one (40) and (6α,8β,9aα)-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-one (39). To a solution of 1.00 g (2.05 mmol) of alcohols **29** and **30** in 7 mL of *N*,*N*-dimethylformamide was added 294 mg (7.47 mmol) of sodium hydride in a single portion at room temperature. The mixture was stirred for 1 h followed by the addition of 1.28 g (7.47 mmol) of benzyl bromide over a 5 min period. The resulting mixture was stirred at room temperature for 36 h, concentrated in vacuo, diluted with 100 mL of dichloromethane, and washed with 100 mL of brine. The aqueous layer was extracted with three 100-mL portions of dichloromethane, and the combined organic layers were washed with two 100-mL portions of brine and 100 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residual yellow oil was chromatographed over a Lobar size C column (eluted with ethyl acetate–hexane, 3:2) to give 801 mg (65%) of benzyl ether **40** as a yellow foam and 121 mg (10%) of isomeric benzyl ether **39** as a yellow foam. Benzyl ether **40**: IR ($CHCl_3$) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–2.68 (m, 10 H, CH_2), 3.60–4.00 (m with s at 3.72, 5 H, NCH, OCH, and OCH_3), 4.23 (s, 2 H, $PhCH_2$), 5.80 (br d, J = 5 Hz, 1 H, Ar CHN), 6.60 (d, J = 9 Hz, 1 H, Ar H_5), 6.75–7.35 (m, 6 H, Ar H_6 and Ar H), 7.68 (br s, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 18.3, 29.6, 31.4, 32.9, 37.4, 47.1, 48.3, 56.1, 69.7, 71.2, 85.7, 110.5, 126.7 (2 C), 127.0 (2 C), 127.9 (2 C), 135.4, 136.8, 138.1, 156.3, 169.6; mass spectrum, m/e (relative intensity) 491 (M^+, 71), 400 (19), 384 (10), 383 (6), 286 (7), 256 (7), 91 (100), 65 (10); exact mass calcd for $C_{23}H_{26}NO_3I$ m/e 491.0951, found m/e 491.0951.

Benzyl ether **39**: IR ($CHCl_3$) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.70 (m, 10 H, CH_2), 2.95–3.35 (m, 1 H, NCH), 3.35–3.75 (m, 1 H, OCH), 3.80 (s, 3 H, OCH_3), 4.47 (s, 2 H, $PhCH_2$), 5.99 (br d, J = 4.5 Hz, 1 H, Ar CHN), 6.60 (d, J = 9 Hz, 1 H, Ar H_5), 6.95 (br d, J = 9 Hz, 1 H, Ar H_6), 7.30 (br s, 5 H, Ar H), 7.42 (br s, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 491 (M^+, 58), 400 (33), 91 (100); exact mass calcd for $C_{23}H_{26}NO_3I$ m/e 491.0951, found m/e 491.0994.

(6α,8α,9aα)-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizine-4-thione (41). A mixture of 461 mg (1.14 mmol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent)[14] and 801 mg (1.63 mmol) of lactam **40** in 10 mL of toluene was warmed at 105 °C under nitrogen for 10 min. The mixture was cooled to room temperature, concentrated in vacuo, and chromatographed over 100 g of silica gel (eluted with ethyl acetate–hexane, 3:7) to give 810 mg (98%) of thiolactam **41** as a white solid, which was recrystallized from dichloromethane–methanol to give 793 mg (96%) of **41** as a colorless solid: mp 175–176 °C; IR ($CHCl_3$) 1255 cm^{-1}; ^1H NMR (CCl_4) δ 1.50–2.80 (m, 8 H, CH_2), 3.12 (m, 2 H, CH_2CS), 3.70–4.15 (m with s at 3.80, 5 H, NCH, OCH, and OCH_3), 4.35 (s, 2 H, $PhCH_2$), 6.74 (d, J = 9 Hz, 1 H, Ar H_5), 6.95–7.40 (m, 7 H, Ar H_6, Ar CHN, and Ar H), 7.78 (d, J = 2 Hz, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 17.8, 29.4, 31.1, 38.0, 42.7, 50.4, 56.4, 57.3, 70.4, 71.5, 85.0, 110.7, 127.1, 127.3 (2 C), 127.4 (2 C), 128.3, 133.2, 137.4, 138.2, 156.9, 201.0; mass spectrum, m/e (relative intensity) 507 (M^+, 27), 475 (16), 474 (62), 380 (16), 91 (100). Anal. Calcd for $C_{23}H_{26}NO_2IS$: C, 54.43; H, 5.17. Found: C, 54.10; H, 4.93.

(6α,8α,9aα)-(±)-Ethyl α-[Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-ylidene]acetate (42). To a solution of 180 mg (0.355 mmol) of thiolactam **41** in 3 mL of chloroform was added 0.42 mL (3.55 mmol) of ethyl iodoacetate in a single portion. The mixture was stirred at room temperature under argon in the dark for 24 h. Triphenylphosphine (186 mg, 0.71 mmol) and 478 mg (4.26 mmol) of 1,4-diazabicyclo[2.2.2]octane were added in a single portion at room temperature. The solution was stirred under reflux for 1 h, concentrated in vacuo, and chromatographed directly over 40 g of silica gel (eluted with ethyl acetate–hexane, 3:7) to give 183 mg (92%) of vinylogous urethane **42** as a yellow foam: IR (CH_2Cl_2) 1675, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.40–2.50 (m, 8 H, CH_2), 3.05–3.35 (m, 2 H, CH_2), 3.60–4.20 (m with s at 3.80, 7 H, OCH, NCH, OCH_3, and OCH_2CH_3), 4.33 (s, 2 H, $PhCH_2$), 4.45 (s, 1 H, =CH), 4.82 (t, J = 4.5 Hz, 1 H, Ar CHN), 6.70 (d, J = 9 Hz, 1 H, Ar H_5), 6.90–7.35 (m, 6 H, Ar H_6 and Ar H), 7.60 (d, J = 2 Hz, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 14.6, 17.3, 28.4, 29.8, 34.2, 38.1, 48.2, 55.1, 56.3, 58.2, 70.0, 71.4, 84.5, 86.2, 110.9, 126.7, 127.1 (2 C), 127.3, 128.2 (2 C), 134.5, 136.9, 138.2, 156.8, 162.0, 169.0; mass spectrum, m/e (relative intensity) 561 (M^+, 54), 91 (100); exact mass calcd for $C_{27}H_{32}NO_4I$ m/e 561.1368, found m/e 561.1367.

(4α,6α,8α,9aα)-(±)-Ethyl α-[Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-yl]acetate (43) and (4β,6α,8α,9aα)-(±)-Ethyl α-[Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-yl]-acetate (44). To a solution of 293 mg (0.522 mmol) of vinylogous urethane **42** in a mixture of 5 mL of methanol and 5 mL of tetrahydrofuran was added a trace of bromocresol green followed by 66 mg (1.04 mmol) of sodium cyanoborohydride. A 1.06 N

methanolic hydrochloric acid solution (1.0 mL) was added dropwise until the reaction mixture maintained a yellow color. After stirring for 10 min at room temperature, the resulting solution was neutralized with 1 N aqueous sodium hydroxide and extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and chromatographed over 40 g of activity I alumina (eluted with ethyl acetate–hexane, 2:3) to give 259 mg (88%) of amino ester **43** as a yellow foam and 30 mg (10%) of isomeric amino ester **44** as a yellow oil. Amino ester **43**: IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.40–2.20 (m, 10 H, CH_2), 2.25 (dd, J = 13, 6.5 Hz, 1 H, $CHCO_2Et$), 2.75 (dd, J = 13, 9.3 Hz, 1 H, $CHCO_2Et$), 3.10–3.25 (m, 1 H, $NCHCH_2CO_2Et$), 3.32–3.75 (m, 2 H, NCH and OCH), 3.80 (s, 3 H, OCH_3), 3.85–4.30 (m, 3 H, Ar CHN and $CO_2CH_2CH_3$), 4.50 (d, J = 12 Hz, 1 H, $PhCH_2$), 4.53 (d, J = 12 Hz, 1 H, $PhCH_2$)), 6.75 (d, J = 9 Hz, 1 H, Ar H_5), 7.20–7.45 (m, 6 H, Ar H_6 and Ar H), 7.70 (br s, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 14.4, 20.5, 20.8, 24.0, 37.3, 37.5, 42.9, 50.0, 51.1, 56.4, 57.3, 60.0, 69.6, 71.9, 85.7, 111.0, 127.5 (3 C), 128.3 (2 C), 128.4, 138.4, 138.8, 144.0, 157.3, 172.1; mass spectrum, m/e (relative intensity) 563 (M^+, 2), 476 (99), 475 (2), 457 (21), 456 (2), 369 (3), 384 (3), 368 (19), 330 (5), 91 (100), 65 (5); exact mass calcd for $C_{27}H_{34}NO_4I$ m/e 563.1534, found m/e 563.1397.

Amino ester **44**: IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.40–2.05 (m, 11 H, CH_2 and CH_2CO_2Et), 2.20–2.35 (m, 1 H, CH_2CO_2Et), 3.05–3.15 (m, 1 H, $NCHCH_2CO_2Et$), 3.35–3.50 (m, 1 H, NCH), 3.70–3.78 (m, 1 H, OCH), 3.85 (s, 3 H, OCH_3), 4.00 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 4.15–5.18 (m with d at 4.18, J = 12 Hz, 2 H, Ar CHN and $PhCH_2$), 4.22 (d, J = 12 Hz, 1 H, $PhCH_2$), 6.65 (d, J = 9 Hz, 1 H, Ar H_5), 7.10–7.35 (m, 5 H, Ar H), 7.46 (br s, 1 H, Ar H_6), 7.84 (br s, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 14.2, 24.3, 29.9, 31.6, 37.2, 38.8, 40.0, 53.7, 56.1, 56.4, 57.1, 60.3, 69.3, 71.4, 85.5, 110.5, 127.3, 127.6 (2 C), 128.3 (2 C), 130.4, 138.7, 139.9 (2 C), 156.9, 172.1; mass spectrum, m/e (relative intensity) 563 (M^+, 2), 476 (58), 475 (24), 457 (3), 369 (8), 368 (25), 330 (3), 91 (100), 65 (8); exact mass calcd for $C_{27}H_{34}NO_4I$ m/e 563.1524, found m/e 563.1567.

(4α,6α,8α,9aα)-(±)-[Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-yl]-3-(dimethoxyphosphinyl)-2-propanone (45). To a solution of 60 mg (0.49 mmol) of dimethyl methylphosphonate in 2 mL of tetrahydrofuran was added 0.36 mL (0.44 mmol) of 1.22 M *n*-butyllithium in hexane over a 2 min period with cooling in an dry ice–acetone bath under nitrogen. The mixture was stirred for 15 min followed by addition of 124 mg (0.22 mmol) of ester **43** in 1 mL of tetrahydrofuran over a 5 min period. The resulting mixture was stirred for 75 min, warmed to room temperature, and poured into 30 mL of diethyl ether. The organic layer was washed with 20 mL of saturated aqueous ammonium chloride and two 30-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with 10% ammonium hydroxide in methanol–chloroform, 1:14) to give 141 mg (99%) of β-keto phosphonate **45** as a yellow oil: IR (CH_2Cl_2) 1710, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–2.25 [m with d's at 3.82 and 3.68 ($P(O)OCH_3$) and an s at 3.85 (OCH_3), 27 H, CH and CH_2 manifold], 4.50 (s, 2 H, $PhCH_2$), 6.78 (d, J = 9 Hz, 1 H, Ar H_5), 7.10–7.45 (m, 6 H, Ar H_6 and Ar H), 7.68 (d, J = 2 Hz, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 20.4, 21.1, 24.0, 37.5, 40.4, 42.4, 45.7, 50.1, 51.0, 52.8 [$P(O)OCH_3$], 52.9 [$P(O)OCH_3$], 56.3, 57.0, 69.6, 71.6, 86.1, 111.0, 127.4 (3 C), 128.3 (2 C), 128.4, 137.9, 138.2, 138.7, 157.4, 200.8, 201.1 (d, C=O); mass spectrum, m/e (relative intensity) 476 ($M^+ - CH_2COCH_2P(O)(OMe)_2$, 7), 475 (8), 368 (5), 294 (100), 293 (67), 279 (6); exact mass calcd for $C_{23}H_{27}NO_2I$ ($M^+ - CH_2COCH_2P(O)(OMe)_2$) m/e 476.1088, found m/e 476.1060.

***trans*-(4α,6α,8α,9aα)-(±)-4-[Octahydro-6-(3-iodo-4-methoxyphenyl)-8-(phenylmethoxy)-4*H*-quinolizin-4-yl]-1-(3-iodo-4-methoxyphenyl)-1-buten-3-one (46).** To a solution of 10.3 mg (0.262 mmol) of sodium hydride in 1 mL of dimethoxyethane was added a solution of 140 mg (0.218 mmol) of β-ketophosphonate **45** in 2 mL of dimethoxyethane under argon at room temperature. The resulting solution was stirred for 1 h followed by addition of 58 mg (0.218 mmol) of aldehyde (**23**) in 2 mL of dimethoxyethane. The reaction mixture was stirred for 6 h, diluted with 20 mL of dichloromethane, concentrated in vacuo, and chromatographed over 30 g of silica gel (eluted with 10% ammonium hydroxide in methanol–chloroform, 1:30) to give 138 mg (81%) of α,β-unsaturated ketone **46** as a white solid: mp 201.5–202 °C (EtOAc–CH_2Cl_2); IR (CH_2Cl_2) 1680, 1650, 1600, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.25 (m, 10 H, CH_2), 2.60 (dd, J = 13, 6 Hz, 1 H, $CHCOCH$=), 3.05 (dd, J = 13, 8 Hz, 1 H, $CHCOCH$=), 3.20–3.30 (m, 1 H, $NCHCH_2CO$), 3.45–3.70 (m, 2 H, NCH and OCH), 3.70 (s, 3 H, OCH_3), 3.80–3.95 (m with s at 3.90, 4 H, Ar CHN and OCH_3), 4.45 (d, J = 12 Hz, 1 H, $PhCH_2O$), 4.52 (d, J = 12 Hz, 1 H, $PhCH_2O$), 6.45 (d, J = 16 Hz, 1 H, COCH=), 6.60 (d, J = 9 Hz, 1 H, Ar H_5), 6.83 (d, J = 9 Hz, 1 H, Ar H_5), 7.10–7.40 (m, 7 H, PhH, =CH Ar and Ar H_6), 7.48 (dd, J = 9, 2 Hz, 1 H, Ar H_6), 7.66 (d, J = 2 Hz, 1 H, Ar H_2), 7.95 (d, J = 2 Hz, 1 H, Ar H_2); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_2), 21.1 (CH_2), 24.2 (CH_2), 37.5 (CH_2), 42.7 (CH_2), 43.8 (CH_2), 50.3 (CH), 51.6 (CH), 56.3 (CH_3), 56.4 (CH_3), 57.3 (CH), 69.7 (CH_2), 71.8 (CH), 85.8 (C), 86.5 (C), 110.9 (CH), 111.1 (CH), 125.2 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 129.4 (C), 130.2 (CH), 138.2 (CH), 138.7 (C), 139.0 (CH), 140.0 (CH), 157.1 (C), 159.6 (C), 199.0 (C) [1 C and 1 CH not resolved]; exact mass calcd for $C_{34}H_{37}NO_4I_2K$ (M^+ + K) m/e 816.0451, found m/e 815.5460. Anal. Calcd for $C_{34}H_{37}NO_4I_2$: C, 52.53; H, 4.80. Found: C, 52.33; H, 4.89.

***trans*-[4α(*R**),6α,8α,9aα]-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-α-[2-(3-iodo-4-methoxyphenyl)ethenyl]-8-(phenylmethoxy)-2*H*-quinolizine-4-ethanol (47) and *trans*-[4α(*S**),6α,8α,9aα]-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-α-[2-(3-iodo-4-methoxyphenyl)ethenyl]-8-(phenylmethoxy)-2*H*-quinolizine-4-ethanol (48).** To a solution of 198 mg (0.255 mmol) of α,β-unsaturated ketone **46** in a mixture of 5 mL of tetrahydrofuran and 2 mL of dichloromethane was added 0.51 mL (0.510 mmol) of 1 M lithium triethylborohydride in tetrahydrofuran with cooling in an ice bath under argon. The mixture was stirred for 30 min during which the solution gradually became homogeneous. The solution was hydrolyzed with 0.2 mL of water and concentrated in vacuo. The residual white foam was chromatographed over 50 g of silica gel (eluted with ethyl acetate–hexane, 3:7) to give 140 (71%) of allylic alcohol **47** as a white foam and 43 mg (22%) of isomeric allylic alcohol **48** as a colorless oil.

Allylic alcohol **47**: mp 100–102 °C (CH_2Cl_2–EtOH); IR (CH_2Cl_2) 3200 (br), 1590, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–2.3 (m, 13 H), 2.90–3.10 (m, 1 H, $NCHCH_2CHOH$), 3.60–4.25 (m with 2 s at 3.85 and 3.90, 10 H, NCH, OCH, $CHOH$, Ar NCH, and 2 OCH_3), 4.52 (d, J = 12 Hz, 1 H, $PhCH_2O$), 4.53 (d, J = 12 Hz, 1 H, $PhCH_2O$), 6.03 (dd, J = 15, 3 Hz, 1 H, $CHOHCH$=CH), 6.45 (br d, J = 15 Hz, 1 H, $CHOHCH$=CH), 6.73 (d, J = 9 Hz, 1 H, Ar H), 6.80–7.80 (m, 10 H, Ar H and PhH); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 22.8 (t), 24.2 (t), 36.1 (t), 37.1 (t), 42.1 (t), 50.6 (d), 55.0 (d), 56.4 (q, 2 C), 57.6 (d), 69.8 (t), 71.2 (d), 73.0 (d), 86.2 (s, 2 C), 110.8 (d, 2 C), 126.8 (d), 127.5 (d, 3 C), 127.7 (d), 128.4 (d, 2 C), 131.6 (d), 132.2 (s), 137.2 (d), 157.5 (s), 157.9 (s); mass spectrum (FAB on glycerol), m/e (relative intensity) 780 (M^+ + H, 3), 779 (M^+, 4), 653 (2), 476 (28), 384 (3), 369 (6), 368 (16), 108 (24), 107 (13), 91 (100).

Allylic alcohol **48**: IR (CH_2Cl_2) 3595 (sharp), 3200 (br), 1590, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–2.12 (m, 12 H), 2.75 (br s, 1 H, OH), 3.10 (m, 1 H, $NCHCH_2CHOH$), 3.50–3.85 (m, 3 H, NCH, OCH, and CHOH), 3.90 (s, 6 H, 2 OCH_3), 3.98 (d, J = 12 Hz, 1 H, Ar CHN), 4.50 (d, J = 12 Hz, 1 H, $PhCH_2O$), 4.52 (d, J = 12 Hz, 1 H, $PhCH_2O$), 5.85 (dd, J = 15, 3 Hz, 1 H, $CHOHCH$=CH), 6.6 (d, J = 15 Hz, 1 H, $CHOHCH$=CH), 6.80 (d, J = 9 Hz, 1 H, Ar H), 7.10 (br s, 1 H, Ar H), 7.20–7.30 (m, 8 H, Ar H), 7.68 (br s, 1 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 19.6, 22.9, 24.1, 29.7, 34.5, 36.4, 40.9, 51.6, 56.5 (2 C), 57.9, 69.8, 70.8, 73.4, 86.2, 110.9, 127.5, 127.8, 128.4, 129.5, 131.5, 132.1, 137.3, 138.4, 139.2, 157.4, 158.2; mass spectrum (FAB on glycerol), m/e (relative intensity) 780 (M^+ + H, 13), 654 (10), 476 (7), 369 (8), 368 (8), 108 (4), 107 (8), 91 (100).

[(4α(*S),6α,8α,9aα]-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-α-[2-(3-iodo-4-methoxyphenyl)ethyl]-8-(phenylmethoxy)-2*H*-quinolizine-4-ethanol (49).** To a solution of 140 mg (0.180 mmol) of allylic alcohol **47** and 335 mg (1.80 mmol) of *p*-toluenesulfono hydrazide in 5 mL of dimethoxyethane warmed under reflux was added a solution of 408 mg (3.00 mmol) of sodium acetate in 5 mL of water over a 4 h period. The mixture was cooled to room temperature, poured into 20 mL of water, and extracted with three 30-mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The resulting yellow solid was

chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 3:7) to give 128 mg (92%) of saturated alcohol **49** as a white solid: mp 163.5–165.5 °C (EtOAc); IR ($CHCl_3$) 3200 (br) 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (br d, J = 10 Hz, 1 H, CH_2), 1.20–2.20 (m, 14 H), 2.64 (t, J = 10 Hz, 2 H, Ar CH_2CH_2), 2.88 (br d, J = 12 Hz, 1 H, $NCHCH_2CHOH$), 3.58–4.10 (m with 2 s at 3.88 and 3.91, 10 H, NCH, OCH, 2 OCH_3, $CHOH$, and Ar CHN), 4.48 (d, J = 12 Hz, 1 H, $PhCH_2O$), 4.56 (d, J = 12 Hz, 1 H, $PhCH_2O$), 6.70 (d, J = 9 Hz, 1 H, Ar H), 6.85 (br s, 1 H, OH), 7.15–7.52 (m, 8 H, Ar H), 7.68 (br s, 1 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 20.7, 22.8, 24.2, 30.3, 35.8, 37.3, 39.4, 42.4, 50.4, 55.0, 56.4, 56.5, 57.5, 69.7, 71.4, 85.8, 110.0, 127.5, 128.4, 129.5, 137.0, 138.7, 139.5, 156.3, 157.7; mass spectrum, m/e (relative intensity) 781 (M^+, 7), 476 (59), 368 (30), 91 (100). Anal. Calcd for $C_{34}H_{41}NO_4I_2$: C, 52.25; H, 5.29. Found: C, 53.00; H, 5.25.

[4α(S*),6α,8α,9aα]-(±)-Octahydro-6-(3-iodo-4-methoxyphenyl)-α-[2-(3-iodo-4-methoxyphenyl)ethyl]-8-(phenylmethoxy)-2*H*-quinolizine-4-ethyl Acetate (50). To a solution of 245 mg (0.314 mmol) of alcohol **49** in 5 mL of dichloromethane were added 0.3 mL (3.18 mmol) of acetic anhydride, 0.3 mL (2.15 mmol) of triethylamine, and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 3 days and diluted with 10 mL of dichloromethane. The excess solvent and reagents were removed in vacuo, and the residual yellow oil was chromatographed over a Lobar size B column (eluted with ethyl acetate–hexane, 3:7) to give 218 mg (85%) of acetate **50** as a white foam: mp 61–64 °C; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–2.30 (m with s at 1.83, 15 H, CH_2 and $COCH_3$), 2.30–2.68 (m, 4 H), 3.30–4.00 (m with 2 s at 3.75 and 3.82, 10 H, NCH, NCH, OCH, 2 OCH_3, and Ar CHN), 4.48 (s, 2 H, Ar CH_2O), 4.70–5.07 (m, 1 H, CHOAc), 6.65 (d, J = 9 Hz, 1 H, Ar H), 6.68 (d, J = 9 Hz, 1 H, Ar H), 7.04 (dd, J = 9, 2 Hz, 1 H, Ar H), 7.15–7.45 (m, 6 H, Ar H), 7.55 (d, J = 2 Hz, 1 H, Ar H), 7.72 (br s, 1 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 21.0 (q), 24.1 (t), 29.6 (t), 30.3 (t), 35.4 (t), 37.5 (t), 42.5 (t), 49.9 (d), 50.1 (d), 56.4 (q), 57.1 (d), 69.6 (t), 71.8 (d), 72.1 (d), 85.5 (s), 85.8 (s), 111.0 (d), 127.5 (d), 128.3 (d), 129.3 (d), 136.1 (s), 138.5 (d), 138.8 (d), 139.1 (d), 156.5 (s), 157.3 (s), 170.7 (s); mass spectrum, m/e (relative intensity) 823 (M^+, 3), 764 (1), 490 (1), 476 (85), 247 (36), 108 (25), 107 (19), 91 (100).

(±)-3-*O*-Benzyllythrancepine II (51). To a suspension of 262 mg (0.237 mmol) of tetrakis(triphenylphosphine)nickel(0) in 5 mL of *N,N*-dimethylformamide in a 100-mL Schlenk flask was added a solution of 130 mg (0.158 mmol) of diiodide **50** in 20 mL of *N,N*-dimethylformamide over a 20-min period at room temperature in a dry box. The mixture was stirred for 30 min, and then the reaction vessel was sealed and taken from the dry box. The mixture was warmed to 55 °C and allowed to stir for 48 h. The resulting black suspension was concentrated in vacuo and purified by preparative thin-layer chromatography twice over 2-mm silica gel plates (eluted with 10% ammonium hydroxide in methanol–ethyl acetate–hexane, 5:12:28) to give 18 mg (20%) of (±)-3-*O*-Benzyllythrancepine II (**51**) as a white solid: mp 169–170 °C (ether–hexane); IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.80–0.95 (m, 1 H), 1.13 (br d, J = 12.8 Hz, 1 H), 1.42 (ddd, J = 15.3, 6.1, 3.3 Hz, 1 H, H_{10}), 1.49 (4 line ddd, J = 11.8, 11.8, 11.8 Hz, 1 H, H_2), 1.57–1.71 (m, 4H), 1.78–1.90 (m, 3 H), 1.97 (s with underlying m, 4 H, $COCH_3$), 2.21 (ddd, J = 12.3, 6.6, 2.7 Hz, 1 H), 2.43 (ddd, J = 15.0, 11.5, 3.4 Hz, 1 H, H_{10}), 2.56 (ddd, J = 16.0, 10.1, 3.4 Hz, 1 H, H_{13}), 2.72 (ddd, J = 16.0, 6.4, 3.8 Hz, 1 H, H_{13}), 3.16 (br d, J = 11.3 Hz, 1 H, H_9), 3.51 (br d, J = 11.8 Hz, 1 H, H_5), 3.70 (tt, J = 11.5, 4.5 Hz, 1 H, H_3), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.99 (dd, J = 11.5, 2.6 Hz, 1 H, H_1), 4.45 (d, J = 11.9 Hz, 1 H, $PhCH_2O$), 4.52 (d, J = 11.9 Hz, 1 H, $PhCH_2O$), 5.35 (m, 1 H, H_{11}), 6.62 (d, J = 2.3 Hz, 1 H, Ar H_2'), 6.81 (d, J = 8.3 Hz, 1 H, Ar H_5 or Ar H_5'), 6.88 (d, J = 8.4 Hz, 1 H, Ar H_5' or Ar H_5), 7.05 (dd, J = 8.1, 2.4 Hz, 1 H, Ar H_6 or Ar H_6'), 7.06 (dd, J = 8.1, 2.4 Hz, 1 H, Ar H_6' or Ar H_6), 7.21–7.33 (m, 5 H, Ar H), 7.42 (d, J = 2.3 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 569 (M^+, 34), 510 (67), 469 (11), 482 (5), 402 (47), 374 (6), 361 (5), 279 (12), 253 (14), 91 (100), 82 (85); exact mass calcd for $C_{36}H_{43}NO_5$ m/e 569.3142, found m/e 569.3111.

(±)-Lythrancepine II (2). To a solution of 8.4 mg (0.015 mmol) of (±)-3-*O*-benzyllythrancepine II (**51**) in 1.5 mL of dichloromethane was added 236 μL (0.059 mmol) of 0.25 M boron tribromide in dichloromethane dropwise with cooling in an ice bath under argon. The mixture was stirred for 3 min, and 1 mL of water and 4 drops of saturated aqueous sodium bicarbonate were added. The solution was partitioned between 10 mL of dichloromethane and 5 mL of water. The aqueous layer was extracted with five 10-mL portions of dichlormethane, dried ($MgSO_4$), concentrated in vacuo. The resulting pale yellow oil was chromatographed over 10 g of silica gel (eluted with 10% ammonium hydroxide in methanol–ethyl acetate–hexane, 1:6:9) to give 3.8 mg (54%) of (±)-lythrancepine II (**2**) as a white solid after crystallization from hexane. This material was identical (500-MHz ^1H NMR, IR, MS, and TLC) with an authentic sample of (+)-lythrancepine II: mp 139–142 °C; IR (CH_2Cl_2) 3685 (sharp), 3600 (sharp), 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–0.93 (m, 1 H), 1.13–1.22 (m, 1 H), 1.37–1.48 (m with 4 line ddd at 1.42, J = 11, 11, 11 Hz, 2 H, H_2), 1.55–1.73 (m, 5 H), 1.81–1.93 (m, 3 H), 1.93–2.06 (m with s at 1.98, 4 H, $C(O)CH_3$), 2.10 (br d, J = 12.7 Hz, 1 H), 2.44 (ddd, J = 14.2, 12.6, 3.0 Hz, 1 H), 2.56 (ddd, J = 16.2, 11.1, 3.5 Hz, 1 H, H_{13}), 2.74 (br d, J = 16.3 Hz, 1 H, H_{13}), 3.18 (br d, J = 10.9 Hz, 1 H, H_9), 3.50 (br d, J = 11.3 Hz, 1 H, H_5), 3.85–4.00 (m with 2 s at 3.87 and 3.89, 7 H, 2 OCH_3 and H_3), 4.03 (br d, J = 10.0 Hz, 1 H, H_1), 5.32 (m, 1 H, H_{11}), 6.64 (br s, 1 H, Ar H_2'), 6.82 (d, J = 8.3 Hz, 1 H, Ar H_5 or Ar H_5'), 6.88 (d, J = 8.3 Hz, 1 H, Ar H_5' or Ar H_5), 7.05 (br d, J = 8.3 Hz, 1 H, Ar H_6 or Ar H_6'), 7.06 (br d, J = 8.3 Hz, 1 H, Ar H_6' or Ar H_6), 7.40 (d, J = 2.2 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 479 (M^+, 62), 420 (100), 402 (61), 392 (9), 379 (20), 374 (5), 279 (6), 253 (9), 82 (94); exact mass calcd for $C_{29}H_{37}NO_5$ m/e 479.2673, found m/e 479.2681.

(±)-Lythrancepine III (3). To a solution of 2.0 mg (0.004 mmol) of (±)-lythrancepine II (**2**) in 0.5 mL of pyridine was added 6 drops of acetic anhydride at room temperature. The mixture was stirred for 6 h followed by concentration in vacuo. The resulting yellow oil was first chromatographed over 5 g of silica gel (eluted with 10% ammonium hydroxide in methanol–ethyl acetate–hexane, 1:7:11) and then further purified by 0.5-mm-thick preparative thin-layer chromatography over SiO_2 (eluted with 10% ammonium hydroxide–ethyl acetate–hexane, 5:16:24) to give 1.4 mg (64%) of (±)-lythrancepine III (**3**) as a white solid after cyrstallization from hexane. The material was identical (500-MHz ^1H NMR, IR, MS, and TLC) with an authentic sample of (+)-lythrancepine III: mp 82–84 °C; IR (CH_2Cl_2) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (br d, J = 10.5 Hz, 1 H), 1.19 (br d, J = 12.8 Hz, 1 H), 1.42 (ddd, J = 15, 6.4, 3.0 Hz, 1 H, H_{10}), 1.51 (4 line ddd, J = 11.8, 11.8, 11.8 Hz, 1 H, H_2), 1.62–1.74 (m, 3 H), 1.70 (td, J = 11.9, 5.3 Hz, 1 H), 1.79 (br d, J = 12.0 Hz, 1 H), 1.84–1.93 (m, 1 H), 1.93–2.06 (m with 2 s at 1.95 and 1.99, 8 H, $COCH_3$ at C(11) and $COCH_3$ at C(3)), 2.12 (br d, J = 11.8 Hz, 1 H), 2.43 (ddd, J = 15, 11.7, 3.0 Hz, 1 H, H_{10}), 2.56 (ddd, J = 16.0, 10.6, 3.2 Hz, 1 H, H_{13}), 2.74 (ddd, J = 16.0, 6.1, 3.7 Hz, 1 H, H_{13}), 3.20 (br d, J = 11.3 Hz, 1 H, H_9), 3.51 (br d, J = 12.9 Hz, 1 H, H_5), 3.87 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.09 (dd, J = 11.5, 2.5 Hz, 1 H, H_1), 5.03 (tt, J = 11.7, 4.5 Hz, 1 H, H_3), 5.34 (m, 1 H, H_{11}), 6.63 (d, J = 2.0 Hz, 1 H, Ar H_2'), 6.81 (d, J = 8.3 Hz, 1 H, Ar H_5 or Ar H_5'), 6.88 (d, J = 8.3 Hz, 1 H, Ar H_5' or Ar H_5), 7.05 (dd, J = 8.3, 2 Hz, 1 H, Ar H_6 or Ar H_6'), 7.06 (dd, J = 8.3, 2.3 Hz, 1 H, Ar H_6 or Ar H_6'), 7.41 (d, J = 2.3 Hz, 1 H, Ar H_2); mass spectrum, m/e (relative intensity) 521 (M^+, 67), 462 (100), 434 (7), 421 (15), 402 (83), 374 (5), 361 (5), 279 (7), 253 (5), 82 (37); exact mass calcd for $C_{31}H_{39}NO_6$ m/e 521.2778, found m/e 521.2752.

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Supplementary Material Available: Experimental procedures for the preparation of **7** and **36**, procedures for the reactions outlined in Schemes I and II, crystallographic details, and ORTEP drawings for compounds **15** and **49** (31 pages). Ordering information is given on any current masthead page.