4.0 Hz, H_{14a}), 1.65 (m, H_{14b}), 1.60 (m, 2 H_{19}), 0.75 (t, J_{18-19} = 6.5 Hz, CH_3).

α-Ethyl-5-methyl-9-formyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole-8-acetaldehyde Ethylene Acetal N_b-Oxide (12). The hydroxy acetal **11** (200 mg, 0.43 mmol) was added to a solution of dry chlorobenzene (2 mL) and benzeneseleninic anhydride (78 mg, 0.21 mmol). The colorless mixture was heated to 110 °C (oil bath temperature) for 15 min. The orange solution which resulted was cooled to room temperature, and the solvent was removed under reduced pressure. The oil which resulted was dissolved in EtOAc (20 mL) and poured into a solution of 1 N NaOH (30 mL). The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOAc/hexane, 30:70) to furnish the aldo acetal N_b-oxide **12** as a single isomer (104 mg, 53%): IR (NaCl) 2950, 2850, 1730, 1470, 1330, 1240, 1035, 730 cm^{-1}; MS (CI, CH_4), *m/e* (relative intensity) 474 (M + 1, 100) 458 (M + 1 - 16, 35.6); ^1H NMR ($CDCl_3$) δ 9.30 (s, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.30-7.10 (m, 7 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 4.79 (d, *J* = 4.9 Hz, 1 H), 4.02-3.45 (m, 8 H), 3.51 (s, 3 H), 3.09 (dd, *J* = 16.8, *J* = 7.0 Hz, 1 H), 2.90 (m, 1 H), 2.53 (m, 1 H), 2.48 (d, *J* = 16.8 Hz, 1 H), 1.73-1.53 (m, 2 H), 1.15 (m, 2 H), 0.60 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 205.00 (d), 140.11 (s), 139.03 (s), 138.20 (s), 129.11 (d), 127.98 (d), 126.85 (d), 127.00 (s), 122.11 (d), 119.94 (d), 119.01 (d), 109.14 (d), 106.50 (d), 104.81 (s), 81.91 (d), 66.00 (t), 65.22 (t), 63.15 (d), 55.80 (t), 48.00 (d), 39.91 (d), 38.2 (d), 29.9 (d), 26.00 (q), 21.92 (t), 20.21 (t), 11.93 (q). Exact mass calcd for $C_{29}H_{34}N_2O_4$: 474.2519. Found: 474.2520.

(±)-N_b-Benzylsuaveoline (14). The aldoacetal N_b-oxide **12** (200 mg, 0.41 mmol) was added to a 5% solution of 2 N HCl in THF (2 mL). The reaction mixture was stirred at 25 °C for 24 h and then poured into a cold aqueous solution of $NaHCO_3$ (10%, 10 mL). The aqueous mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude dialdehyde **13** as an oil (160 mg, 0.37 mmol, 91%). The crude dialdehyde was dissolved in anhydrous EtOH (5 mL) and hydroxylamine hydrochloride (128 mg, 1.86 mmol) was added. The reaction mixture was heated to reflux for 16 h under an atmosphere of nitrogen. The red solution which resulted was cooled to room temperature, and the solvent was removed under reduced pressure. The oil which resulted was dissolved in CH_2Cl_2 (10 mL) and poured into an aqueous solution of $NaHCO_3$ (10%, 10 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure to afford an oil. The oil was chromatographed (SiO_2, EtOH/$CHCl_3$, 7:93) to afford N_b-benzylsuaveoline (**14**) (R_f = 0.42) as an oil (64 mg, 40% yield from **12**). MS (CI, CH_4), *m/e* (relative intensity) 394 (M + 1, 100); ^1H NMR ($CDCl_3$) δ 8.30 (s, H_{17}), 8.15 (s, H_{21}), 7.45 (d, J_{9-10} = 8.0 Hz, H_9), 7.40-7.20 (m, $H_{12,phenyl}$), 7.19 (t, $J_{11-10(12)}$ = 7.9 Hz, H_{11}), 7.09 (t, $J_{10-9(11)}$ = 7.9 Hz, H_{10}), 4.41 (d, J_{5-6a} = 6.5 Hz, H_5), 4.27 (d, J_{3-14a} = 6.6 Hz, H_3), 3.98-3.75 (q, J_{AB} = 13.8 Hz, 2 H_{benzyl}), 3.65 (s, N_aCH_3), 3.48 (dd, J_{6AB} = 16.4, J_{6a-5} = 6.6 Hz, H_{6a}), 3.25 (dd, J_{14AB} = 16.9, J_{14a-3} = 6.6 Hz, H_{14a}), 2.77 (d, J_{6AB} = 16.4 Hz, H_{6b}), 2.75 (d, J_{14AB} = 16.9 Hz, H_{14b}), 2.50 (q, J_{19-18} = 7.1 Hz, 2 H_{19}), 1.15 (t, J_{18-19} = 7.0 Hz, 3 H_{18}). This material was converted into (±)-suaveoline (**1**) on treatment with hydrogen over Pd/C (see supplementary material for details).

Acknowledgment. We thank Dr. Suzanne Wehrli and Dr. David Nettesheim for the 500-MHz and 250-MHz NMR spectra. We acknowledge Dr. Dennis W. Bennett and Desiree Grubisha for the crystal structure of **9a** as well as Frank Laib for the FABS mass spectra. Special thanks are due to Dr. Dave Soerens, Dr. Etsuji Yamanaka, and Dr. Robert Weber for earlier contributions in this area. This work was supported by a grant from the NIH (NS-22287).

Supplementary Material Available: Experimental procedure and spectral data for compounds **1**, **5**, **6**, **7**, **10a,b**, **11a,b**, and **15** (13 pages). Ordering information is given on any current masthead page.

Free-Radical Cyclizations: Application to the Total Synthesis of *dl*-Pleurotin and *dl*-Dihydropleurotin Acid†

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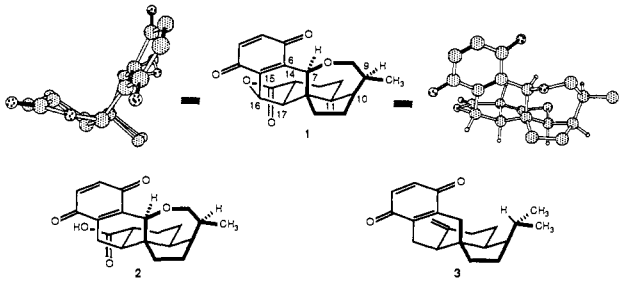
Abstract: Total syntheses of the antitumor antibiotic pleurotin (**1**) and dihydropleurotin acid (**2**) are described. Early stages of the synthesis feature the construction of a trans perhydroindan substructure using a stereoselective free-radical cyclization, and the final stage of the synthesis involves the biomimetic conversion of dihydropleurotin acid (**2**) to pleurotin (**1**).

Pleurotin (**1**) is an fungal metabolite first isolated from *Pleurotus grieseus* and later obtained from *Hohenbuehelia geogenius*.[1,2] Two structurally related natural products, dihydropleurotin acid (**2**) and pleurogrisein (**3**), have also been isolated from fungal sources.[3] Pleurotin displays antibiotic activity against Gram-positive bacteria and antitumor activity against Erlich ascites carcinoma, L-1210 lymphoid leukemia, and mammary tumors.[1,2] The structure of pleurotin was originally assigned on the basis of degradative studies[4] and later confirmed by X-ray crystallographic analysis of a derivative[5] and the natural product itself.[2]



Although the carbocyclic nucleus of **1** is uncommon, pleurotin does contain two substructures that appear in a variety of natural products. One of these substructures is the trans-fused perhydroindan common to numerous terpenoids. The other is a

† This paper is dedicated to Professor William G. Dauben on the occasion of his 70th birthday.

(1) Robbins, W. J.; Kavanaugh, F.; Hervey, A. *Proc. Natl. Acad. Sci. U.S.A.* **1947**, *33*, 171.
(2) Cohen-Addad, P. C.; Riondel, J. *Acta Crystallogr.* **1981**, *B37*, 1309. Riondel, J.; Beriel, H.; Dardas, A.; Carraz, G.; Oddoux, L. *Arzneim. Forsch.* **1981**, *31*, 293.
(3) Erb, B. Ph.D. Thesis, Eidgenossischen Technischen Hochschule, Zurich, Switzerland, 1986.
(4) Schelling, H. Ph.D. Thesis Eidgenossischen Technischen Hochschule, Zurich, Switzerland, 1968.
(5) Dobler, M. *Cryst. Struct. Commun.* **1975**, *4*, 253.

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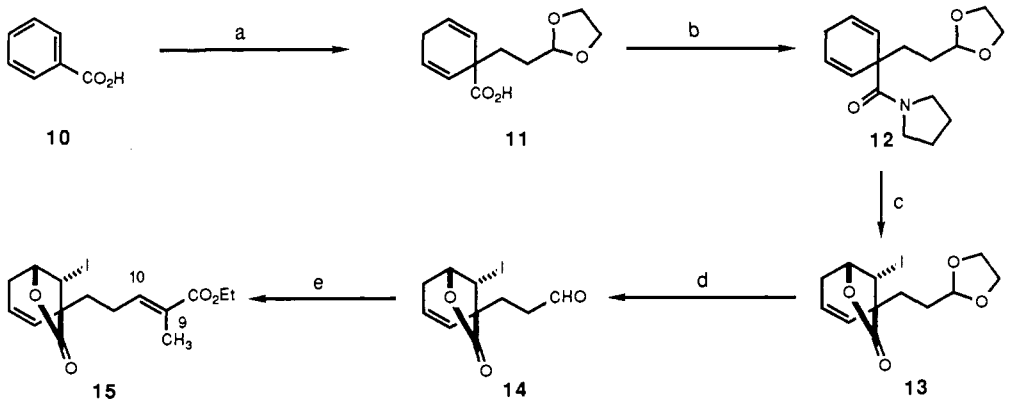
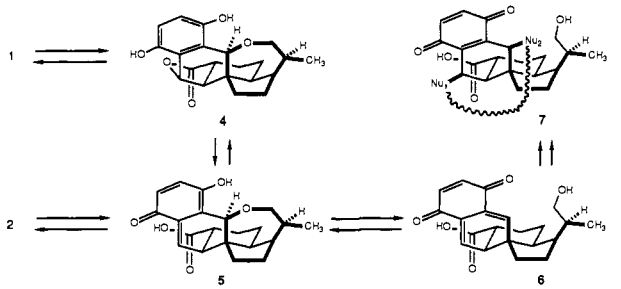
Scheme I[a]



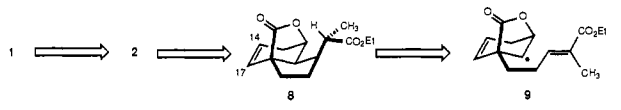
[a](a) Li, NH_3; $BrCH_2CH_2CH(OCH_2CH_2O)$; (b) DPPA, Et_3N, pyrrolidine, THF; (c) I_2, THF, H_2O; (d) HCO_2H, H_2O; (e) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2.

quinone substituted with two "benzylic" leaving groups. This array of functional groups appears in numerous antitumor agents classified as bioreductive bisalkylating agents.[6] In the case of pleurotin, it has been suggested that bioactivation might occur by reduction of **1** to hydroquinone **4** followed by an elimination



to generate quinone methide **5**. Quinone methide **5** could behave as an alkylating agent toward biologically relevant nucleophiles or undergo an elimination to afford **6**. Disruption of some biologically important event by cross-linking (**5** → → **7**) might ultimately be responsible for cell damage. One might imagine the interconversion of pleurotin (**1**) and dihydropleurotin acid (**2**) via a similar sequence of events. Thus, tautomerization of dihydropleurotin acid (**2**) would generate **5**. Cyclization of **5** followed by oxidation of **4** would afford pleurotin (**1**). In fact, the Arigoni group has demonstrated that **2** is converted to **1** by cultures of *P. griseus*.[7]

Due in part to the interesting structural features and biological properties cited above, a total synthesis of pleurotin was undertaken. The projected end game was based on the aforementioned in vivo interconversion of **1** and **2**. Thus, dihydropleurotin acid was set as the initial objective. It was felt that **2** could be prepared from trans-fused perhydroindan **8**. It was anticipated that the C(14)–C(17) double bond would provide a handle for construction of the C(16)–C(17) bond and introduction of the C(14) carboxyl group. The lactone carbonyl group was expected to provide a handle for introduction of the C(6)–C(7) bond. It was felt that perhydroindan **8** would be preparable by cyclization of free radical **9** using methodology previously developed in these laboratories.[8] The remainder of this paper describes the realization of this plan and peripheral studies performed along the way.[9]



Preparation of Perhydroindan 8 and Related Studies. The preparation of a precursor to free radical **9** is outlined in Scheme I. Birch reduction of benzoic acid (**10**) followed by alkylation of the resulting dianion with (2-(2-bromoethyl)-1,3-dioxane gave acid **11** in 89% yield.[10] Treatment of **11** with diphenylphosphoryl azide[11] and pyrrolidine gave a 74% yield of amide **12**, which was converted to iodolactone **13** (94%) upon exposure to iodine in aqueous tetrahydrofuran.[12] Hydrolysis of the acetal using aqueous formic acid gave aldehyde **14** (88%) and a Wittig reaction gave α,β-unsaturated ester **15** (94%). The assignment of the olefin geometry in **15** was based on the downfield chemical shift of H(10) (δ 6.81) and small H(10)–Me coupling constant (1 Hz) relative to those observed in the corresponding *Z*-geometrical isomer (vide infra).

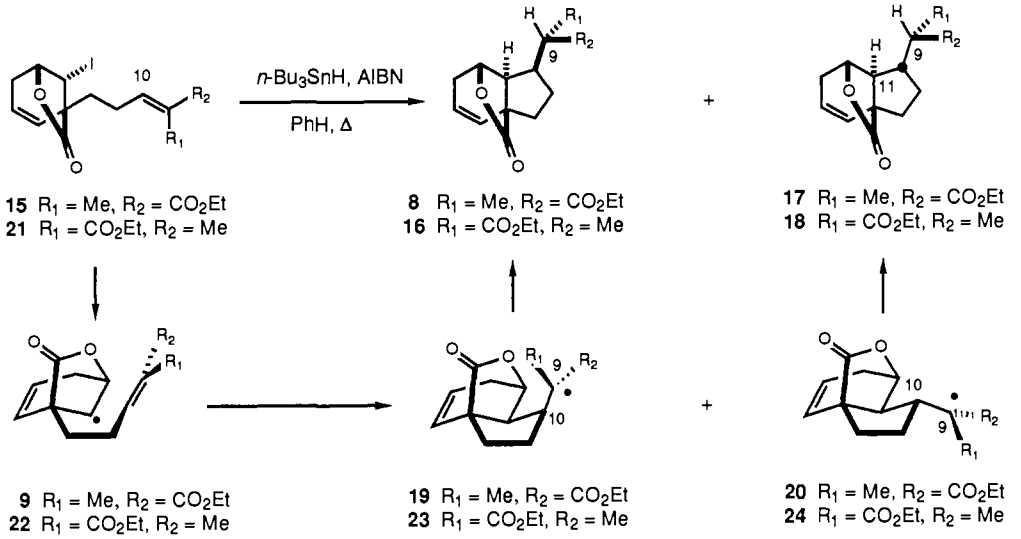
As shown in Scheme II, treatment of iodolactone **15** with tri-*n*-butyltin hydride and AIBN in benzene at 60 °C gave a separable mixture of diastereomeric perhydroindans **8**, **16**, **17**, and **18** in 80%, 4%, 4%, and 4% isolated yields, respectively.[13,14] The isolated product ratio was in agreement with results obtained by capillary GLC (**8**:**16**:**17**:**18** = 80:2:10:4) and ^1H NMR (**8**:**16**:**17**+**18** = 16:1:1) analyses of the product mixture before purification. The structure of **8** was established by X-ray crystallography. The diastereomeric relationships between **8**/**16** and **17**/**18** were established by epimerization studies (NaOEt, EtOH). Although the stereochemistry at C(11) of **17** and **18** was not proven, models suggest that formation of the C(11) diastereomer is unlikely due to the ring strain that would be introduced in a trans-fused oxabicyclo[3.3.0]octane substructure.

The high stereoselectivity observed in the radical cyclization (**15** → **9** → **8**) was a welcome surprise.[15] The initial step in this

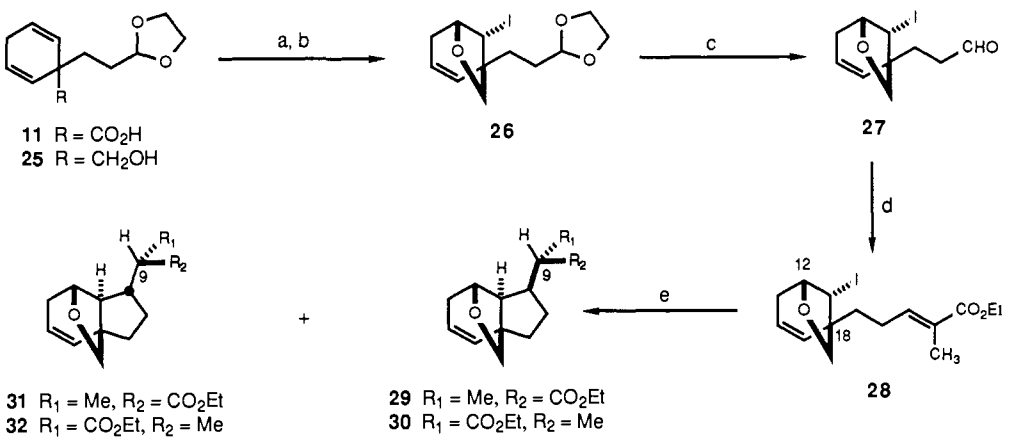
(6) Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527.
(7) Vogt, P. M. Ph.D. Thesis, Eidgenossischen Technischen Hochschule, Zurich, Switzerland, 1982.
(8) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210. Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782.

(9) For preliminary accounts of portions of this work, see: (a) Hart, D. J.; Huang, H.-C. *J. Am. Chem. Soc.* **1988**, *110*, 1634. (b) Hart, D. J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, 3749. Structures **3** and **13** in this article should be corrected (vide infra).
(10) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35. Van Bekkum, H.; Von Den Bosch, C. B.; Van Minnenpathius, G.; DeMoss, J. C.; Van Wijk, A. M. *Recl. Trav. Chem. Pays-Bas* **1971**, *90*, 137. Birch, A. J.; Smith, H. *Q. Rev.* **1958**, *12*, 17.
(11) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(12) Faffaut, R. F. *J. Am. Chem. Soc.* **1952**, *74*, 4460. Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.
(13) For reviews of tin hydride chemistry, see: Neumann, W. P. *Synthesis* **1987**, 665. Kuivila, H. F. *Synthesis* **1970**, 499. Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.
(14) For reviews discussing radical cyclizations, see: Curran, D. P. *Synthesis* **1988**, 417, 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1986. Hart, D. J. *Science* **1984**, *223*, 883. Ueno, Y.; Yuki, J. *J. Synth. Org. Chem., Jpn.* **1984**, *42*, 1121. Stork, G. In *Current Trends in Organic Synthesis*; Pergamon Press: New York, 1983; p 359. Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, A. A., Ed.; Plenum Press: New York, 1981; Vol. 2, p 121. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Wilt, J. W. In *Free Radicals*; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1, p 466.

Scheme II



Scheme III[a]



[a] (a) $LiAlH_4$, THF; (b) I_2, THF, H_2O; (c) HCO_2H, H_2O; (d) $Ph_3P{=}C(CH_3)CO_2Et$; (e) *n*-Bu_3SnH, AIBN, PhH, Δ.

transformation must be cyclization of **9** to a pair of radicals that are diastereomeric at C(10). We imagine that these radicals are born in conformations **19** and **20**. Reduction of **19** affords **8** and **16**, while reduction of **20** gives **17** and **18**. Reduction of **20** is obviously not selective, while reduction of **19** is quite selective. One unlikely explanation for the selective reduction is that the lactone bridge induced a barrier to rotation around the C(9)–C(10) bond that renders interconversion of **19** and **23** slower than reduction of **19** by tri-*n*-butyltin hydride. Reduction of **19** from the sterically most accessible face is expected to afford **8**. Another explanation is that **19** is simply the thermodynamically most stable conformation of the α-carbethoxy radical (vide infra). These explanations are testable. Cyclization of radical **22** should initially afford **23** and **24**, conformational isomers of **19** and **20**, respectively. The "unlikely" explanation predicts that **23** should then afford **16** while the "thermodynamic" explanation predicts that **8** should remain the major product. Thus, (*Z*)-olefin **21** was prepared [H(10) appears at δ 6.00 and the H(10)–Me coupling constant is 2.0 Hz][16] and subjected to the aforementioned cyclization conditions to afford perhydroindans **8**, **16**, **17**, and **18** in 37%, 2%, 15%, and 12% isolated yields, respectively. Thus, although erosion of endo selectivity was observed (**8**/**16** vs **17**/**18**), selectivity in the partitioning between **8** and **16** (**17** and **18**) remained constant. This result established that the stereoselectivity at C(9) was not a function of initial olefin geometry and was most likely due to a conformational preference of the α-carbethoxy radical.[17]

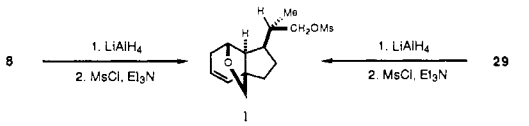
In an attempt to see if structural modifications of the lactone bridge would effect the stereochemical course of related cyclizations, the preparation of cyclization of bicyclic ether **28** was pursued as outlined in Scheme III. Reduction of **11** gave alcohol **25** (80%), and haloetherification afforded **26** (62%). Acetal hydrolysis gave **27** (69%), and a Wittig reaction completed the preparation of **28** (69%). Treatment of **28** with tri-*n*-butyltin hydride and AIBN gave a combined 79% yield of cyclization products **29**, **30**, **31**, and **32** in a 10:1:1:4:1.3 ratio, respectively.[18]

(15) The stereoselectivity observed during formation of the C(10)–C(11) bond is consistent with the stereochemical course of related cyclizations: Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. Wolff, S.; Agosta, W. C. *J. Chem. Res., Synop.* **1981**, 78. Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613.

(16) Treatment of **14** with the appropriate stabilized phosphorane in methanol gave **15** (64%) and **21** (15%) as a separable mixture. See: House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.

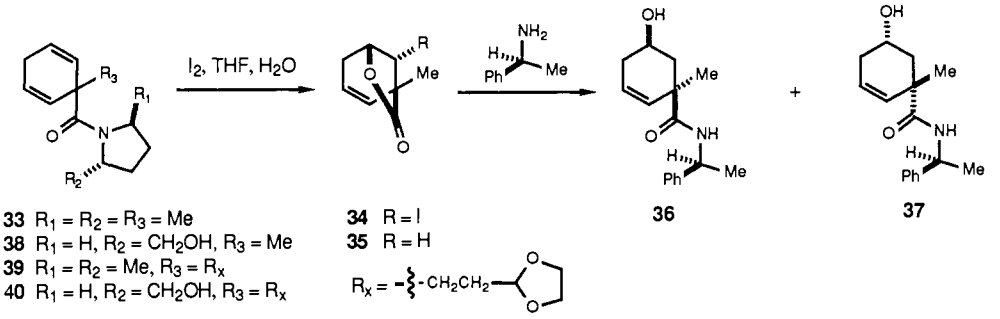
(17) For another example where olefin geometry dramatically effects the stereochemical course of a radical conjugate addition, see: Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546.

(18) The stereochemical assignments for **29**–**32** were based on chemical correlation of **8** with **29** and epimerization experiments. Thus, reduction of **8** with excess lithium aluminum hydride followed by treatment of the resulting

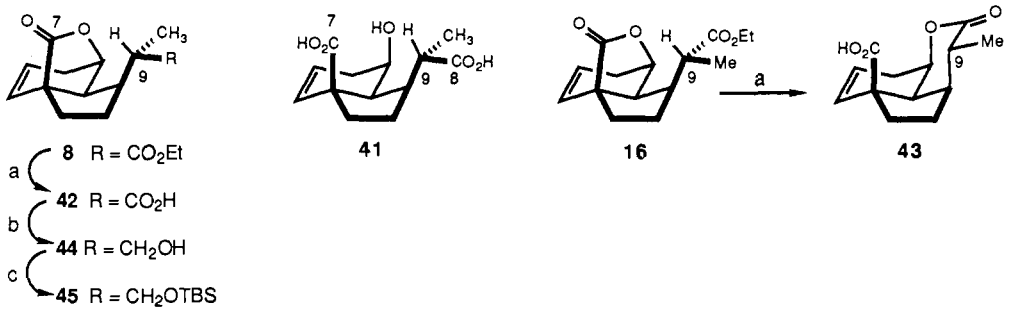


crude triol with methanesulfonyl chloride and pyridine gave mesylate i. Similar treatment of **29** also afforded i. Epimerization of **29** (NaOEt, EtOH) established the relationship between **29** and **30**. Similar epimerization studies with **31** and **32** established the isomeric relationship between these compounds.

Scheme IV



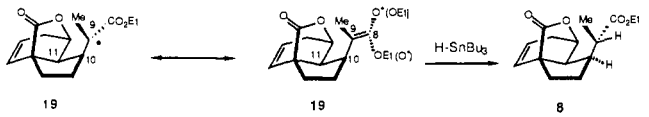
Scheme V[a]



[a] (a) LiOEt, MeOH, H_2O; HCl, H_2O; (b) $(COCl)_2$; $NaBH_4$; (c) *t*-$BuMe_2SiCl$, imidazole, DMF.

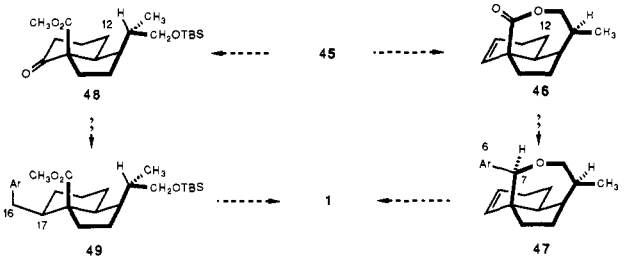
Thus, changing the lactone to an epoxymethano bridge did not have a pronounced effect on the stereochemical course of reduction at C(9) (**29**:**30** = 10:1), although it did affect the stereochemical course of the cyclization (**29**+**30**:**31**+**32** = 4:1).

Our current explanation for the *acyclic diastereoselection* observed in the cyclizations of iodides **15** (Scheme II) and **28** (Scheme III) is based on allylic asymmetric induction models proposed by Houk and others.[19] In the cyclization of **15**, stereochemistry at C(9) is established during reduction of α-carbethoxy radical **19**/**23** by tri-*n*-butyltin hydride. The observed stereochemistry is consistent with the following assumptions: (1) the α-carbethoxy radical is delocalized, (2) the conformation from which reduction takes place is that in which $A^{(1,3)}$ interactions are minimized and the largest allylic substituent [C(11)] is roughly perpendicular to the C(8)–C(9) π-bond, and (3) reduction takes place at C(9) along a trajectory that minimizes torsional strain [antiperiplanar to the C(10)–C(11) bond]. The later two assumptions are based on models proposed by Houk for the addition of a hydrogen atom to propene. It will be interesting to see if this analysis predicts the stereochemical course of other free-radical reactions that proceed with high acyclic diastereoselectivity.



Before continuing with the synthesis of pleurotin (**1**), one additional problem will be addressed. The synthesis of **8** described in Scheme II provides racemic material. It was anticipated that use of a homochiral amide in place of **12** might lead to enantioselective generation of **13**, an intermediate in the synthesis of **8**. To simplify analytical problems, this notion was addressed by using amide **33** as shown in Scheme IV.[20] Treatment of **33** with iodine in aqueous tetrahydrofuran gave iodolactone **34** (47%) as an optically active substance. The enantiomeric excess of this material was determined by conversion to a pair of separable diastereomers. Thus, tri-*n*-butyltin hydride reduction of **34** gave **35** (48%) and treatment of **35** with α-phenethylamine gave a 65:35 mixture of diastereomers **36** and **37** in 67% combined yield.[21] Thus, only a low level of enantioselectivity (30% ee) was observed in this reaction. Halolactonization of amide **38** also gave optically active **34** (78%).[22] Conversion of this material to a mixture of **36** and **37** (85%) indicated that this halolactonization had produced a 42% ee. No attempt was made to determine the absolute stereochemistry of the major enantiomer. Although electrophile-initiated cyclizations of cyclohexa-2,5-diene-1-carboxamides carrying larger C(1) substituents (**39** or **40**) might be more selective, such studies were not pursued.

Scheme VI



Adjustment of Oxidation State at C(8) and Reduction of the C(12)–Oxygen Bond. The next stage of the synthesis of pleurotin (**1**) called for differentiation between the oxidation states of C(7) and C(8). This was accomplished as outlined in Scheme V Treatment of **8** with lithium hydroxide in aqueous methanol afforded crude diacid **41**, which gave lactone **42** (89%) upon warming with aqueous hydrochloric acid. To eliminate concern

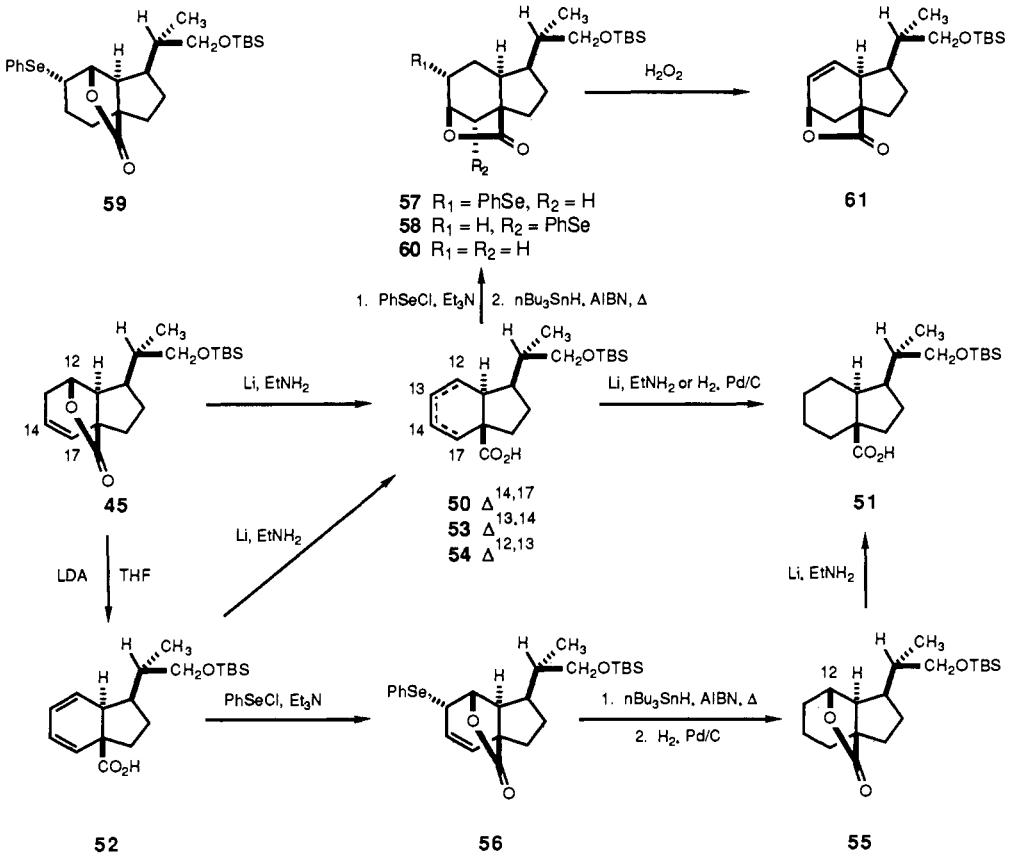
(19) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. We thank Professor David A. Evans for stimulating discussions that led to our recognizing the relationship between this reaction and the Houk model.

(20) Sequential treatment of 1-methyl-2,5-cyclohexadiene-1-carboxylic acid with oxalyl chloride (PhH, room temperature) and (*S*)-2,5-dimethylpyrrolidine (Felman, S. W.; Whitesell, J. K. *J. Org. Chem.* **1988**, *53*, 5383. Iwanowicz, E. J.; Schlessinger, R. H. *Tetrahedron Lett.* **1987**, 2083) gave amide **33** in 64% yield.

(21) Diastereomers **36** and **37** were easily separable by chromatography over silica gel and gas chromatography (see Experimental Section). Product ratios (**36**:**37**) were determined before separation with GC and by integration of appropriate signals in the ^1H NMR spectrum of the mixture (see Experimental Section). Experiments using racemic **35** indicated that little or no kinetic resolution occurred under the conditions used to convert **35** to **36** and **37**. The absolute configurations of **36** and **37** were not determined and may be the reverse of those shown in Scheme IV.

(22) Sequential treatment of 1-methyl-2,5-cyclohexadiene-1-carboxylic acid with oxalyl chloride (PhH, room temperature) and (*S*)-prolinol gave amide **38** in 79% yield.

Scheme VII



over possible isomerization at C(9) during the hydrolysis, isomeric ester **16** was subjected to identical reaction conditions and the crude mixture of acids was treated with diazomethane. This treatment resulted in the formation of the methyl ester corresponding to γ-lactone **16** (51%) and δ-lactone **43** (13%), establishing that isomerization of **8** had not occurred. It is interesting that the C(9) stereochemistry influences the regiochemistry of lactone formation, but understandable in terms of steric interactions that would be present in the C(9) isomer of **43**. Continuing with the synthesis, sequential treatment of **42** with oxalyl chloride and sodium borohydride gave alcohol **44**. Hydroxyl group protection was achieved by using *tert*-butyldimethylsilyl chloride and imidazole to afford **45** in 95% overall yield from **42**.[23] Some time after completing this straightforward sequence (**8** → **45**) it was discovered that treatment of **8** with lithium aluminum hydride directly gave alcohol **44** in 95% yield. This provides a rather special example in which an ester is reduced at a greater rate than a lactone, undoubtedly due to steric effects.

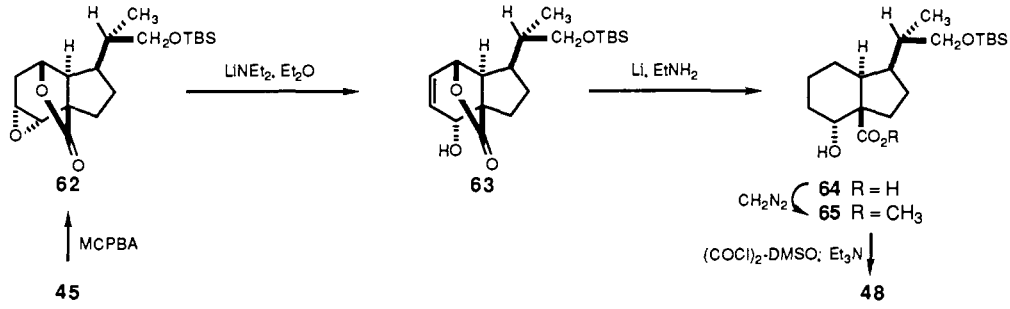
With the oxidation-state differentiation completed (**8** → → **45**), two general plans for appending the quinonoid substructure of pleurotin were evaluated (Scheme VI). One plan (**45** → **46** → **47** → **1**) involved sequential construction of the C(6)–C(7) and C(16)–C(17) bonds, while the other (**45** → **48** → **49** → **1**) focused on construction of these bonds in the reverse order. Both plans required initial reduction of the C(12)–oxygen bond of **45**. This was initially accomplished as outlined in Scheme VII. Treatment of **45** with lithium in ethylamine gave a 40% yield of an olefinic acid, initially assigned and published as structure **50**, along with small amounts of **51**.[9b,24] As will be seen, the assignment of structure **50** was incorrect.[9b] Catalytic hydrogenation of the presumed **50** gave **51**, establishing in part the structural relationship between these two compounds. The structure assigned to the olefinic acid derived from the dissolving-metal reduction came into question when a 35% yield of diene **52** was isolated from one attempted reduction of **45**. Furthermore, treatment of **52** with lithium in ethylamine gave an 84% yield of the same olefinic acid originally assigned structure **50**. These observations suggested that the presumed reduction of the C(12)–oxygen bond was taking place via an initial elimination reaction (**45** → **52**) followed by reduction of the resulting diene. Of course, this suggested that the olefin acid initially assigned structure **50** might in fact be **53** or **54**. In addition, if diene **52** was an intermediate in the reduction, it was possible that isomerization of the ring juncture via an intermediate pentadienyl anion or triene had taken place.

To address these issues (ring juncture stereochemistry and **50** vs **53** vs **54**), additional experiments were performed (Scheme VII). First, it was shown that treatment of **45** with lithium diisopropylamide in tetrahydrofuran gave diene **52** (84%). This result provided evidence that a base-mediated elimination was indeed possible. It was also demonstrated that the C(14)–C(17) double bond was needed to observe this elimination. Thus, catalytic hydrogenation of **45** gave lactone **55** (95%). This lactone was recovered unchanged upon treatment with lithium diisopropylamide, but was converted to **51** (20%) by using lithium in ethylamine. This result also suggested that the trans perhydroindan ring juncture had been maintained, since it is difficult to imagine a means by which the C(12)–oxygen bond in **55** could be reduced with isomerization at C(11) and without intervention of an elimination reaction. It was also established that diene **52** maintained a trans ring fusion through correlation with **55** as follows. Treatment of **52** with benzeneselenenyl chloride gave lactone **56** (58%), and sequential reduction of **56** with tri-*n*-butyltin hydride and hydrogen over palladium on charcoal gave **55** (73%).[25,26]

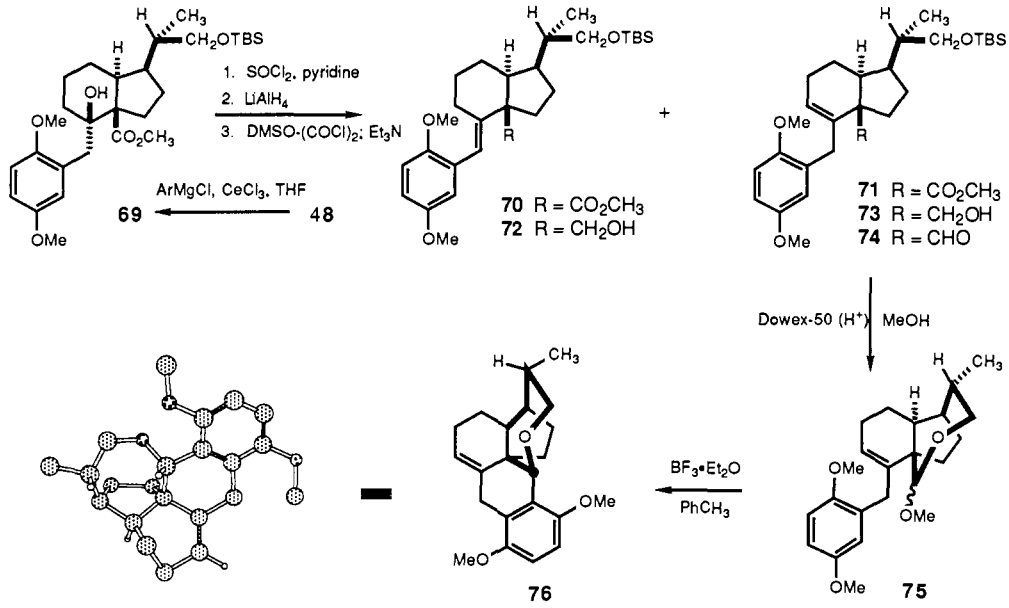
With the question of ring juncture stereochemistry resolved, the question of olefin regiochemistry (**50** vs **53** vs **54**) was ad-

(23) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(24) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokapiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.
(25) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.
(26) Clive, D. L. J.; Chittattu, G.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1978**, 41. Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293. Corey, E. J.; Pearce, H. L.; Szekely, I.; Ishigura, M. *Tetrahedron Lett.* **1978**, 1023.

Scheme VIII



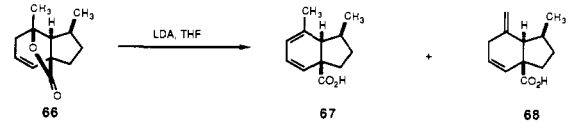
Scheme IX



dressed. Treatment of the olefinic acid with benzeneselenenyl chloride gave a γ-lactone in a 50% yield.[25] The γ-lactones expected from **50**, **53**, and **54** were **57**, **58**, and **59**, respectively. Treatment of the selenolactone with tri-*n*-butyltin hydride and AIBN gave a new lactone that differed from lactone **55**, which was therefore assigned structure **60** (99%). This result eliminated **59** as a candidate for the selenolactone and **54** for the olefinic acid. Oxidation of the selenolactone using hydrogen peroxide gave an olefinic lactone that was assigned structure **61** (28%), eliminating selenolactone **58** and olefinic acid **50** from contention.[27] In conclusion, treatment of **45** with lithium in ethylamine affords **53** by a mechanism that involves diene **52** as an intermediate. This transformation is best accomplished, however, by use of the aforementioned elimination–reduction sequence.

The unexpected double-bond migration in the reduction of **45** stalled efforts to gain rapid access to lactone **46**, and alternate tactics for reducing the C(12)–oxygen bond were adopted (Scheme VIII). Treatment of **45** with *m*-chloroperoxybenzoic acid gave epoxide **62** (87%). This material rearranged to allylic alcohol **63** (76%) upon exposure to lithium diethylamide in ether, and reduction of **63** using lithium in ethylamine gave **64** in 67% yield.[28,29] Esterification using diazomethane gave hydroxy ester **65** (100%), and a Swern oxidation completed the synthesis of projected intermediate **48** (88%).[30] From an operational standpoint, it was most convenient to combine the epoxide opening and reduction steps in a one-pot procedure. In this manner, **65** could be obtained in a 59% overall yield from **62**.

In closing this section, it is noted that the elimination reaction cited in Scheme VII may be of general interest in the area of terpene synthesis and is not limited to compound **45**. For example, treatment of lactone **66** with lithium diisopropylamide gave a separable mixture of dienes **67** (40%) and **68** (28%) along with 8% of recovered starting material.[31]



Introduction of the Quinonoid Substructure: Preparation of Pentacycle 76. The next stage of the synthesis called for construction of the C(16)–C(17) and C(6)–C(7) bonds. Guided by a large number of experiments that will not be discussed here for the sake of brevity, this transformation was accomplished as shown in Scheme IX.[32] Treatment of keto ester **48** with the reagent derived from (2,5-dimethoxybenzyl)magnesium chloride and cerium trichloride gave tertiary alcohol **69** (91%).[33] Dehydration of alcohol **69** using thionyl chloride in pyridine gave a quantitative yield of olefins **70** and **71** as an inseparable 1:1 mixture. This

(27) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, *36*. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(28) Crandall, J. K.; Chang, L. H. *J. Org. Chem.* **1967**, *32*, 435. Crandall, J. K.; Lin, L. H. C. *J. Org. Chem.* **1968**, *33*, 2375. Rickborn, B.; Thummel, R. P. *J. Org. Chem.* **1969**, *34*, 3583.

(29) Hallsworth, A. S.; Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 1969.

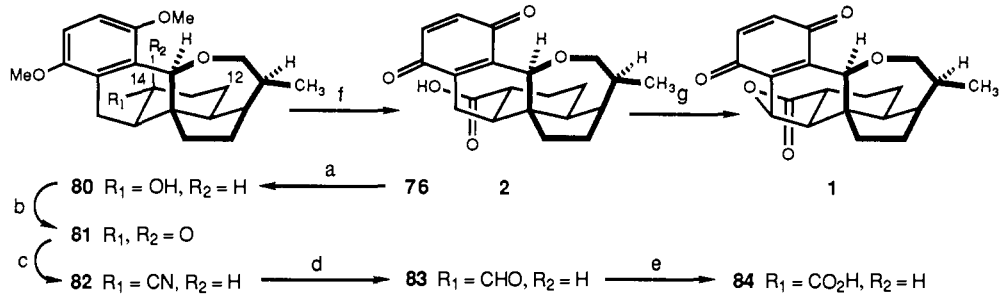
(30) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(31) Lactone **66** also gave **67** and **68** upon treatment with classical nucleophiles such as *n*-butyllithium and (2,5-dimethoxyphenyl)magnesium bromide. This underscores the propensity for lactones of this type to undergo elimination reactions faster than nucleophilic additions.

(32) For a discussion of the events that lead to adoption of the following sequence as well as other approaches to pleurotin, see: Huang, H.-C. Ph.D. Thesis, The Ohio State University, Columbus, OH, 1987.

(33) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

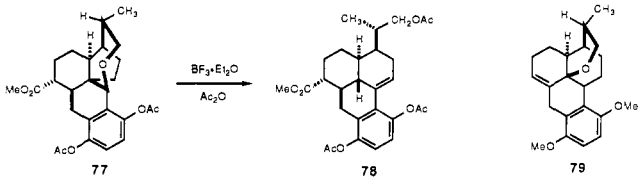
Scheme X[a]



[a] (a) BH_3-THF; NaOH, H_2O_2 (b) DMSO-$(COCl)_2$; Et_3N (c) TosMIC, KOtBu, DME (d) iBu_2AlH, $PhCH_3$ (e) Ag_2O, NaOH (f) CAN, CH_3CN, H_2O (g) MnO_2, CH_2Cl_2.

result was somewhat discouraging since C(14)–C(17) unsaturation was ultimately needed to introduce the C(14) carboxyl group.[34] Nonetheless, we proceeded as follows. Treatment of the mixture of **70** and **71** with lithium aluminum hydride gave **72** (50%) and **73** (43%), easily separated by chromatography over silica gel. Swern oxidation of **73** gave aldehyde **74** (85%),[30] setting the stage for construction of the C(6)–C(7) bond using an intramolecular electrophilic aromatic substitution reaction. Treatment of **74** with acidic Dowex-50 in methanol gave a 99% yield of crude acetal **75** as a mixture of diastereomers, which was used in subsequent reactions without purification.

Construction of the C(6)–C(7) bond (**75** → **76**) was approached with caution. During the course of degradation studies, the Arigoni group reported that dihydropleurotin acid derivative **77** rearranged



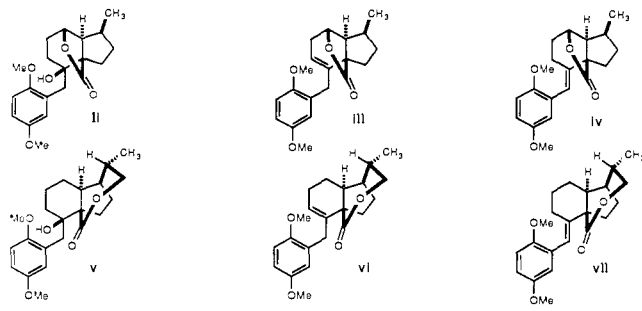
to diene **78** in 56% yield upon treatment with boron trifluoride etherate in acetic anhydride at room temperature.[3] This suggested that the desired cyclization might be complicated by acid-catalyzed rearrangement of the desired product **76**. In the event, treatment of **75** with boron trifluoride etherate in toluene at −18 °C for 2 h did afford **76** (52%) along with 11% of recovered starting material and 9% of an isomeric substance. The gross structure of **76** was supported by spectral data including the presence of only two aromatic protons (singlet at δ 6.66), the appearance of H(7) as a singlet at δ 4.62, and signals at δ 3.51 and 3.98 due to the C(8) protons. These chemical shift data compared favorably with those reported for **77**.[3,35] Although molecular mechanics calculations suggested that **76** was 2.0 kcal mol^{-1} more stable than its C(7) diastereomer, proof of the stereochemical assignment had to await further studies.[36]

The course of the cyclization was quite sensitive to reaction conditions. For example, when the reaction was conducted in toluene at room temperature, in dichloromethane, or in chlorobenzene, the aforementioned isomeric substance became the major product. This material, itself prone to decomposition upon prolonged exposure to acid, has been tentatively assigned structure **79** based on spectral data and the aforementioned behavior of **77**.[37]

Introduction of the C(14) Carboxyl Group and Biomimetic Conversion of Dihydropleurotin Acid (2) to Pleurotin (1). To complete the syntheses of dihydropleurotin acid (**2**) and pleurotin (**1**) it was necessary to add the elements of formic acid across the C(14)–C(17) double bond, oxidize the hydroquinone dimethyl ether to a quinone, and accomplish the biomimetic end game discussed in the introduction. The first of these tasks was accomplished as outlined in Scheme X. Hydroboration–oxidation of **76** gave alcohol **80** (90%).[38] The geometry of **76** dictated that the addition take place with the desired stereochemistry, and the stereochemical relationship between C(14) and C(17) was easily established by the large 11-Hz coupling between H(14) and H(17).[39] Oxidation of **80** using the conditions of Swern gave ketone **81** (92%), and treatment of **81** with tosylmethyl isocyanide under basic conditions afforded nitrile **82** (75%).[31,40] The stereochemistry at C(14) of the **82** was again assigned on the basis of an 11-Hz coupling between H(14) and H(17). In addition, irradiation of the C(7) proton showed an enhancement of the signals due to the C(14) and C(12) axial protons, establishing the stereochemistry at C(7) for the first time.[41]

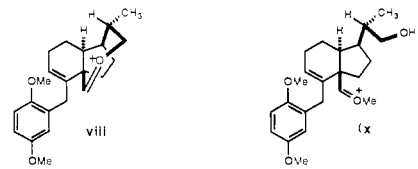
Although nitrile **82** could be hydrolyzed to the corresponding primary amide by using basic hydrogen peroxide, conversion of the amide to acid **84** was problematic. Reduction of **82** with diisobutylaluminum hydride, however, gave aldehyde **83** (93%), and oxidation of this material using basic silver oxide did afford acid **84** in 62% yield.[42,43] Treatment of **84** with ceric ammonium nitrate in aqueous acetonitrile gave *dl*-dihydropleurotin acid (**2**)

(34) A number of alternative dehydration procedures failed to produce larger **71**:**70** ratios. The regiochemical course of this dehydration was sensitive to subtle variations in structure. For example, dehydration of alcohol ii using thionyl chloride in pyridine gave a 2.5:1 mixture of iii and iv in 91% yield while v gave a 5.5:1 mixture of vi and vii in 95% yield.[32]



(35) For some relevant spectroscopic data, see: Grandjean, J.; Huls, R. *Tetrahedron Lett.* **1974**, 1893.

(36) Although it is tempting to suggest that thermodynamics may control the stereochemical course of this reaction (**75** → **76**), the situation is actually quite complex. For example, we do not know whether the electrophile is oxonium ion viii or ix. If one assumes an antiperiplanar relationship between



the C(6)–C(7) bond and the developing lone pair on oxygen, molecular mechanics calculations modeling the cyclization of vii suggest that **76** should also be the product of kinetic control. We thank Mr. Sean Kerwin for performing these calculations at The University of California using the MM2 force field of MACROMODEL.

(37) The appearance of a quaterary carbon at 81.6 ppm in the ^{13}C NMR spectrum of the minor isomer is suggestive of structure **79** and excludes the C(7) diastereomer of **76** as a candidate for this substance.

(38) Brown, H. C. *Boranes in Organic Synthesis*; Cornell University Press: Ithaca, NY, 1972.

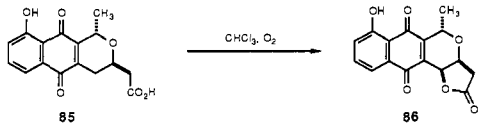
(39) On one occasion when oxygen was not carefully excluded from the hydroboration–oxidation mixture, the C(14) isomer of **80** was obtained as a minor product. The H(14)–H(17) coupling for this material was 2.6 Hz.[32]

(40) Oldenziel, O. H.; Van Leusen, D.; Van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.

(41) For a discussion, see: Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: New York, 1987; pp 113–118.

in 89% yield.[44] This material was chromatographically (TLC) and spectrally (IR, MS, ^{1}H NMR) identical with material prepared by degradation of natural pleurotin.[45]

Aside from the in vivo conversion of dihydropleurotin acid (**2**) to pleurotin (**1**), precedent for this transformation can be found in the chemistry of tetrasubstituted *p*-benzoquinones.[46] For example, duroquinone and 2,3-dimethyl-1,4-naphthoquinone are known to react with a variety of nucleophiles such as enolates or amines to give side-chain oxidation products. In terms of natural product synthesis, this internal redox strategy has been used to convert nanaomycin A (**85**) to nanaomycin D (**86**).[47] Dihydropleurotin acid (**2**), however, is a disubstituted *p*-benzoquinone, and it is known that such compounds tend to give ring addition products rather than side-chain oxidation products.[46] It was our hope that in the absence of external nucleophiles, it would be possible to accomplish the desired internal redox process (**2** → **4**) and that oxidation of **4** would complete the synthesis of **1**. Initial attempts to effect the desired transformation, using bases (triethylamine, DBU, potassium carbonate) in the absence and presence of oxygen, met with failure. Finally, when dihydropleurotin acid (**2**) was stirred with a large excess of manganese dioxide in dichloromethane for 2 days, a 32% yield of *dl*-pleurotin (**1**) was obtained along with recovered starting material (33%). Although we like to imagine that the excess oxidant provides a driving force for the transformation, the mechanistic details remain uncertain.



85 86

In summary, pleurotin (**1**) was prepared in 26 steps from benzoic acid in 0.3% overall yield, an average of 80% yield per step. The synthesis features a highly stereoselective free-radical cyclization. Variants of this cyclization may be applicable to a more general problem in the area of terpene synthesis, that of ring construction with concommitant control of branched side-chain stereochemistry.

Experimental Section

All melting points and boiling points are uncorrected. ^{1}H NMR spectra are reported as follows: chemical shift [multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants in hertz, integration, interpretation]. ^{13}C NMR data are reported as follows: chemical shift (multiplicity determined from off-resonance decoupled, DEPT or INEPT spectra). Mass spectra were obtained at an ionization energy of 70 eV. Compounds for which exact mass is reported exhibited no significant peaks at *m/e* greater than that of the parent. Procedures for the preparation of compounds **11–14** have already been published.[8] Only experiments along the final route to **1** and **2** are presented below. The remaining experiments, as well as a description of general experimental considerations, are available as supplementary material.

***rel*-[1*R*(*E*),5*R*,8*R*]-Ethyl 5-(8-Iodo-7-oxo-6-oxabicyclo[3.2.1]oct-2-en-1-yl)-2-methyl-2-pentenoate (15).** To a solution of 10.85 g (35.5 mmol) of aldehyde **14** in 165 mL of dry benzene under argon was added 19.01 g (52.5 mmol) of 1-(carbethoxy)ethylidene triphenylphosphorane in one portion. The resulting solution was stirred at 75 °C for 4.5 h, and solvent was removed in vacuo. The residue was chromatographed over 150 g of silica gel (eluted with ethyl acetate–hexane, 1:6) to give 13.06 g (94.4%) of ester **15** as a white solid: mp 74–76 °C; IR (CCl_4) 1780, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H, CH_3), 1.63–2.12 (m with d at 1.88, J = 1 Hz, 7 H, =CCH_3, =CCH_2CH_2), 2.55 (dq, J = 19, 2 Hz, 1 H, =CC*H*HCO), 2.85 (dq, J = 19, 4 Hz, 1 H, =CC*H*HCO), 4.20 (q, J = 7 Hz, 2 H, OCH_2), 4.52 (dd, J = 5, 2 Hz, 1 H, ICH), 4.83 (m, 1 H, OCH), 5.40 (ddd, J = 9.5, 3.8, 1.8 Hz, 1 H, =CH), 5.88 (ddd, J = 9.5, 3.6, 1.5 Hz, 1 H, =CH), 6.81 (tq, J = 7.2, 1.3 Hz, 1 H, O=CC=CH); ^{13}C NMR ($CDCl_3$) δ 12.33 (q), 14.24 (q), 22.82 (t), 23.41 (d), 28.78 (t), 30.08 (t), 48.47 (s), 60.49 (t), 76.24 (d), 127.01 (d), 129.52 (s), 130.0 (d), 139.5 (d), 168.00 (s), 171.5 (s); mass spectrum, *m/e* (relative intensity) 390 (M^+, 1), 344 (43), 173 (16), 145 (27), 117 (27), 91 (100), 79 (13); exact mass calcd for $C_{15}H_{19}O_4I$ *m/e* 390.0328, found 390.0343. Anal. Calcd for $C_{15}H_{19}O_4I$: C, 46.15; H, 4.87. Found: C, 46.19; H, 4.83.

***rel*-(1*S*,3a*S*,7*R*,7a*S*)-Ethyl 1,2,3,6,7,7a-Hexahydro-α(*R*)-methyl-9-oxo-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (16), *rel*-(1*R*,3a*S*,7*R*,7a*S*)-Ethyl 1,2,3,6,7,7a-Hexahydro-α(*R* or *S*)-methyl-9-oxo-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (17 or 18) and *rel*-(1*S*,3a*S*,7*R*,7a*S*)-Ethyl 1,2,3,6,7,7a-Hexahydro-α(*S*)-methyl-9-oxo-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (8). Cyclization of 15.** To a solution of 20.3 g (52 mmol) of iodoester **15** and 18 mg of AIBN in 440 mL of dry benzene under argon was added 19.0 mL (72 mmol) of tri-*n*-butyltin hydride in one portion. The reaction mixture was stirred at 60 °C for 3.5 h, and solvent was removed in vacuo. The residue was partitioned between 350 mL of acetonitrile and 170 mL of hexane. The hexane layer was extracted with 100 mL of acetonitrile. The combined acetonitrile layers were washed with three 180-mL portions of hexane and concentrated in vacuo. The residue was recrystallized from ethyl acetate–hexane to give 9.80 g (71.4%) of the major diastereomeric ester **8** as a white solid: mp 79–81 °C; IR (CH_2Cl_2) 1765, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3 H, $OCCH_3$), 1.26 (d, J = 7 Hz, 3 H, CCH_3), 1.40–2.73 (m, 9 H, CH and CH_2 manifold), 4.11 (q, J = 7 Hz, 2 H, OCH_2), 4.90 (m, 1 H, OCH), 5.70 (dt, J = 9, 3 Hz, 1 H, =CH), 6.10 (dt, J = 9, 2 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.21 (q), 18.04 (q), 28.65 (t), 31.05 (t), 34.99 (t), 41.39 (d), 41.71 (d), 52.10 (d), 54.84 (s), 60.36 (t), 75.83 (d), 127.00 (d), 130.23 (d), 175.66 (s), 178.78 (s); mass spectrum, *m/e* (relative intensity) 220 ($M^+ - CO_2$, 1), 119 (100), 118 (47), 117 (35), 91 (28). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.58. Found: C, 68.40; H, 7.70.

The mother liquor was concentrated and purified (multiple runs, combining only pure fractions) by medium-pressure liquid chromtography over a Lobar size C silica gel column (eluted with ethyl acetate–hexane, 1:14) to give, in the order from least polar to most polar, 0.57 g (4%) of ester **16**, 0.56 g (4%) of ester **17**, and 0.72 g (4.2%) of ester **18** as pale yellow oils. For ester **16**: IR (neat) 1765, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 7 Hz, 3 H, CCH_3), 1.26 (t, J = 7 Hz, 3 H, $OCCH_3$), 1.43–2.90 (m, 9 H, CH and CH_2 manifold), 4.16 (q, J = 7 Hz, 2 H, OCH_2), 4.58 (m, 1 H, OCH), 5.71 (dt, J = 9, 3 Hz, 1 H, =CH), 6.05 (dt, J = 9, 2 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.07 (q), 16.75 (q), 28.51 (t), 30.31 (t), 34.58 (t), 39.79 (d), 41.52 (d), 52.72 (d), 54.37 (s), 60.43 (t), 76.04 (d), 127.08 (d), 129.82 (d), 176.70 (s), 179.01 (s); mass spectrum, *m/e* (relative intensity) 220 ($M^+ - CO_2$, 3), 191 (25), 119 (100), 118 (78), 117 (63), 91 (74). For ester **17**: IR (neat) 1775, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 7 Hz, 3 H, CCH_3), 1.26 (t, J = 7 Hz, 3 H, $OCCH_3$), 1.40–2.73 (m, 9 H, CH and CH_2 manifold), 4.16 (q, J = 7 Hz, 2 H, OCH_2), 4.60 (m, 1 H, OCH), 5.68 (dt, J = 9, 3 Hz, 1 H, =CH), 6.00 (dt, J = 9, 2 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.23 (q), 15.92 (q), 26.86 (t), 29.37 (t), 33.36 (t), 42.17 (d), 44.08 (d), 54.08 (s), 55.07 (d), 60.37 (t), 76.77 (d), 126.58 (d), 130.08 (d), 175.24 (s), 179.39 (s); mass spectrum, *m/e* (relative intensity) 191 ($M^+ - CO_2 - C_2H_5$, 2), 119 (100), 118 (43), 117 (30), 91 (34), 41 (6). For ester **18**: IR (neat) 1775, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 7 Hz, 3 H, CCH_3), 1.25 (t, J = 7 Hz, 3 H, $OCCH_3$), 1.43–2.76 (m, 9 H, CH and CH_2 manifold), 4.14 (q, J = 7 Hz, 2 H, OCH_2), 4.72 (m, 1 H, OCH), 5.68 (dt, J = 9, 3 Hz, 1 H, =CH), 6.00 (dt, J = 9, 2 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.17 (q), 14.99 (q), 27.08 (t), 28.99 (t), 33.31 (t), 41.67 (d), 43.26 (d), 53.98 (s), 54.30 (d), 60.32 (t), 77.05 (d), 126.53 (d), 130.08 (d), 174.97 (s), 179.23 (s); mass spectrum, *m/e* (relative intensity) 192 ($M^+ - CO_2 - C_2H_4$, 0.5), 191 ($M^+ - CO_2 - C_2H_5$, 2), 119 (100), 118 (54), 117 (36), 91 (49), 41 (13). Continued elution gave an additional 1.31 g (9.5%) of ester **8** as a white solid: mp 73–78 °C.

The ratio of the four diastereomers was also determined by GLC integration and 500-MHz ^{1}H NMR integration of peaks at δ 4.60, 4.72, and 4.90 due to the C(12) hydrogen of esters **16+17**, **18**, and **8**, respectively. The ratio of esters **16**, **17**, **18**, and **8** was calculated to be 1:2:5:42 from GLC analysis of peaks with retention times of 6.22, 6.52, 6.71, and 6.94 min, respectively, (conditions: HP Ultra-II column, initial temperature 200 °C, 4 °C/min, final temperature 220 °C, final time 6 min). Integration of peaks in the 500-MHz NMR spectrum gave the following ratio of esters **16+17**, **18**, and **8**, respectively, 1:1:15.

***rel*-(1*S*,3a*S*,7*R*,7a*S*)-1,2,3,6,7,7a-Hexahydro-α(*S*)-methyl-9-oxo-7,3a-(epoxymethano)-3a*H*-indene-1-acetic acid (42).** To a solution of 4.05 g (15.34 mmol) of ester **8** in 67 mL of methanol was added 67 mL of 5% aqueous lithium hydroxide in one portion. The resulting solution was stirred under reflux for 4 h, cooled to room temperature, and con-

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(47) Omura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320.

centrated in vacuo to one-third of its original volume. The remaining light green solution was acidified with 3 N aqueous hydrochloric acid (~55 mL) to pH 1 and stirred at 100 °C for 50 min. The cooled solution was saturated with sodium chloride and extracted with four 100-mL portions of dichloromethane. The combined extracts were washed with 200 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The solid residue was recrystallized from ethyl acetate–hexane to give 3.21 g (89%) of acid **42** as a white solid: mp 170–171 °C; IR ($CHCl_3$) 3300–2500 (br), 1765, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.75 (m with d at 1.30, J = 6 Hz, 12 H, CH_3, $=CCH_2$, CH, and CH_2 manifold), 4.90 (m, 1 H, OCH), 5.70 (dt, J = 9, 3 Hz, 1 H, =CH), 6.10 (dt, J = 9, 2 Hz, 1 H, =CH), 10.91 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$) δ 17.78 (q), 28.61 (t), 31.12 (t), 34.95 (t), 41.29 (d d, 2 C's), 52.12 (d), 54.85 (s), 75.79 (d), 127.02 (d), 130.13 (d), 178.74 (s), 181.25 (s); mass spectrum m/e (relative intensity) 147 ($M^+ - CO_2 - CO_2H$, 2), 119 (100), 118 (40), 117 (19), 92 (15), 91 (57), 41 (21). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.14; H, 6.65.

***rel*-(1*R*,3a*S*,7*R*,7a*S*)-1-[2-Hydroxy-1(*S*)-methylethyl]-1,2,3,6,7,7a-hexahydro-7,3a-(epoxymethano)-3a*H*-inden-9-one (44). From 42.** To a mixture of 3.09 g (13.09 mmol) of acid **42** in 25 mL of dichloromethane and 90 mL of dry benzene under argon, cooled in an ice–water bath, was added 8.0 mL (91.65 mmol) of oxalyl chloride over a 15-min period. The mixture was stirred cold for 5 min and then at room temperature for 2.5 h. The clear, light yellow solution was concentrated in vacuo and the solid residue was dissolved in 34 mL of *N*,*N*-dimethylformamide and 100 mL of tetrahydrofuran. To the solution, cooled in a dry ice–acetone bath, was added a suspension of 1.30 g (34.39 mmol) of sodium borohydride in 12 mL of *N*,*N*-dimethylformamide over a 15-min period. The reaction mixture was stirred cold for 15 min and then without cooling for 1.2 h. To the solution, cooled in an ice–water bath, was added dropwise 50 mL of 1 N aqueous hydrochloric acid and the resulting solution was extracted with two 250-mL portions of dichloromethane. The combined extracts were washed with three 100-mL portions of water and 150 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give a light yellow oil. Most of the *N*,*N*-dimethylformamide was removed by drying overnight on a high-vacuum rotary evaporator and the resulting viscous, light yellow oil was recrystallized from ethyl acetate–hexane to give 2.32 g (80%) of alcohol **44** as a white solid (mp 104–107 °C). The mother liquor was heated at 45 °C on a Kugelrohr (0.4 Torr) for 30 min to give an additional 0.64 g (20%) of alcohol **102** as a light yellow oil, which solidified upon standing: mp 98–105 °C; IR (CH_2Cl_2) 3620, 3505, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, J = 7 Hz, 3 H, CH_3), 1.20–2.65 (m, 10 H, OH, CH, and CH_2 manifold), 3.42 (dd, J = 11, 6 Hz, 1 H, OC*H*H), 3.64 (dd, J = 11, 4 Hz, 1 H, OC*H*H), 4.93 (m, 1 H, OCH), 5.70 (dt, J = 9, 3 Hz, 1 H, =CH), 6.11 (dt, J = 9, 2 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 18.04 (q), 28.98 (t), 30.67 (t), 35.15 (t), 36.47 (d), 41.39 (d), 52.54 (d), 54.62 (s), 65.99 (t), 76.38 (d), 127.11 (d), 130.28 (d), 179.38 (s); mass spectrum, m/e (relative intensity) 160 ($M^+ - CO_2 - H_2O$, 1), 147 (2), 119 (100), 117 (16), 91 (51), 69 (30), 41 (16). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.18. Found: C, 69.98; H, 8.04.

From 8. To a suspension of 10.8 mg (0.198 mmol) lithium aluminum hydride in 2.0 mL of dry tetrahydrofuran cooled in an ice bath was added dropwise a solution of 25 mg (0.095 mmol) of lactone **8** in 1 mL of tetrahydrofuran. The reaction mixture was stirred for 1 h followed by sequential addition of 3 mL of ethyl acetate and 25 mL of water. The mixture was filtered, and the residue was transferred with 25 mL of ether. The aqueous layer was extracted with two 50-mL portions of ether, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from ethyl acetate–hexane to give 20 mg (95%) of alcohol **44** as a white solid: mp 103–106 °C.

***rel*-(1*R*,3a*S*,7*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-(*S*)-methylethyl]-1,2,3,6,7,7a-hexahydro-7,3a-(epoxymethano)-3a*H*-inden-9-one (45).** To a solution of 2.90 g (13.06 mmol) of alcohol **44** and 3.03 g (20.07 mmol) of (1,1-dimethylethyl)dimethylsilyl chloride in 23.0 mL of *N*,*N*-dimethylformamide under argon was added 2.31 g (33.97 mmol) of imidazole in one portion, and the resulting solution was stirred at 35 °C for 18.5 h. The solution was diluted with 300 mL of ether and washed with 100 mL of water. The aqueous layer was extracted with two 100-mL portions of ether. The combined extracts were washed with three 100-mL portions of water and 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residual *N*,*N*-dimethylformamide was removed on a high-vacuum rotary evaporator. The solid residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 1:8) to give 4.31 g (98%) of silyl ether **45** as a white solid: mp 56–58 °C; IR (CCl_4) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $C(CH_3)_3$), 1.10 (d, J = 6 Hz, 3 H, CCH_3), 1.15–2.20 (m, 5 H, CH and CH_2 manifold), 2.32 (dd, J = 11.7, 7.3 Hz, 1 H, C*H*H), 2.45 (d, J = 11.7 Hz, 1 H, C*H*H), 2.50–2.60 (m, 2 H, $=CCH_2$), 3.41–3.59 (m, 2 H, OCH_2), 4.85–5.02 (m, 1 H, OCH), 5.70 (dtd, J = 10.2, 3.4, 0.8 Hz, 1 H, =CH), 6.11 (dt, J = 10.2, 1.8 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ −5.60 (q), 18.19 (t), 25.63 (s), 25.83 (q), 28.90 (d), 30.58 (t), 35.06 (t), 36.41 (d), 41.08 (d), 52.41 (d), 54.62 (s), 65.79 (t), 76.34 (d), 127.05 (d), 130.36 (d), 179.40 (s); mass spectrum, m/e (relative intensity) 279 ($M^+ - C_4H_9$, 13), 251 (13), 160 (23), 159 (60), 117 (100), 91 (28).

***rel*-(1*R*,3a*R*,4*S*,5*R*,7*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl)oxy]-1(*S*)-methylethyl]-4,5-epoxy-1,2,3,4,5,6,7,7a-octahydro-7,3a-(epoxymethano)-3a*H*-inden-9-one (62).** A solution of 4.31 g (128 mmol) of olefin **45** and 5.41 g (260 mmol) of *m*-chloroperbenzoic acid in 130 mL of dichloromethane was stirred at room temperature for 68 h and diluted with 300 mL of dichloromethane. The solution was washed with 100 mL of saturated aqueous sodium bisulfite and 100 mL of saturated aqueous sodium bicarbonate. This procedure was repeated three times. The extract was washed with 120 mL of water and 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 1:7) to give 3.93 g (87%) of epoxide **62** as a white solid: mp 68–71 °C; IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $C(CH_3)_3$), 1.08 (d, J = 6.4 Hz, 3 H, CH_3), 1.20–2.35 (m with td at 1.66, J = 12, 6 Hz, and dd at 2.28, J = 12, 6 Hz, 9 H, CH and CH_2 manifold), 2.70 (d, J = 10.8 Hz, 1 H, OCH), 3.08 (octet, J = 1.5 Hz, 1 H, OCH), 3.42 (dd, J = 9.5, 5.4 Hz, 1 H, OC*H*H), 3.48 (dd, J = 9.5, 3.4 Hz, 1 H, OC*H*H), 4.69 (m, 1 H, O=COCH); ^{13}C NMR ($CDCl_3$) δ −5.58 (q), −5.55 (q), 18.07 (q), 18.21 (s), 25.83 (q), 28.60 (t), 30.72 (t), 31.37 (t), 36.35 (d), 40.55 (d), 45.38 (d), 48.04 (d), 52.13 (d), 56.12 (s), 65.67 (t), 76.06 (d), 178.23 (s); mass spectrum, m/e (relative intensity) 295 ($M^+ - C_4H_9$, 29), 175 (25), 159 (19), 157 (19), 133 (36), 117 (54), 89 (26), 75 (91). Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15. Found: C, 64.97; H, 8.82.

***rel*-(1*R*,3a*R*,4*R*,7*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-1(*S*)-methylethyl]-1,2,3,4,7,7a-hexahydro-4-hydroxy-7,3a-(epoxy-methano)-3a*H*-inden-9-one (63).** To a solution of 0.42 mL (4.06 mmol) of diethylamine in 6.7 mL of ether under argon, cooled in an ice–water bath, was added 2.5 mL (3.69 mmol) of *n*-butyllithium in hexane (1.50 M) over a 6-min period, and the resulting solution was stirred cold for 10 min and then at room temperature for 25 min. To a solution of 500 mg (1.42 mmol) of epoxide **62** in 11.0 mL of ether at room temperature was added the lithium diethylamide solution over a 1-min period, and the resulting yellow mixture was stirred for 15 min. The reaction was quenched with 5 mL of water, neutralized with 10 mL of saturated aqueous ammonia chloride, and extracted with two 70-mL portions of dichloromethane. The combined extracts were washed with 30 mL of 1 N aqueous hydrochloric acid, 30 mL of water, and 30 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to give 349 mg (69%) of allylic alcohol **63** as a white solid: mp 116.5–117.5 °C; IR ($CHCl_3$) 3420 (br), 1765, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 1.08 (d, J = 6.3 Hz, 3 H, CH_3), 1.31 (qd, J = 12.3, 6 Hz, 1 H, C*H*H), 1.51–1.62 (m, 1 H, CH), 1.76–2.04 (m, 4 H, OH, CH, CH_2), 2.13 (dd, J = 12, 6 Hz, 1 H, C*H*H), 2.83 (d, J = 10.7 Hz, 1 H, CH), 3.47 (dd, J = 9.8, 5.4 Hz, 1 H, OC*H*H), 3.53 (dd, J = 9.8, 3.1 Hz, 1 H, OC*H*H), 4.46 (m, 1 H, OCH), 4.90 (d, J = 5.6 Hz, 1 H, O=COCH), 5.92 (ddd, J = 9.2, 4.2, 0.5 Hz, 1 H, =CH), 6.47 (ddd, J = 9.1, 5.3, 0.4 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ −5.49 (q), 18.02 (q), 18.28 (s), 25.94 (q), 28.75 (t), 30.10 (t), 36.67 (d), 41.72 (d), 47.41 (d), 61.40 (s), 65.93 (t), 67.40 (d), 75.07 (d), 133.52 (d), 134.73 (d), 181.04 (s); mass spectrum, m/e (relative intensity) 295 ($M^+ - C_4H_9$, 3), 265 (10), 175 (43), 157 (19), 133 (81), 131 (22), 117 (28), 91 (9), 75 (45), 73 (24), 69 (74). Anal. Calcd for $C_{19}H_{32}O_4$: C, 64.73; H, 9.15. Found: C, 64.77; H, 9.04.

***rel*-(1*R*,3a*R*,4*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-(*S*)-methylethyl]-1,2,3,4,5,6,7,7a-octahydro-4-hydroxy-3a*H*-indene-3a-carboxylic Acid (64). From Lactone 63.** To a solution of 166 mg (0.472 mmol) of lactone **63** in 10 mL of freshly distilled ethylamine under argon was added 55 mg (7.9 mmol) of freshly cut lithium wire in small portions, and the mixture was stirred until it turned dark blue. The dark blue solution was stirred for an additional 1.5 h followed by careful addition of 1.0 mL of methanol to discharge the color. The excess of lithium was removed, and solvent was evaporated in vacuo. The residue was dissolved in 30 mL of 1 N aqueous hydrochloric acid and extracted with three 25-mL portions of dichloromethane. The combined extracts were washed with 30 mL of 1 N aqueous hydrochloric acid and 30 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate–hexane, 1:6 progressing to 1:2) to give 108 mg (67%) of acid **64** as an oil: IR (neat) 3550–2500 (br), 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $Si(CH_3)_2$), 0.92 (s, 9 H, $C(CH_3)_3$), 1.02 (d, J = 5 Hz, 3 H, CH_3), 1.3–2.2 (m, 14 H, OH, CH, and CH_2 manifold), 3.33 (dd, J = 9.8, 5.4 Hz, 1 H, OC*H*H), 3.50 (dd, J = 9.8, 2.7 Hz, 1 H, OC*H*H), 4.34 (m, 1 H, OCH), acid proton was not observed; ^{13}C NMR ($CDCl_3$) δ −5.44 (q), 18.28 (q, s, 2 C's), 20.68 (t), 25.07 (t), 25.92 (q), 28.26 (t), 30.16 (t), 32.13 (t), 38.02 (d), 41.25 (d), 41.72 (d), 58.80 (s), 67.34 (t), 69.23 (d), 181.64 (s); mass

spectrum, *m/e* (relative intensity) 299 ($M^+ - C_4H_9$, 1), 281 ($M^+ - C_4H_9 - H_2O$, 10), 161 (100), 121 (16), 119 (27), 105 (16), 91 (21), 75 (97), 73 (25).

From Epoxide 62. To a solution of 0.34 mL (3.28 mmol) of diethylamine in 5.4 mL of ether under argon, cooled in an ice–water bath, was added 2.0 mL (3.05 mmol) of *n*-butyllithium in hexane (1.54 M) over a 6-min period, and the resulting solution was stirred cold for 20 min and then at room temperature for 40 min. To a solution of 500 mg (1.42 mmol) of epoxide **62** in 11 mL of ether at room temperature was added the lithium diethylamide solution over a 4-min period, and the mixture was stirred for 40 min. The solvent was removed in vacuo. To the dark red solid residue was added 20 mL of freshly distilled ethylamine followed by 160 mg (23 mmol) of freshly cut lithium wire in small portions. The mixture was stirred until it turned dark blue (~25 min). The dark blue solution was stirred at room temperature for an additional 1.2 h and carefully quenched with dropwise addition of 10 mL of methanol. The solvent was removed in vacuo. The residue, cooled in an ice–water bath, was dissolved, acidified with 25 mL of 1 N aqueous hydrochloric acid, and extracted with 175 mL of dichloromethane. The extract was washed with 40 mL of 1 N aqueous hydrochloric acid, 40 mL of water, and 50 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to give 285 mg (56%) of alcohol **64** as an oil. The material was identical by 200-MHz ^1H NMR with alcohol **64** prepared by reduction of lactone **63**.

***rel*-(1*R*,3a*R*,4*R*,7a*S*)-Methyl 1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,4,5,6,7,7a-octahydro-4-hydroxy-3a*H*-indene-3a-carboxylate (65). From Epoxide 62.** To a solution of 0.80 mL (7.77 mmol) of diethylamine in 12.8 mL of ether under argon, cooled in an ice–water bath, was added 4.6 mL (6.94 mmol) of 1.50 M *n*-butyllithium in hexane over a 6-min period, and the resulting solution was stirred cold for 10 min and then at room temperature for 40 min. To a solution of 1.23 g (3.494 mmol) of epoxide **62** in 30 mL of ether at room temperature was added the lithium diethylamide solution over a 6-min period, and the mixture was stirred for 30 min. The solvent was removed in vacuo. To the dark red solid residue, cooled in a dry ice–acetone bath, was added 406 mg (58 mmol) of freshly cut lithium wire in small pieces followed by addition of 55 mL of freshly distilled ethylamine in one portion. The mixture was stirred cold for 5 min and then at room temperature until it turned dark blue (~8 min). The dark blue solution was stirred at room temperature for an additional 1 h and carefully quenched with dropwise addition of 15 mL of methanol. The solvent was removed in vacuo. The residue, cooled in an ice–water bath, was dissolved in 1 N aqueous hydrochloric acid and extracted with three 65-mL portions of dichloromethane. The combined extracts were washed with 50 mL of water and 50 mL of brine. The aqueous layers were extracted with 100 mL of dichloromethane, and the combined extracts were treated with diazomethane, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate–hexane, 1:8) to give 752 mg (58%) of ester **65** as a pale yellow oil: IR (neat) 3450, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 1.03 (d, J = 6 Hz, 3 H, CH_3), 1.13–2.40 (m, 14 H, OH, CH, and CH_2 manifold), 3.33 (dd, J = 10.5, 5.5 Hz, 1 H, OC*H*H), 3.46 (dd, J = 10.5, 2.1 Hz, 1 H, OC*H*H), 3.59 (s, 3 H, OCH_3), 4.25 (m, 1 H, OCH); ^{13}C NMR ($CDCl_3$) δ −5.50 (q), 18.21 (q, s, 2 C's), 20.60 (t), 25.13 (t), 25.87 (q), 28.28 (t), 30.17 (t), 31.96 (t), 38.05 (d), 41.12 (d), 41.83 (d), 51.26 (q), 58.82 (s), 67.25 (t), 69.04 (d), 176.02 (s); mass spectrum, *m/e* (relative intensity) 355 ($M^+ - CH_3$, 2), 339 ($M^+ - CH_3O$, 1), 314 (24), 313 (100), 161 (43), 133 (15), 119 (33), 91 (23), 89 (38), 75 (40), 73 (32), 57 (30), 55 (29).

***rel*-(1*R*,3a*R*,7a*S*)-Methyl 1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,4,5,6,7,7a-octahydro-4-oxo-3a*H*-indene-3a-carboxylate (48).** To a solution of 0.57 mL (6.53 mmol) of oxalyl chloride in 10.5 mL of dichloromethane under argon, cooled in a dry ice–acetone bath, was added a solution of 0.91 mL (12.83 mmol) of dimethyl sulfoxide in 2.1 mL of dichloromethane over a 6-min period. The resulting mixture was stirred cold for 25 min. To the mixture was added a solution of 1.56 g (4.21 mmol) of alcohol **65** in 5.0 mL of dichloromethane over a 6-min period, and the mixture was stirred cold for 1 h. To the mixture was added 3.4 mL (24.4 mmol) of triethylamine over a 5-min period, and the mixture was stirred cold for 15 min and then without cooling for 50 min. The resulting mixture was poured into 10 mL of water and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined extracts were washed with 70 mL of 1 N aqueous hydrochloric acid, 50 mL of water, and 50 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate–hexane, 1:20, then 1:10) to give 1.37 g (88%) of ketone **48** as an oil: IR (neat) 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 1.06 (d, J = 6 Hz, 3 H, CH_3), 1.46–2.60 (m, 13 H, CH and CH_2 manifold), 3.45 (dd, J = 16.5, 5 Hz, 1 H, OC*H*H), 3.51 (dd, J = 16.5, 3 Hz, 1 H, OC*H*H), 3.66 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ −5.60 (q), 18.13 (s), 18.16 (q), 24.04 (t), 25.77 (q), 27.38 (t), 27.72 (t), 30.01 (t), 37.53 (d), 39.36 (t), 42.12 (d), 51.90 (q), 53.92 (d), 66.77 (t), 67.42 (s), 171.57 (s), 206.44 (s); mass spectrum, *m/e* (relative intensity) 353 ($M^+ - CH_3$, 2), 311 ($M^+ - C_4H_9$, 100), 235 (18), 177 (32), 159 (40), 149 (15), 147 (15), 119 (29), 117 (18), 107 (19), 91 (31), 89 (86), 81 (21), 79 (29), 77 (18), 75 (74), 73 (60), 59 (31), 55 (21).

***rel*-(1*S*,3a*R*,4*R*,7a*S*)-Methyl 1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,4,5,6,7,7a-octahydro-4-hydroxy-4-[(2,5-dimethoxyphenyl)methyl]-3a*H*-indene-1-carboxylate (69).** To a suspension of 2.55 g (10.34 mmol) of cerium trichloride in 60 mL of tetrahydrofuran, which had been stirred at room temperature for 19 h, cooled in a dry ice–acetone bath, was added under argon 29 mL (11.36 mmol) of 2,5-dimethoxybenzylmagnesium chloride (0.39 M) over 1 h, and the resulting greenish mixture was stirred cold for 35 min. To the mixture was added a solution of 1.37 g (3.72 mmol) of ketone **48** in 14 mL of tetrahydrofuran via cannula over a 15-min period, and the resulting solution was stirred cold for 2 h. To the mixture at −78 °C was added 15 mL of water. The mixture was allowed to warm to room temperature and extracted with two 200-mL aliquots of dichloromethane. The combined extracts were washed with 70 mL of saturated aqueous ammonium chloride and 70 mL of brine. The aqueous layers were extracted with 100 mL of dichloromethane, and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 1:50 progressing to 1:15) to give 0.8 g of impure material and 1.174 g (60%) of alcohol **69** as a white solid: mp 90–90.5 °C; IR (CH_2Cl_2) 3510, 1710, 1605, 1590, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 0.98 (d, J = 6.4 Hz, 3 H, $CHCH_3$), 1.15–2.32 (m with d at 2.28, J = 14 Hz, 14 H, ArCH, CH, and CH_2 manifold), 3.13 (d, J = 14 Hz, 1 H, ArCH), 3.30 (dd, J = 9.6, 6.6 Hz, 1 H, OC*H*H), 3.40 (br s, 1 H, OH), 3.50 (dd, J = 9.7, 3.2 Hz, 1 H, OC*H*H), 3.68 (s, 3 H, O=$COCH_3$), 3.75 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 6.63 (d, J = 2.8 Hz, 1 H, aromatic), 6.72 (dd, J = 8.8, 2.9 Hz, 1 H, aromatic), 6.79 (d, J = 8.9 Hz, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) δ −5.37 (q), 17.96 (q), 18.27 (s), 22.28 (t), 25.16 (t), 25.92 (q), 26.96 (t), 28.11 (t), 32.31 (t), 38.50 (d), 40.28 (t), 41.86 (d), 46.94 (d), 51.20 (q), 55.66 (q), 56.01 (q), 61.15 (s), 67.18 (t), 74.52 (s), 111.41 (d), 112.06 (d), 118.97 (d), 126.72 (s), 151.55 (s), 153.66 (s), 176.17 (s); mass spectrum, *m/e* (relative intensity) 520 (M^+, 1), 464 (2), 463 (6), 302 (11), 177 (20), 152 (90), 151 (73), 91 (17), 75 (13), 73 (16); exact mass calcd for $C_{29}H_{48}O_6Si$ *m/e* 520.3220, found *m/e* 520.3258. Anal. Calcd for $C_{29}H_{48}O_6Si$: C, 66.88; H, 9.29. Found: C, 67.51; H, 9.15.

The impure sample was purified by medium-pressure liquid chromatography over a Lobar size B silica gel column (eluted with ethyl acetate–hexane, 1:50 progressing to 1:10) to give an additional 0.61 g (31%) of alcohol **69** as a white solid.

***rel*-(1*S*,3a*R*,7a*S*)-Methyl 1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,6,7,7a-hexahydro-4-[(2,5-dimethoxyphenyl)methyl]-3a*H*-indene-1-carboxylate (71) and *rel*-(1*S*,3a*R*,7a*S*)-Methyl 1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,4,5,6,7,7a-octahydro-4(*E*)-[(2,5-dimethoxyphenyl)methylene]-3a*H*-indene-1-carboxylate (70).** To a solution of 1.66 g (3.19 mmol) of alcohol **69** in 26 mL of pyridine under argon, cooled in an ice–water bath, was added 3.8 mL (53 mmol) of thionyl chloride over a 6-min period, and the resulting yellow mixture was stirred cold for 1 h. The reaction was carefully quenched, cooled in a dry ice–carbon tetrachloride bath, with 15 mL of water. The mixture was poured into 100 mL of 1 N aqueous hydrochloric acid and 200 mL of dichloromethane. The aqueous layer was extracted with two 150-mL portions of dichloromethane, and the combined extracts were washed with 200 mL of 1 N aqueous hydrochloric acid, 150 mL of saturated aqueous sodium bicarbonate, and 150 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:20) to give 1.60 g (quantitative) of an inseparable 1:1 mixture of olefins **71** and **70** as a pale yellow oil: IR (neat) 1720 (strong), 1645, 1600, 1580, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, as a 1:1 mixture of isomers) δ 0.01 and 0.02 (2 s, 6 H, $Si(CH_3)_2$), 0.88 and 0.89 (2 s, 9 H, $C(CH_3)_3$), 0.99 and 1.07 (2 d, $J_1 = J_2$ = 6.5 Hz, 3 H, CH_3), 1.15–2.90 (m, 13 H, CH and CH_2 manifold), 3.15–4.00 (m with 2 s at 3.50 and 3.63, 11 H, OCH_2, O=$COCH_3$, OCH_3, OCH_3), 5.19 and 6.37 (2 m, 1 H, =CH), 6.55–6.98 (m, 3 H, aromatic); mass spectrum, *m/e* 502 (M^+, 3), 445 (16), 311 (20), 302 (32), 177 (5), 151 (61), 121 (19), 91 (12), 89 (12), 75 (11), 73 (12), 41 (12); exact mass calcd for $C_{29}H_{46}O_5Si$ *m/e* 502.3114, found *m/e* 502.3121.

***rel*-(1*S*,3a*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,6,7,7a-hexahydro-3a-(hydroxymethyl)-4-[(2,5-dimethoxyphenyl)methyl]-3a*H*-indene (73) and *rel*-(1*S*,3a*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1(*S*)-methylethyl]-1,2,3,4,5,6,7,7a-octahydro-3a-(hydroxymethyl)-4(*E*)-[(2,5-dimethoxy-**

phenyl)methylene]-3a*H*-indene (72). To a suspension of 0.46 g (3.20 mmol) of lithium aluminum hydride in 13 mL of dry ether under argon, cooled in an ice–water bath, was added a solution of 1.63 g (3.25 mmol) of esters **71** and **70** (~1:1, respectively) in 24 mL of ether over a 10-min period. The resulting mixture was stirred cold for 30 min, at room temperature for 1 h, and then under reflux for 1 h. The reaction was carefully quenched with cooling by sequential addition of 0.46 mL of water, 0.92 mL of 15% aqueous sodium hydroxide, and 0.46 mL of water. The mixture was stirred cold for 5 min and at room temperature for 10 min and filtered. The filtrate was concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:30 progressing to 1:3) to give 0.667 g (43%) of alcohol **73** as a white solid: mp 68–71 °C; IR (CCl_4) 3530, 1610, 1590, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $C(CH_3)_3$), 1.03 (d, J = 6 Hz, 3 H, CH_3), 1.18–2.15 (m, 11 H, CH and CH_2 manifold), 3.07 (dd, J = 16.5, 1.8 Hz, 1 H, ArCH), 3.33–3.82 (m with 2 s at 3.73 and 3.76, 12 H, =CC*H*H, OCH_2, CH_2OH, OCH_3, OCH_3), 5.00 (m, 1 H, =CH), 6.67–6.86 (m, 3 H, aromatic); ^{13}C NMR ($CDCl_3$) δ −5.42 (q), 18.29 (s), 18.68 (q), 21.17 (t), 25.93 (q), 27.16 (t), 27.90 (t), 32.06 (t), 33.82 (t), 39.18 (d), 41.78 (d), 49.22 (d), 50.94 (s), 55.62 (q), 55.88 (q), 65.85 (t), 67.27 (t), 111.24 (d), 111.39 (d), 117.96 (d), 124.23 (d), 129.66 (s), 140.74 (s), 151.18 (s), 153.59 (s); mass spectrum, m/e (relative intensity) 444 ($M^+ - CH_2O$, 5), 387 (11), 312 (12), 269 (10), 173 (9), 162 (8), 161 (69), 152 (21), 151 (100), 131 (9), 119 (11), 117 (8), 91 (16), 75 (14), 73 (16), 41 (10). Anal. Calcd for $C_{28}H_{46}O_4Si$: C, 70.84; H, 9.77. Found: C, 70.15; H, 9.77.

Further elution gave 0.771 g (50%) of alcohol **72** as a white solid: mp 81–83 °C; IR (CH_2Cl_2) 3510, 1640, 1600, 1580, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 1.00 (d, J = 6.5 Hz, 3 H, CH_3), 1.10–2.00 (m, 11 H, CH and CH_2 manifold), 2.12 (dd, J = 11.5, 7.3 Hz, 1 H, C*H*H), 2.45 (dd, J = 14, 5 Hz, 1 H, =CC*H*H), 3.30–3.50 (m with dd at 3.39, J = 9.7, 3.5 Hz and d at 3.40, J = 10.6 Hz, 2 H, SiOC*H*H and OC*H*H), 3.57 (dd, J = 9.7, 3.5 Hz, 1 H, SiOC*H*H), 3.66–3.80 (m with 2 s at 3.72 and 3.74, 8 H, *H*OC*H*H, OCH_3, OCH_3), 6.16 (br s, 1 H, =CH), 6.62–6.83 (m, 3 H, aromatic); ^{13}C NMR ($CDCl_3$) δ −5.41 (q), 18.29 (s), 18.66 (q), 24.36 (t), 25.20 (t), 25.93 (q), 26.35 (t), 28.07 (t), 31.48 (t), 39.34 (d), 42.35 (d), 51.55 (d), 54.60 (s), 55.71 (q), 55.96 (q), 60.50 (t), 67.04 (t), 111.26 (d), 112.08 (d), 116.34 (d), 119.73 (d), 127.85 (s), 145.84 (s), 151.25 (s), 153.16 (s); mass spectrum, m/e (relative intensity) 474 (M^+, 1), 444 (9), 387 (14), 312 (13), 161 (59), 152 (11), 151 (48), 119 (12), 91 (11), 75 (15), 73 (15), 57 (11), 55 (11), 43 (10), 41 (13); exact mass calcd for $C_{28}H_{46}O_4Si$ m/e 474.3165, found m/e 474.3169.

***rel*-(1*S*,3a*R*,7a*S*)-1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-(*S*)-methylethyl]-3a-formyl-1,2,3,6,7,7a-hexahydro-4-[(2,5-dimethoxyphenyl)methyl]-3a*H*-indene (74).** To a solution of 0.31 mL (3.55 mmol) of oxalyl chloride in 5.5 mL of dichloromethane under argon, cooled in a dry ice–acetone bath, was added a solution of 0.55 mL (7.76 mmol) of dimethyl sulfoxide in 1.5 mL of dichloromethane dropwise over an 8-min period. The resulting mixture was stirred cold for 30 min. To the solution was added a solution of 778 mg (1.64 mmol) of alcohol **73** in 4.5 mL of dichloromethane over a 10-min period. The reaction mixture was stirred cold for 1 h. To the mixture was added 1.83 mL (13.1 mmol) of triethylamine over a 6-min period, and the resulting viscous mixture was stirred cold for 20 min and then without cooling for 30 min. The resulting solution was poured into 50 mL of 1 N aqueous hydrochloric acid and 150 mL of dichloromethane. The aqueous layer was extracted with two 175-mL portions of dichloromethane. The combined extracts were washed with 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:50 progressing to 1:10) to give 658 mg (85%) of aldehyde **74** as an oil: IR (neat) 2720, 1708, 1610, 1590, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $C(CH_3)_3$), 1.00 (d, J = 6.5 Hz, 3 H, CH_3), 1.20–2.38 (m, 10 H, CH and CH_2 manifold), 2.44 (ddd, J = 12, 8.6, 1.1 Hz, 1 H, =CC*H*H), 3.04 (d, J = 16 Hz, 1 H, ArCH), 3.16 (d, J = 16 Hz, 1 H, ArCH), 3.36 (dd, J = 9.7, 6 Hz, 1 H, OC*H*H), 3.46 (dd, J = 9.8, 3.3 Hz, 1 H, OC*H*H), 3.72 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 5.31 (m, 1 H, =CH), 6.63 (d, J = 2.7 Hz, 1 H, aromatic), 6.70 (dd, J = 8.8, 2.8 Hz, 1 H, aromatic), 6.76 (d, J = 8.7 Hz, 1 H, aromatic), 9.72 (d, J = 1.4 Hz, 1 H, O=CH); ^{13}C NMR ($CDCl_3$) δ −5.45 (q), −5.49 (q), 18.14 (q), 18.26 (s), 21.21 (t), 25.90 (q), 27.33 (t), 27.64 (t), 28.43 (t), 32.60 (t), 37.90 (d), 41.72 (d), 50.46 (d), 55.64 (q), 56.15 (q), 61.53 (s), 66.69 (t), 111.45 (d), 111.73 (d), 117.32 (d), 127.34 (d), 129.18 (s), 134.91 (s), 151.88 (s), 153.38 (s), 201.39 (s); mass spectrum, m/e (relative intensity) 442 ($M^+ - CH_2O$, 2), 385 (7), 310 (10), 166 (9), 161 (16), 159 (10), 152 (23), 151 (93), 149 (28), 117 (12), 109 (11), 97 (16), 95 (15), 91 (15), 85 (14), 83 (19), 82 (11), 81 (22), 75 (34), 73 (31), 71 (26), 57 (45), 55 (33), 43 (39), 41 (40).

***rel*-(3*S*,4*S*,4a*S*,12b*S*,12c*R*)-2,3,4,4a,5,6,8,12b-Octahydro-9,12-dimethoxy-3-methyl-12c*H*-4,12c-ethanoanthra[9,1-*bc*]oxepin (76) and (79).** A mixture of 610 mg (1.29 mmol) of aldehyde **74** and 0.45 g of acid-washed Dowex-50w resin in 62 mL of absolute methanol was stirred at room temperature for 18 h, and the mixture was filtered. This filtrate was concentrated in vacuo to give 477 mg (99%) of crude acetal **75** as an oil. This material was used in subsequent reactions without full characterization or further purification.

To a solution of 223 mg (0.599 mmol) of crude acetal **75** in 148 mL of dry toluene under argon, cooled in a dry ice–carbon tetrachloride bath, was added 0.40 mL (3.25 mmol) of boron trifluoride etherate over a 4-min period, and the resulting yellow solution was stirred cold for 2.2 h. The reaction was quenched cold with 2 mL of saturated aqueous sodium bicarbonate, and the mixture was extracted with three 50-mL portions of dichloromethane. The combined extracts were washed with 70 mL of water and 70 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:40 progressing to 1:20) to give 106 mg (52%) of pentacyclic ether **76** as a white solid: mp 135.5–136.5 °C; IR (CH_2Cl_2) 1660, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 7 Hz, 3 H, CH_3), 1.37 (td, J = 11.4, 6.3 Hz, 1 H, CH), 1.67–2.28 (m, 10 H, CH and CH_2 manifold), 3.12 (d, J = 6.8 Hz, 1 H, =CC*H*H), 3.31 (dm, J = 6.8 Hz, 1 H =CC*H*H), 3.51 (dd, J = 12.2, 6.7 Hz, 1 H, OC*H*H), 3.76 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.98 (dd, J = 12.3, 8.5 Hz, 1 H, OC*H*H), 4.62 (br s, 1 H, OCH), 5.37 (m, 1 H, =CH), 6.66 (s, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 19.77 (t), 21.09 (q), 25.63 (t), 27.14 (t), 31.61 (t), 31.76 (t), 32.21 (d), 45.49 (d), 49.16 (s), 49.43 (d), 55.73 (q), 56.27 (q), 74.23 (t), 79.25 (d), 108.86 (d), 109.37 (d), 119.43 (d), 128.24 (s), 129.64 (s), 140.04 (s), 150.23 (s), 154.27 (s); mass spectrum, m/e (relative intensity) 340 (M^+, 57), 325 (19), 311 (7), 281 (6), 201 (10), 119 (8), 91 (7), 41 (12); exact mass calcd for $C_{22}H_{28}O_3$ m/e 340.2039, found m/e 340.2021. Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 76.96; H, 8.45.

The mother liquor was purified by medium-pressure liquid chromatography over a Lobar size A silica gel column (eluted with ethyl acetate–hexane, 1:40) to give 24 mg (11%) of a mixture of acetal **75** and cyclic ether **76** as an oil. Continued elution gave 17 mg (9%) of isomeric cyclic ether **79** as a pale yellow solid: IR (CH_2Cl_2) 2840, 1590, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (d, J = 6.5 Hz, 3 H, CH_3), 0.80–2.62 (m, 11 H, CH and CH_2 manifold), 3.23 (t, J = 11.4 Hz, 1 H, ArCH), 3.53 (br s, 2 H, OCH_2), 3.70–3.90 (m with 2 s at 3.77 and 3.79, 7 H, ArCH, OCH_3, OCH_3), 4.10 (br s, 1 H, OCH), 5.73 (ddd, J = 8.3, 5.7, 2.6 Hz, 1 H, =CH), 6.66 (s, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.70 (q), 18.80 (t), 21.32 (t), 24.62 (t), 27.57 (d), 31.60 (t), 34.95 (t), 44.25 (d), 46.98 (d), 54.73 (d), 55.46 (q), 55.70 (q), 66.84 (t), 81.61 (s), 108.46 (d), 109.06 (d), 120.79 (d), 132.09 (s), 134.03 (s), 142.50 (s), 149.96 (s), 151.16 (s); mass spectrum (GC–MS), m/e (relative intensity) 340 (M^+, 100), 325 (4), 312 (11), 311 (43), 281 (25), 253 (7), 241 (14), 239 (9), 215 (11), 202 (60), 201 (22), 189 (18), 187 (38), 175 (13), 159 (19), 128 (19), 115 (25), 67 (23), 55 (37), 41 (54), 39 (17).

***rel*-(3*S*,4*S*,4a*S*,7*R*,7a*R*,12b*S*,12c*R*)-2,3,4,4a,5,6,7,7a,8,12b-Decahydro-7-hydroxy-9,12-dimethoxy-3-methyl-12c*H*-4,12c-ethanoanthra[9,1-*bc*]oxepin (80).** To a degassed solution of 191 mg (0.562 mmol) of olefin **76** in 6.0 mL of tetrahydrofuran, cooled in an ice–water bath, was added 0.85 mL (0.85 mmol) of borane–tetrahydrofuran complex solution (1.0 M) over a 7-min period, and the resulting solution was stirred cold for 1.25 h. To the solution, cooled in an ice–water bath, was carefully added 0.85 mL of degassed absolute ethanol, and the solution was stirred at room temperature until gas evolution ceased. To the solution was added 0.85 mL of 6 N aqueous sodium hydroxide, and the resulting mixture was stirred until gas evolution ceased. To the mixture, cooled in an ice–water bath, was added 1.70 mL of 30% hydrogen peroxide over a 5-min period, and the mixture was stirred at room temperature for 5 min and then at 50 °C for 2.5 h. To the cooled mixture was added 10 mL of saturated aqueous ammonium chloride, and the mixture was extracted with two 60-mL portions of dichloromethane. The combined extracts were washed with 20 mL of water and 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was passed through 0.5 g of silica gel (eluted with dichloromethane and then ethyl acetate) and concentrated in vacuo. The residue was recrystallized from ethyl acetate–hexane to give 153 mg (76%) of alcohol **80** as a white solid: mp 164–165.5 °C; IR ($CHCl_3$) 3600, 3440, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 3 H, CH_3), 1.13–2.28 (m with 2 ddd at 1.38, J = 17, 12, 4.5 Hz, and 2.18, J = 12, 9, 2.8 Hz, 13 H, OH, CH, and CH_2 manifold), 2.58 (dd, J = 17.8, 4.9 Hz, 1 H, ArCH), 3.10 (dd, J = 17.8, 1.7 Hz, 1 H, ArCH), 3.31 (td, J = 10.9, 4.7 Hz, 1 H, HOC*H*), 3.42 (dd, J = 12.2, 7.2 Hz, 1 H, OC*H*H), 3.75 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.98 (dd, J = 12.2, 8.7 Hz, 1 H, OC*H*H), 4.53 (s, 1 H, OCH), 6.53 and 6.68 (AB q, J_{AB} = 9 Hz, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 20.92 (q), 21.00 (t), 21.52 (t), 25.83 (t), 31.82 (d), 34.81 (t), 35.61 (t), 45.90 (d), 48.34 (s), 50.95 (d), 52.27 (d) 55.73 (q), 56.06 (q), 68.10 (d), 72.90 (d), 73.78 (t), 108.78 (d), 109.06 (d), 125.60 (s), 126.33 (s), 151.10 (s), 153.70 (s); mass spectrum, m/e (relative intensity) 358 (M^+, 63), 241 (6), 193 (7), 181 (8), 180 (9), 165 (8), 135 (6), 119 (14), 91 (8); exact mass calcd for $C_{22}H_{30}O_4$ m/e 358.2144, found m/e 358.2169.

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.44; H, 8.42.

The mother liquor was chromatographed over 10 g of silica gel (eluted with ethyl acetate–hexane, 1:10 progressing to 1:2) to give an additional 28 mg (14%) of alcohol **80** as a white solid.

***rel*-(3*S*,4*S*,4a*S*,7a*R*,12b*S*,12c*R*)-2,3,4,4a,5,6,7,7a,8,12b-Decahydro-9,12-dimethoxy-3-methyl-7-oxo-12c*H*-4,12c-ethanoanthra[9,1-*bc*]oxepin (81).** To a solution of 95 μL (1.09 mmol) of oxalyl chloride in 1.7 mL of dichloromethane under argon, cooled in a dry ice–acetone bath, was added a solution of 153 mL (2.16 mmol) of dimethyl sulfoxide in 0.45 mL of dichloromethane over a 6-min period. The resulting mixture was stirred cold for 23 min. To the mixture was added a solution of 129 mg (0.36 mmol) of alcohol **80** in 1.5 mL of dichloromethane over a 6-min period, and the mixture was stirred cold for 50 min. To the mixture was added 0.51 mL (3.67 mmol) of triethylamine over a 4-min period, and the mixture was stirred cold for 10 min and then without cooling for 50 min. The resulting mixture was poured into 10 mL of water and 15 mL of dichloromethane. The aqueous layer was extracted with two 10-mL portions of dichloromethane. The combined extracts were washed with 10 mL of 1 N aqueous hydrochloric acid and 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 7 g of silica gel (eluted with ethyl acetate–hexane, 1:10 progressing to 1:4) to give 118 mg (92%) of ketone **81** as a white solid: mp 207.5–208.5 °C; IR ($CHCl_3$) 1708, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, J = 6.9 Hz, 3 H, CH_3), 1.45 (td, J = 11.5, 6.6 Hz, 1 H, CH), 1.78–2.55 (m, 11 H, ArCH, CH, and CH_2 manifold), 2.66 (d, J = 5 Hz, 1 H, O=CCH), 3.20 (d, J = 17.7 Hz, 1 H, ArCH), 3.55 (dd, J = 12.7, 5.6 Hz, 1 H, OC*H*H), 3.74 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.98 (dd, J = 12.6, 8.7 Hz, 1 H, OC*H*H), 4.38 (s, 1 H, OCH), 6.61 and 6.65 (AB q, J_{AB} = 8.8 Hz, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 20.17 (t), 21.12 (q), 22.46 (t), 26.25 (t), 32.45 (d), 34.56 (t), 40.06 (t), 45.31 (d), 50.93 (d), 51.04 (s), 55.46 (d), 55.61 (q), 55.90 (q), 74.06 (d), 74.53 (t), 108.63 (d), 108.83 (d), 125.30 (s), 126.02 (s), 150.51 (s), 154.54 (s), 210 (s); mass spectrum, m/e (relative intensity) 356 (M^+, 97), 326 (11), 325 (39), 217 (18), 180 (21), 165 (12), 119 (16), 91 (10), 81 (8), 41 (12); exact mass calcd for $C_{22}H_{28}O_4$ m/e 356.1987, found m/e 356.1985. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.33; H, 8.04.

***rel*-(3*S*,4*S*,4a*S*,7*R*,7a*S*,12b*S*,12c*R*)-7-Cyano-2,3,4,4a,5,6,7,7a,8,12b-decahydro-9,12-dimethoxy-3-methyl-12c*H*-4,12c-ethanoanthra-[9,1-*bc*]oxepin (82).** To a mixture of 111 mg (0.57 mmol) of tosylmethyl isocyanide in 1.1 mL of freshly distilled 1,2-dimethoxyethane under argon, cooled in an ice–water bath, was added 155 mg (1.38 mmol) of potassium *tert*-butoxide in one portion, and the resulting brown mixture was stirred cold for 8 min. To the mixture was added 47 mg (0.132 mmol) of ketone **81** as a solid in one portion, and the brown mixture was stirred cold for 30 s followed by addition of 8 mL of absolute ethanol. The mixture was stirred cold for 1.5 min followed by addition of 11 mL of dimethyl sulfoxide. The mixture was stirred cold for 10 min and then gradually warmed to 20 °C over a 50-min period. The mixture was stirred at room temperature for 2 h and then at 45 °C for 2 h. The reaction was quenched with 3 mL of water and 6 mL of 1 N aqueous hydrochloric acid. The mixture was extracted with two 25-mL portions of dichloromethane. The combined extracts were washed with 15 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed over 8 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to give 37 mg (75%) of nitrile **82** as a white solid: mp 174–175.5 °C; IR ($CHCl_3$) 2240, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 3 H, CH_3), 1.23 (td, J = 11.3, 6.7 Hz, 1 H, CH), 1.54–2.35 (m with ddd at 1.95, J = 11.6, 4.5, 1.2 Hz, 12 H, $ArCH_2CH$, NCCH, CH, and CH_2 manifold), 2.82 (dd, J = 18, 4.7 Hz, 1 H, ArCH), 3.11 (dd, J = 18, 1.3 Hz, 1 H, ArCH), 3.42 (dd, J = 12.2, 7.4 Hz, 1 H, OC*H*H), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.98 (dd, J = 12.2, 8.6 Hz, 1 H, OC*H*H), 4.50 (s, 1 H, OCH), 6.70 (s, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 20.78 (q), 21.48 (t), 24.74 (t), 24.82 (t), 28.79 (d), 30.43 (t), 31.69 (d), 34.82 (t), 46.11 (d), 46.21 (d), 46.52 (s), 51.67 (d), 55.84 (q), 56.04 (q), 71.77 (d), 73.71 (t), 109.15 (d), 109.54 (d), 121.93 (s), 124.35 (s), 124.88 (s), 151.14 (s), 153.57 (s); mass spectrum, m/e (relative intensity) 367 (M^+, 60), 336 (12), 268 (14), 181 (6), 180 (33), 179 (10), 165 (17), 149 (11), 111 (12), 99 (11), 97 (19), 95 (11), 85 (25), 83 (21), 81 (14), 71 (36), 70 (13), 69 (31), 57 (55), 56 (10), 55 (26), 43 (32), 41 (20); exact mass calcd for $C_{23}H_{29}O_3$ m/e 367.2147, found m/e 367.2122.

***rel*-(3*S*,4*S*,4a*S*,7*R*,7a*S*,12b*S*,12c*R*)-2,3,4,4a,5,6,7,7a,8,12b-Decahydro-9,12-dimethoxy-3-methyl-12c*H*-4,12c-ethanoanthra[9,1-*bc*]oxepin-7-carboxaldehyde (83).** To a solution of 47 mg (0.128 mmol) of nitrile **82** in 2.2 mL of dry toluene under argon, cooled in a dry ice–acetonitrile bath, was added 0.21 mL (0.368 mmol) of diisobutylaluminum hydride in toluene (25%) over a 3-min period. The resulting solution was stirred cold for 15 min and then without cooling for 1.4 h. To the solution at 5 °C was added 70 mL of ethyl acetate followed by 2.2 mL of 1 N aqueous hydrochloric acid, and the resulting mixture was stirred at room temperature for 10 min. The mixture was diluted with 3 mL of water, saturated with sodium chloride, and extracted with two 25-mL portions of dichloromethane. The combined extracts were washed with 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (eluted with ethyl acetate–hexane, 1:10 and 1:8) to give 44 mg (93%) of aldehyde **83** as a white solid: mp 140–141 °C; IR ($CHCl_3$) 2710, 1718, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 3 H, CH_3), 1.24 (td, J = 11.5, 6.5 Hz, 1 H, CH), 1.43 (qd, J = 12.5, 5 Hz, 1 H, C*H*H), 1.55–2.30 (m, 11 H, CH and CH_2 manifold), 2.65–2.86 (m, 2 H, $ArCH_2$), 3.44 (dd, J = 12.3, 7.2 Hz, 1 H, OC*H*H), 3.71 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.01 (dd, J = 12.2, 8.6 Hz, 1 H, OC*H*H), 4.58 (s, 1 H, OCH), 6.67 (s, 2 H, aromatic), 9.50 (d, J = 3.3 Hz, 1 H, O=CH); ^{13}C NMR ($CDCl_3$) δ 20.89 (q), 21.44 (t), 23.97 (t), 24.95 (t), 26.60 (t), 31.83 (d), 34.78 (t), 43.27 (d), 46.21 (d), 46.66 (s), 48.45 (d), 52.05 (d), 55.81 (q), 56.03 (q), 72.62 (d), 73.84 (t), 108.94 (d), 109.35 (d), 124.90 (s), 125.74 (s), 150.98 (s), 153.70 (s), 204.89 (d); mass spectrum, m/e (relative intensity) 370 (M^+, 41), 339 (2), 297 (5), 217 (15), 201 (4), 180 (11), 179 (3), 91 (8), 69 (5), 7 (4), 55 (5), 41 (6); exact mass calcd for $C_{23}H_{30}O_4$ m/e 370.2144, found m/e 370.2162.

***rel*-(3*S*,4*S*,4a*S*,7*R*,7a*S*,12b*S*,12c*R*)-2,3,4,4a,5,6,7,7a,8,12b-Decahydro-9,12-dimethoxy-3-methyl-12c*H*-4,12c-ethanoanthra[9,1-*bc*]oxepin-7-carboxylic Acid (84).** A suspension of 38 mg (0.103 mmol) of aldehyde **83** and 154 mg (0.66 mmol) of silver oxide in 8.0 mL of 15% aqueous sodium hydroxide was stirred at 80–84 °C for 23 h. The mixture was filtered through Celite and rinsed with 20 mL of 1 N aqueous hydrochloric acid, 10 mL of 3 N aqueous hydrochloric acid, 25 mL of dichloromethane, and 85 mL of ethyl acetate. The aqueous layer was extracted with 20 mL of dichloromethane, and the combined extracts were washed with 15 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel (eluted with ethyl acetate–hexane, 1:6 and 1:3, and then with ethyl acetate–hexane–acetic acid, 25:73:2) to give 24.5 mg (62%) of acid **84** as a white solid: mp 218–219.5 °C; IR ($CHCl_3$) 3500–2500 (br), 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 3 H, CH_3), 1.24 (td, J = 12, 6 Hz, 1 H, CH), 1.55–2.28 (m, 12 H, CH and CH_2 manifold), 2.72 (d, J = 3.2 Hz, 2 H, $ArCH_2$), 3.43 (dd, J = 12.3, 7.1 Hz, 1 H, OC*H*H), 3.72 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.00 (dd, J = 12.2, 8.6 Hz, 1 H, OC*H*H), 4.56 (s, 1 H, OCH), 6.64, 6.70 (AB q, J = 10 Hz, 2 H, aromatic), acid proton was not observed; ^{13}C NMR ($CDCl_3$) δ 20.98 (q), 21.86 (t), 24.58 (t), 25.05 (t), 30.43 (t), 31.90 (d), 34.94 (t), 42.58 (d), 44.99 (d), 46.34 (d), 46.81 (s), 52.07 (d), 56.07 (q, q, 2 C's), 72.72 (d), 73.94 (t), 108.95 (d), 109.75 (d), 125.52 (s), 125.59 (s), 151.21 (s), 153.88 (s), 180.99 (s); mass spectrum, m/e (relative intensity) 386 (M^+, 93), 355 (10), 287 (9), 241 (5), 238 (5), 181 (8), 180 (44), 179 (8), 173 (7), 165 (21), 164 (16), 161 (11), 151 (9), 91 (12), 55 (8), 44 (8), 43 (7), 43 (11), 41 (13); exact mass calcd for $C_{23}H_{30}O_5$ m/e 386.2093, found m/e 386.2108.

Dihydropleurotin Acid: *rel*-(3*S*,4*S*,4a*S*,7*R*,7a*S*,12b*S*,12c*R*)-2,3,4,4a,5,6,7,7a,8,9,12,12b-Dodecahydro-3-methyl-9,12-dioxo-12c*H*-4,12c-ethanoanthra[9,1-*bc*]-oxepin-7-carboxylic Acid (2). To a solution of 16 mg (0.042 mmol) of acid **84** in 4.0 mL of acetonitrile and 1.6 mL of ether under argon, cooled in an ice–brine bath, was added a solution of 57 mg (0.104 mmol) of ceric ammonium nitrate in 1.0 mL of water over a 3-min period. The resulting yellow solution was stirred cold for 30 min. The light yellow solution was diluted with 8 mL of water and extracted with two 25-mL portions of dichloromethane. The combined extracts were washed with 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The solid residue was chromatographed over 0.6 g of silica gel (eluted with ethyl acetate–hexane, 1:3 progressing to 1:1 with 2% acetic acid) to give 10.5 mg (89%) of quinone acid **2** as a pale yellow solid: mp 212–223 °C dec; IR (CH_2Cl_2) 3500–2400 (br), 1740, 1705, 1660, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.3 Hz, 3 H, CH_3), 1.22 (td, J = 11.6, 7.3 Hz, 1 H, CH), 1.55–2.22 (m, 12 H, CH and CH_2 manifold), 2.42–2.62 (m, 2 H, $=CCH_2$), 3.46 (dd, J = 12.6, 6.4 Hz, 1 H, OC*H*H), 3.99 (dd, J = 12.5, 8.6 Hz, 1 H, OC*H*H), 4.44 (s, 1 H, OCH), 6.68, 6.71 (AB q, J = 10.1 Hz, 2 H, CH=CH), acid proton was not observed; mass spectrum, m/e (relative intensity) 358 (M^+ + 2, 34), 356 (M^+, 100), 338 (32), 325 (23), 310 (28), 299 (29), 298 (61), 297 (51), 281 (18), 253 (28), 252 (26), 251 (54), 249 (29), 239 (13), 237 (13), 226 (23), 224 (19), 211 (28), 207 (31), 165 (24), 163 (25), 161 (80), 152 (18), 150 (21), 136 (42), 119 (76), 117 (37), 115 (29), 105 (34), 93 (29), 91 (83), 81 (31), 79 (37), 77 (39), 67 (36), 55 (37), 55 (45), 44 (12), 43 (19), 43 (37), 41 (91); exact mass calcd for $C_{21}H_{24}O_5$ m/e 356.1624, found m/e 356.1631.

Pleurotin: *rel*-(2a*R*,4a*S*,5*S*,6*S*,8a*S*,12b*S*,12c*S*,12d*R*)-2a,3,4,4a,5,6,7,8a,12b,12c-Decahydro-6-methyl-2*H*-5,12d-ethanofuro-[4′,3′,2′:4,10]anthra[9,1-*bc*]oxepin-2,9,12-trione (1). A suspension of 9 mg (0.0253 mmol) of quinone acid **2** and 167 mg (1.92 mmol) of active manganese dioxide in 2.3 mL of dichloromethane was stirred at room temperature in a sealed vessel for 48 h. The mixture was filtered through

Celite and rinsed with 1.0 mL of dichloromethane, 1.0 mL of ethyl acetate, 12 mL of dichloromethane with 2% acetic acid, and 10 mL of ethyl acetate with 1% acetic acid. The filtrate was concentrated in vacuo to give a brown solid. The residue was chromatographed over 0.6 g of silica gel (eluted with ethyl acetate–hexane, 1:5 progressing to 1:1, and then with ethyl acetate–hexane–acetic acid, 66:31:2) to give 2.9 mg (32%) of pleurotin (**1**) as a pale yellow solid: mp 205–208 °C; IR ($CHCl_3$) 3030, 2870, 1790, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 3 H, CH_3), 1.17 (td, J = 11.6, 6.3 Hz, 1 H, CH), 1.38 (qd, J = 12, 4 Hz, 1 H, C*H*H), 1.55 (ddd, J = 12.8, 6.1, 3.7 Hz, 1 H, C*H*H), 1.70 (qd, J = 13.2, 4.0 Hz, 1 H, C*H*H), 1.72–1.98 (m, 4 H, CH and CH_2 manifold), 2.06 (ddd, J = 12.1, 8.8, 3.2 Hz, 1 H, C*H*H), 2.12 (dd, J = 7.7, 6.7 Hz, 1 H, CH), 2.24, 2.78 (AB, then doublet, J_{AB} = 7.0 Hz, J_d = 3.4 Hz, 2 H, CH_2), 2.36 (dd, J = 14.3, 6.8 Hz, 1 H, O=CCH), 3.35 (dd, J = 12.1, 8.8 Hz, 1 H, OC*H*H), 4.02 (dd, J = 12.1, 8.5 Hz, 1 H, OC*H*H), 4.49 (d, J = 1.3 Hz, 1 H, OCH), 5.46 (dd, J = 6.8, 1.7 Hz, 1 H, O=COCH), 6.76, 6.79 (AB q, J = 10.2 Hz, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$, broad band) δ 20.17, 22.50, 23.94, 24.83, 30.56, 32.73, 39.57, 44.61, 47.23, 48.77, 52.09, 69.44, 71.37, 73.81, 136.07 (two peaks), 137.96, 143.81, 174.58, 185.32, 186.74; mass spectrum, m/e (relative intensity) 356 (M^+ + 2, 31), 354 (M^+, 60), 336 (21), 325 (16), 310 (19), 296 (24), 295 (28), 294 (28), 267 (32), 251 (48), 250 (39), 249 (56), 237 (33), 223 (38), 211 (39), 210 (30), 197 (29), 128 (40), 119 (69), 117 (36), 115 (48), 93 (32), 91 (100), 79 (48), 77 (54), 67 (40), 65 (36), 55 (48), 55 (55), 44 (15), 41 (90); exact mass calcd for $C_{21}H_{22}O_5$ m/e 354.1468, found m/e 354.1492. The IR, ^1H NMR, ^{13}C NMR (broad band), and mass spectra, as well as TLC behavior of the synthetic pleurotin (**1**) were indistinguishable from those of the natural product. Further elution gave 3.0 mg (33%) of quinone acid **2** as a pale yellow solid.

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Supplementary Material Available: Experimental procedures for all reactions not presented in the Experimental Section (18 pages). Ordering information is given on any current masthead page.

The Macrolactins, a Novel Class of Antiviral and Cytotoxic Macrolides from a Deep-Sea Marine Bacterium

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Abstract: Eight new secondary metabolites, macrolactins A–F (**1–6**) and macrolactinic and isomacrolactinic acids (**7** and **8**), of an unprecedented C_{24} linear acetogenin origin, have been isolated from the culture broth of an apparently taxonomically unclassifiable marine bacterium. The new compounds include 24-membered ring lactones and related glucose β-pyranosides and open-chain acids. Macrolactin A (**1**), the parent aglycon, shows selective antibacterial activity and inhibits B16-F10 murine melanoma cancer cells in vitro assays. Macrolactin A also shows significant inhibition of mammalian *Herpes simplex* viruses (types I and II) and protects T-lymphoblast cells against human HIV viral replication.

Studies of the natural-products chemistry of terrestrial microorganisms, initiated at least 4 decades ago, have illustrated that bacteria and fungi of largely soil origin are prolific sources for structurally unique, highly bioactive, and biomedically utilitarian secondary metabolites. Of the over 10000 compounds described from terrestrial microorganisms, at least 100 have proven effective as chemotherapeutic agents in the treatment of human and animal diseases. The fact that there is a continuing international focus on microbial products by the pharmaceutical and agrichemical industries points to their recognized importance in the development of new therapeutic agents. Although both shallow and deep marine habitats have been observed to contain taxonomically diverse microorganisms, progress in the isolation and mass culture of these organisms has been slow. Several studies of marine-derived actinomycetes[1] and of bacteria isolated from seawater[2] have, however, illustrated that unique metabolites may be produced.

As part of a new program to explore methods for the successful culture and chemical evaluation of marine microorganisms, we have focused our attention on those microorganisms that are adapted to saline environments, living within marine sediments or in close association with other marine organisms. An unusual Gram-positive bacterium, which could not be readily identified by using normal taxonomic methods,[3] was obtained from a deep-sea sediment core[4] and subsequently grown in liquid culture. This bacterial isolate was found to produce a novel family of antiviral and cytotoxic macrocyclic lactones. One of these macrolides is active against several pathogenic viruses, including the human immunosuppressive virus (HIV), the causative agent of AIDS.[5] In this paper, we report the structural elucidation and preliminary biological properties of these novel bacterial metabolites.

Cultures of the unicellular bacterium were grown for periods of 5–15 days at 20 °C, and the whole-cell suspension was extracted

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(2) (a) Wratten, S. J.; Wolfe, M. S.; Andersen, R. J.; Faulkner, D. J. *Antimicrob. Agents Chemother.* **1977**, *11*, 411–414. (b) Burkholder, P. R.; Pfister, R. M.; Leitz, F. H. *Appl. Microbiol.* **1966**, *14*, 649–653. (c) Umezawa, H.; Okami, Y.; Kurasawa, S.; Ohnuki, T.; Ishizuka, M.; Takeuchi, T.; Shiio, T.; Yugari, Y. *J. Antibiot.* **1983**, *36*, 471–477.

(3) The microorganism in question, isolate C-237, is a motile, Gram-positive, oxidase and catalase positive, unicellular bacterium with a strong salt requirement for growth. With use of biochemical methods, isolate C-237 could not be placed within any previously defined bacterial class. Further studies including rRNA sequence measurements are planned. We gratefully acknowledge Professor Kenneth Nealson, University of Wisconsin—Milwaukee, for his assistance with this preliminary taxonomic investigation.

(4) The sediment core sample was collected as part of the "Deep Sea Drilling Program" in the North Pacific (37° 12.4′ N, 123° 04.6′ W) at a depth of −980 m on June 21, 1970.

(5) Gallo, R. C.; Sarin, P. S.; Gelmann, E. P.; Robert-Guroff, M.; Richardson, E.; Kalyanaraman, V. S.; Mann, D. L.; Sidhu, G.; Stahl, R. E.; Zolla-Pazner, S.; Liebowitch, J.; Popovic, M. *Science* **1983**, *220*, 865–867. Barre'-Sinoussi, F.; Chermann, J. C.; Rey, R.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868–871. Coffin, J.; Haase, A.; Levy, J. A.; Montaginer, L.; Oroszlan, S.; Teich, N.; Temin, H.; Toyoshima, K.; Varmus, H.; Vogt, P.; Weiss, R. *Science* **1986**, *232*, 697.

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