Total Synthesis of the *Lycopodium* Alkaloids Magellanine and Magellaninone by Three-fold Annulation of 2-Cyclopentenone

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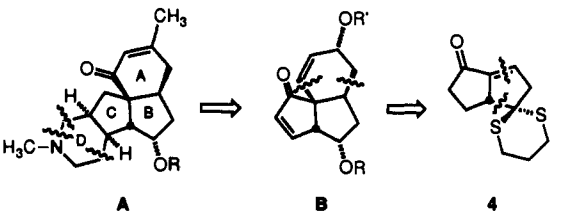
Abstract: A stereocontrolled synthesis of the complete diquinane-based framework of the two unusual *Lycopodium* alkaloids magellanine and magellaninone is reported. Michael–Michael ring annulation of the α,β-unsaturated ketone **4** obtained by dehydration of **5a** rapidly led to enedione **7**, functional group manipulation within which gave rise to **11**. Once oxidation to the cyclopentenone had been accomplished, the piperidine ring part structure was incorporated by an unprecedented sequence that ultimately allowed for installation of the requisite cis ring juncture through epimerization. With **17a** available, oxidation levels were concisely adjusted with concomitant incorporation of a methyl group to produce magellaninone (**2**). To complete the route to magellanine (**1**), **2** was chemoselectively reduced and subjected to a Mitsunobu protocol.

Magellanine (**1**),[2] magellaninone (**2**),[3] and paniculatine (**3**),[4] discovered by Castillo et al. in the mid to late 1970s, were immediately recognized to represent a structurally unique subset of *Lycopodium* alkaloids. Produced by the club mosses *L. magellanicum* and *L. paniculatum*, **1–3** have no known structural counterparts. Their tetracyclic frameworks share in common a diquinane core that is fused in entirely different ways to a cyclohexenone or a cyclohexanol and to a piperidine ring. The unusual features of these highly condensed bases, originally established by X-ray diffraction,[5] seem not to have formed the basis of a concerted synthetic thrust until very recently. The requirement for strict stereochemical control at six of the eight carbons of the bicyclo[3.3.0]octane substructure certainly contributes to the challenge of their *de novo* construction. Research groups headed by Crimmins,[6] Mehta,[7] and Overman[8] have by means of their model studies given evidence of the numerous complexities associated with suitable assembly of **1–3**. Recently, we[9] and Overman[10] have successfully completed syntheses of both magellanine and magellaninone. Reported herein are the complete details of our synthetic approach.

Scheme 1



Retrosynthetic Analysis

The retrosynthetic analysis to which we were attracted involved disconnection of the strategic bonds indicated by the wavy lines in Scheme 1. Disassembly of **A** in this fashion was expected to allow for implementation of a novel means for incorporation of the fused piperidine ring. Particularly convergent would be proper adaptation of a tandem vicinal difunctionalization process,[11] to be initiated by 1,4-addition to **B** of a suitable nitrogen-containing nucleophile.

The construction of **B** was to rely upon the cyclohexannulation of 4 in a manner that had necessarily to differ intrinsically from a conventional Diels–Alder process because of the need to position the double bond and oxygenated carbon atom regioselectively as shown. Thus, rupture of the two bonds in **B** was to require that a new and preparatively useful process be devised which would eventuate in the smooth conversion of **4** to an immediate precursor of this pivotal intermediate.

For these reasons, bicyclic ketone **4** was to serve as the starting point of our synthetic effort. We had previously reported a convenient method for making **4** readily available from 2-cyclopentenone.[12] A further improvement in this early step is detailed below. The advantages of this overall strategy include the likelihood of dependable stereochemical control at essentially every stage of the pathway, the potential of kinetic resolution at several stages, and the flexibility of chemically manipulating ring A and/or ring D as needed for the further elaboration of analogues.

Assembly of the ABC Network. To incorporate ring A in the most direct manner possible, the intramolecular aldol cyclization to produce **5a** and **5b** was performed in 20% aqueous HCl as

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(5) Optical methods were utilized for the absolute configurational assignments to these alkaloids.

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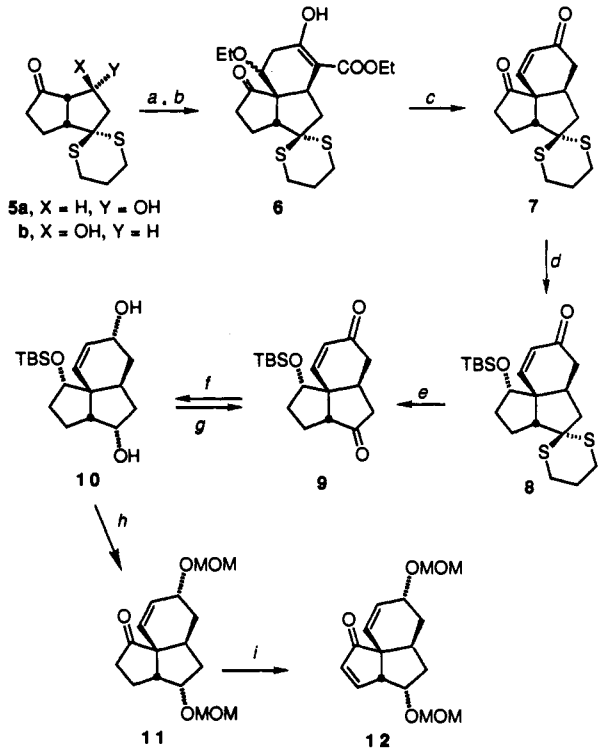
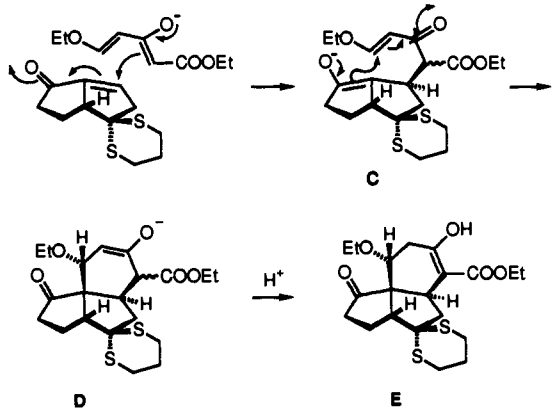
Scheme 2[a]



[a] MsCl, Et_3N. [b] (*E*)-EtOCH=CHC(O)CH_2COOEt, K_2CO_3, Al_2O_3, THF/C_2H_5OH, room temperature. [c] TsOH (catalytic), C_6H_6, Δ; NaCl, DMF, Δ. [d] $NaBH_4$, EtOH, CH_2Cl_2, 0 °C; TBSOTf, imid, CH_2Cl_2, room temperature. [e] $Tl(NO_3)_3$, MeOH, THF. [f] Dibal-H, CH_2Cl_2, −78 °C. [g] PCC on Al_2O_3, CH_2Cl_2, room temperature. [h] MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; $Bu_4N^+F^-$, HMPA, 3-Å sieves, room temperature; PCC on Al_2O_3, CH_2Cl_2. [i] $LiN(SiMe_3)_2$, THF; PhSeCl; H_2O_2, py.

Scheme 3



before,[12] but chromatograhic separation need not be performed. Instead, the epimeric mixture can be directly mesylated and eliminated to generate **4** (and its β,γ-unsaturated isomer)[13] in the immediate presence of ethyl 5-ethoxy-3-oxo-4-pentenoate[14] and K_2CO_3 in a THF–ethanol solvent system maintained at 25 °C (Scheme 2). This protocol maximizes the efficiency with which the desired sequential Michael reactions operate to provide the multiply functionalized, cyclohexannulated product **6** (56%). The stereochemical constraints placed upon this process follow from steric approach control to the less sterically encumbered surface of the strained double bond in **4** to give **C** (Scheme 3). The progression from **C** to product is offered little opportunity for loss of stereocontrol for two reasons: (a) the electrophilic partner in the second-stage intramolecular 1,4-addition is already positioned on the β surface of the intermediate enolate anion and (b) the diquinane substructure possesses a strong thermodynamic driving force to become cis- rather than trans-fused.[15] Accordingly, C–C bond formation giving rise to **D** occurs as shown to give **E** (and the β-ethoxy epimer) after protonation.

Heating **6** with a catalytic quantity of *p*-toluenesulfonic acid in benzene promoted the β-elimination of ethanol. Following decarboxylation by means of the Krapcho procedure,[16] the enedione **7** was obtained as a homogeneous, colorless, crystalline solid.

The prospect of chemoselective reduction of the cyclopentanone carbonyl in **7** was considered to be feasible notwithstanding its congested environment because of reactivity ordering well established in many examples.[17] Particularly suited to our purposes was the general method developed by Ward and Rhee[18] which utilizes $NaBH_4$ in a solvent system composed of 50% methanol and 50% dichloromethane at reduced temperatures. In the specific case of **7**, the reduction proved also to be completely stereoselective in 1:1 ethanol–dichloromethane.

Further protection of the hydroxyl group as its *tert*-butyldimethylsilyl ether[19] set the stage for removal of the dithiane protecting group. Recourse to thallium(III) nitrate[20] afforded **9** in 65% yield. Diol **10** predominated when **9** was reduced with diisobutylaluminum hydride at −78 °C. Advantageously, **10** was easily purified by chromatography, thereby enabling us to convert its unwanted diastereomers back to **9** in quantitative yield via oxidation with pyridinium chlorochromate on alumina.[21] In this way, the overall efficiency for the production of **10** was raised to 76%. The stereochemical assignment accorded to **10** was corroborated by high-field NOE measurements performed directly on this diol as well as derivatives thereof prepared subsequently.

A three-step sequence led from **10** to **11**, thereby making possible acquisition of the desired enone **12** through application of standard organoselenium technology.[22]

The assignment of relative stereochemistry to C-5, C-11, and C-15 of **10** (the numbering used is that of Castillo et al.[2]) rests on the following evidence. (a) C-11 was verified by NOE-D at the stage of **9**, which in turn applies also to **8** and **10**; double irradiation of H-13 (δ 6.53) induced a 6.5% integral enhancement of the H-11 signal at δ 4.18. (b) C-5 and C-15 were verified by NOE-D at the stage of **12**, these findings being relevant as well to **10**, **11**, and **13–18**; thus

irradiate H-3 (δ 7.26) → H-4_β (δ 2.82, 4%);
no NOE at H-5_β (δ 4.03)

irradiate H-5_β (δ 4.03) → H-$8'_\beta$ (δ 1.27, 3.5%);
no NOE at H-7_α (δ 2.55)

irradiate H-15_β (δ 3.94) → H-$6'_\beta$ (δ 1.45, 2%);
no NOE at H-7_α (δ 2.55)

(13) As demonstrated earlier,[12] epimer **5a** serves as the exclusive precursor to 4 under these conditions. For **5b**, the kinetically favored E_2 pathway leads to the β,γ-unsaturated enone isomer of 4.

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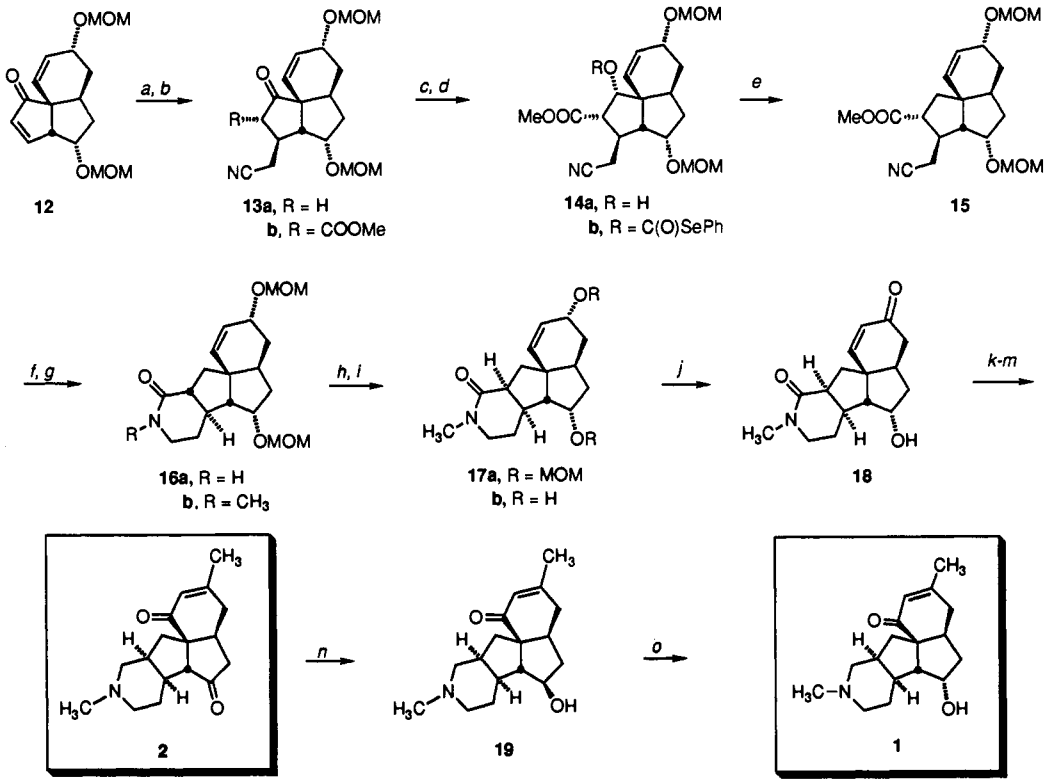
Scheme 4[a]



[a] $LiCH(CN)SiMe_3$, HMPA, THF; KF, aqueous CH_3CN. [b] LDA, NCCOOMe. [c] $NaBH_4$, MeOH, −20 °C. [d] $COCl_2$, py, THF; PhSeH. [e] $(Me_3Si)_3SiH$, AIBN, C_6H_6, Δ. [f] $NaBH_4$, $CoCl_2$, CH_3OH; KOH, CH_3OH; H_3O^+. [g] NaH, CH_3I, THF. [h] LDA, THF, −78 °C → −10 °C; H_2O at −78 °C. [i] HCl, H_2O, THF. [j] MnO_2, $CHCl_3$. [k] CH_3Li, THF, −78 °C. [l] $LiAlH_4$, THF, Δ. [m] Jones oxidation. [n] $NaBH_4$, C_2H_5OH. [o] Ph_3P, DEAD, HCOOH, THF; 10% KOH, CH_3OH.

These data indicate further that **12** does not adopt a single distinct low-energy conformation but is equilibrating between conformations in which 5_α-OMOM and C-8 are projected pseudoequatorially from ring B. The first arrangement leads to the H-5_β → H-$8'_\beta$ NOE and the second to the H-15_β → H-$6'_\beta$ NOE.

To appreciate the significance of the NOE-D data for **12**, one must also recognize that two other diastereomers of **12**, *viz.* **F** and **G**, have also been closely examined spectroscopically in a comparable manner. The relevant NOE-D results for these compounds are as follows:

for **F**

irradiate H-3 (δ 7.08) → H-4_β (δ 2.84, 4%);
H-5_β (δ 3.47, 2%)

irradiate H-7_α (δ ~ 1.80) → H-5_α (δ 3.47, 5%);
no NOE at H-15_β (δ 4.05)

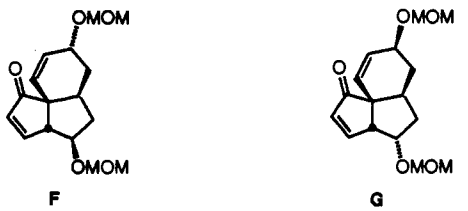
irradiate H-15_β (δ 4.05) → H-6_β (δ ~ 1.70, 4%);
no NOE at H-7_α

for **G**

irradiate H-3 (δ 7.34) → H-4_β (δ 2.87);
no NOE at H-5_β (δ 4.11)

irradiate H-15_α (δ 4.18) → H-7_α (δ ~ 1.80, 4%)

With **12** in hand, the time had arrived to appraise the plan for incorporation of the piperidine ring. In light of important precedent from the earlier work of Koga,[23] bond construction based on the propensity of lithiated (trimethylsilyl)acetonitrile



to add in conjugate fashion to α,β-unsaturated carbonyl systems was considered first. Diastereofacial guidance should be provided by the overall topography of **12**. Gratifyingly, the proposed addition proceeded in the required regiocontrolled manner and with the proper facial sense to deliver **13a** (Scheme 4). Furthermore, the enolate of **13a** was very amenable to stereoselective C-acylation with methyl cyanoformate[24] in order to gain access to **13b**. Although the **12** → **13b** conversion could be accomplished in a single laboratory operation, higher yields of **13b** were obtained when the two steps were performed separately.

The tactical role of the C-ring carbonyl had now been played out, and its removal was mandated. For chemoselectivity reasons, this transformation was accomplished by two-stage reduction, making recourse first to sodium borohydride and subsequently to cleavage of the derived selenocarbonate[25] with tris(trimethylsilyl)silane[26] and AIBN in benzene. These steps were met with an 87% overall yield of **15**. Once this intermediate was reached, it was possible to confirm by NOE studies at 300 MHz that the newly introduced side chains had indeed been incorporated in the

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manner shown. Accordingly, it would ultimately prove necessary to epimerize the stereogenic center adjacent to the ester functionality. This requirement was to be addressed after cyclization to form ring D.

The assignment of relative stereochemistry at C-3 and C-10 of **15** rests in particular on the following NOE-D evidence:

irradiate H-13 (δ 5.70) → H-4$_\beta$ ($\delta \sim$ 2.20, 4%); H-10$_\beta$ (δ 2.88, 5%); H-11$_\beta$ (δ 2.06, 1.5%)

irradiate H-10$_\beta$ (δ 2.88) → H-13 (δ 5.70, 7%); H-11$_\beta$ (δ 2.06, 4%)

irradiate H-5$_\beta$ (δ 4.17) → H-4$_\beta$ ($\delta \sim$ 2.20, 8.5%); H-8 ($\delta \sim$ 1.70, 2%); H-6$_\beta$ (δ 1.82, 3%)

irradiate H-3$_\alpha$ (δ 2.78) → H-11$_\alpha$ (δ 1.90, 1.5%); H-6$_\alpha$ (δ 1.98, 1%)

irradiate 2-CH_2 (δ 2.65) → H-10$_\beta$ (δ 2.88, 3%); H-4$_\beta$ ($\delta \sim$ 2.20, 3%)

In addition, the relative stereochemistry at C-11 in **14a** was ascertained in a similar manner:

irradiate H-13 (δ 5.35) → H-11$_\beta$ (δ 3.94, 2%); H-10$_\beta$ (δ 2.93, 12%); H-4$_\beta$ (δ 1.83, 3.5%); no NOE at H-3$_\alpha$ (δ 3.07)

Finally, lactam **18** was amenable to NOE analysis:

irradiate H-10$_\alpha$ (δ 3.05) → H-11$_\alpha$ (δ 2.39, 3.5%); H-3$_\alpha$ and H-7$_\alpha$ (δ 2.72–2.58, total 14%)

irradiate H-4$_\beta$ (δ 2.21) → H-5$_\beta$ (δ 4.32, 6%); H-13 (δ 4.65, 4.5%); H-3$_\alpha$ ($\delta \sim$ 2.65, 1%)

irradiate H-13 (δ 6.45) → H-11$_\beta$ (δ 1.83, 5%); H-4$_\beta$ (δ 2.21, 4.5%)

These latter data are significant together with the large coupling (J = 12 Hz) between H-10$_\alpha$ (δ 3.05) and H-11$_\beta$ (δ 1.83).

The combination of sodium borohydride and cobaltous chloride is recognized to be uniquely suited to the reduction of nitrile groups.[27] The inertness of carbalkoxy substituents to this reagent system suggested that it might be serviceable in delivering **16a**. When **15** was treated in this manner and the reaction mixture was directly basified with KOH in methanol, the conversion to **16a** was indeed realized. While concomitant epimerization was not seen, small levels of double bond saturation in ring A could not be totally suppressed. For this reason, progression to the N-methyl derivative **16b** was undertaken prior to chromatographic purification. The yield of **16b** was 54%.

We focused next on the epimerization issue. It was reasoned that the enolate anion produced from **16b** is sufficiently encumbered on its β face to exhibit a decided bias for kinetically controlled protonation from the α direction. In practice, the deprotonation of this lactam with lithium diisopropylamide followed by rapid introduction of a 1:4 mixture of water and THF at −78 °C resulted in quantitative conversion to the cis-fused isomer **17a**. Following removal of the MOM protecting groups, controlled oxidation with manganese dioxide provided the pivotal intermediate **18**, which was to serve as the progenitor of both magellanine and magellaninone.

Arrival at these alkaloids required the introduction of a methyl group as well as suitable adjustment in the oxidation levels resident in rings A, B, and D. The final thrust was initiated by exploiting the regioselective addition of methyllithium to **18**. Reduction of the resulting tertiary allylic alcohol with lithium aluminum hydride succeeded in liberating the piperidine ring. Subsequent Jones oxidation occurred with allylic rearrangement as expected. In this way, it was possible to achieve efficient conversion (67%) to magellaninone (**2**) without the need for deploying blocking groups. Our assignment to **2** is securely supported by the identity of its ^{1}H and ^{13}C NMR spectra with those reported previously by the original discoverers.[3]

In contrast to the directionality established for hydride reduction of the B-ring carbonyl in **9**, the action of sodium borohydride on **2** afforded exclusively the 5β-alcohol **19**. Thus, one sees that the presence of the fused piperidine ring provides sufficient steric congestion on the convex surface of the bicyclo[3.3.0]octanone core to relegate nucleophilic attack to the concave face only. This stereochemical outcome required only that configurational inversion be undertaken in order to produce magellanine (**1**). Submission of **19** to conventional Mitsunobu conditions[28] proceeded very much in keeping with precedent to afford the targeted magellanine. As before, the identity of the high-field spectral features of **1** with those of the natural alkaloid provided complete confidence that its total synthesis had been accomplished.

Conclusion

The structurally novel *Lycopodium* alkaloids magellanine and magellaninone have been prepared in stereocontrolled fashion by three-fold annulation of 2-cyclopentenone. The construction of each ring was keyed to new synthetic methodology adopted specifically to bring about relatively easy assembly. A 1,3-dicarbonyl dipole equivalent was the device that served to make **4** readily available.[12] The ability of ethyl 5-ethoxy-3-oxo-4-pentenoate to enter into Michael–Michael reaction with **4** advanced A-ring assembly. In achieving ring D annulation, advantage was taken of the tendency exhibited by lithiated (trimethylsilyl)acetonitrile for 1,4-addition to enones and of the chemoselective reducing properties of the $NaBH_4$–$CoCl_2$ reagent system. Furthermore, the means adopted for construction of this piperidine part structure also offered the latitude for epimerization and economic adjustment of oxidation levels with simultaneous incorporation of a methyl substituent late in the synthesis.

Experimental Section

Ethyl (3a*R,5a*S**,9a*R**)-9-Ethoxy-1,2,3,3a,5,5a,8,9-octahydro-7-hydroxy-1-oxospiro[4*H*-cyclopent[*c*]indene-4,2′-*m*-dithiane]-6-carboxylate (6).** Methanesulfonyl chloride (0.85 mL, 11 mmol) was added to a mixture of **5a** (1.3 g, 5.5 mmol) and triethylamine (3.1 mL, 22 mmol) in CH_2Cl_2 (28 mL) at 0 °C. After 30 min, the reaction mixture was washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine solutions, dried, and concentrated. The residue was dissolved in ethanol (3 mL) and THF (3 mL) and added to a mixture of ethyl 5-ethoxy-3-oxo-4-pentenoate (1.5 g, 7.9 mmol), powdered K_2CO_3 (1.2 g, 8.4 mmol), and alumina (0.2 g) in ethanol (40 mL) at room temperature. After 6 h, the solvent was evaporated and the residue redissolved in CH_2Cl_2 (20 mL) prior to filtration and evaporation. Chromatography of the remaining oil on silica gel (elution with 20% ethyl acetate in petroleum ether) provided **6** as an inseparable 2:1 mixture of epimers (1.3 g, 56%): IR (KBr, cm^{-1}) 3600–3250, 1730, 1640, 1615; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.23 and 12.13 (2 s, 1 H total), 4.22–4.04 (m, 2 H), 3.76–3.44 (series of m, 2 H), 3.33–2.62 (series of m, 7 H), 2.58–1.90 (series of m, 10 H), 1.22 and 1.20 (2 t, J = 7.0 Hz, 3 H total) 1.07 and 1.01 (2 t, J = 7.0 Hz, 3 H total). The major epimer could be obtained pure by crystallization as a white solid, mp 174–176 °C (from EtOH): ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.5,

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171.9, 170.2, 97.5, 77.0, 65.0, 60.7, 60.5, 59.6, 58.1, 49.6, 40.9, 39.9, 31.7, 29.2, 27.9, 25.1, 21.7, 15.4, 14.2; MS *m/z* (M^+) calcd 412.1378, obsd 412.1355.

Anal. Calcd for $C_{20}H_{28}O_5S_2$: C, 58.23; H, 6.84. Found: C, 58.23; H, 6.78.

(3a*R,5a*S**,9a*S**)-3,3a,5a,6-Tetrahydrospiro[4*H*-cyclopent[*c*]indene-4,2′-*m*-dithiane]-1,7(2*H*,5*H*)-dione (7).** *p*-Toluenesulfonic acid (2.0 g, 11 mmol) was added to a solution of **6** (24.0 g, 57 mmol) in benzene (1 L), and the mixture was refluxed overnight, cooled, treated with saturated $NaHCO_3$ solution to achieve neutralization, and extracted with ether (4 × 500 mL). The combined organic phases were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in petroleum ether) provided 14.0 g (67%) of the α,β-unsaturated keto ester as a white solid, mp 154–155 °C (from ethanol): IR (KBr, cm^{-1}) 1735, 1660, 1620, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 11.99 (s, 1 H), 5.98 (d, J = 9.5 Hz, 1 H), 5.77 (d, J = 9.5 Hz, 1 H), 4.25–4.05 (m, 2 H), 3.25 (dd, J = 9.5, 8.0 Hz, 1 H), 3.05–2.70 (m, 6 H), 2.59 (ddd, J = 19.5, 8.5, 7.5 Hz, 1 H), 2.39 (dt, J = 19.5, 8.5 Hz, 1 H), 2.18–2.10 (m, 2 H), 2.04–1.84 (m, 3 H), 1.25 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 171.6, 163.5, 135.6, 122.5, 95.2, 61.6, 61.0, 60.2, 55.4, 50.9, 37.2, 37.1, 28.8, 27.7, 24.7, 21.3, 14.1; MS *m/z* (M^+) calcd 366.0959, obsd 366.0958.

Anal. Calcd for $C_{18}H_{22}O_4S_2$: C, 58.99; H, 6.05. Found: C, 58.82; H, 6.18.

A mixture of the above material (19.0 g, 52 mmol), NaCl (9.3 g, 0.15 mol), and water (3 mL) in DMF (400 mL) was heated at reflux for 5 h. After the solution was cooled, additional water (200 mL) was introduced, and the product was extracted into ether (6 × 250 mL). The combined organic phases were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether) provided **7** (13.3 g, 89%) as fine white needles, mp 142–143 °C (from ether–ethyl acetate): IR (KBr, cm^{-1}) 1725, 1675; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (dd, J = 10, 2 Hz, 1 H), 6.14 (d, J = 10 Hz, 1 H), 3.06 (t, J = 8 Hz, 1 H), 2.97–2.80 (m, 5 H), 2.78–2.60 (m, 3 H), 2.54–2.24 (m, 4 H), 2.14–1.97 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 196.4, 146.6, 129.7, 61.6, 61.1, 56.5, 48.4, 38.8, 38.3, 36.3, 29.2, 28.7, 24.5, 22.6; MS *m/z* (M^+) calcd 294.0748, obsd 294.0731.

Anal. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.19; H, 6.16. Found: C, 61.11; H, 6.24.

(1*R,3a*S**,9a*R**)-1-(*tert*-Butyldimethylsiloxy)-1,2,3,3a,8,9-hexahydrospiro[4*H*-cyclopent[*c*]indene-4,2′-*m*-dithian]-7(5*H*)-one (8).** Sodium borohydride (104 mg, 2.7 mmol) was added to a solution of **7** (3.4 g, 12 mmol) in ethanol (70 mL) and CH_2Cl_2 (35 mL) at 0 °C. After 1 h, the reaction mixture was washed with saturated NH_4Cl solution and brine, dried, and concentrated in vacuo. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether) provided the hydroxy ketone (3.1 g, 91%) as a colorless solid, mp 124–126 °C (from petroleum ether–ethyl acetate): IR (neat, cm^{-1}) 3550–3200, 1665; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, J = 10, 1.5 Hz, 1 H), 5.88 (d, J = 10 Hz, 1 H), 3.99 (dd, J = 9.5, 6.5 Hz, 1 H), 3.00–2.50 (m, 7 H), 2.50–2.05 (m, 3 H), 2.05–1.70 (m, 6 H), 1.66–1.52 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 154.5, 127.3, 79.3, 63.0, 57.3, 57.1, 48.1, 38.1, 36.7, 34.5, 29.5, 27.9, 25.1, 22.9; MS *m/z* (M^+) calcd 296.0905, obsd 296.0905.

Anal. Calcd for $C_{15}H_{20}O_2S_2$: C, 60.78; H, 6.80. Found: C, 60.67; H, 6.83.

To a solution of the hydroxy ketone (8.84 g, 0.03 mol) and imidazole (6.0 g, 0.09 mmol) in dry CH_2Cl_2 (280 mL) under N_2 was added dropwise 13.7 mL (0.06 mol) of *tert*-butyldimethylsilyl triflate. After being stirred for 12 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with water (100 mL) and brine (100 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) furnished **8** (11.72 g, 96%) as a white solid, mp 104–106 °C: IR (KBr, cm^{-1}) 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 10, 1.5 Hz, 1 H), 5.98 (d, J = 10 Hz, 1 H), 3.99 (dd, J = 9.5, 7 Hz, 1 H), 3.07–2.89 (m, 4 H), 2.79–2.67 (m, 3 H), 2.40–2.22 (m, 3 H), 2.12–1.80 (m, 5 H), 1.70–1.55 (m, 1 H), 0.85 (s, 9 H), 0.03 (s, 3 H), –0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 154.7, 127.5, 80.2, 62.3, 57.6, 57.2, 48.0, 38.1, 37.1, 34.8, 29.6, 27.9, 25.8 (3 C), 25.2, 22.8, 18.0, –4.8 (2 C); MS *m/z* (M^+ – *t*-Bu) calcd 253.1065, obsd 253.1048.

Anal. Calcd for $C_{21}H_{34}O_2S_2Si$: C, 61.41; H, 8.34. Found: C, 61.46; H, 8.36.

(1*R,3a*S**,5a*R**,9a*R**)-1-(*tert*-Butyldimethylsiloxy)-3,3a,5a,6-tetrahydro-1*H*-cyclopent[*c*]indene-4,7(2*H*,5*H*)-dione (9).** A solution of **8** (960 mg, 2.3 mmol) in THF (5 mL) was added to a solution of thallium(III) nitrate (900 mg, 2.3 mmol) in methanol (25 mL). Additional portions of $Tl(NO_3)_3$ (3 × 50 mg) were introduced until all of the starting material was consumed. The precipitate was removed by filtration and rinsed with ether (25 mL). The combined filtrates were washed with water and brine prior to drying and solvent evaporation. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in petroleum ether) provided **9** (410 mg, 65%) as a pale yellow oil: IR ($CHCl_3$, cm^{-1}) 1735, 1675; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (dd, J = 10, 1.5 Hz, 1 H), 6.12 (br d, J = 10 Hz, 1 H), 4.18 (dd, J = 9.5, 6 Hz, 1 H), 2.99 (dd, J = 16.5, 6 Hz, 1 H), 2.94–2.83 (m, 1 H), 2.52–2.38 (m, 3 H), 2.26 (ddd, J = 17, 12.5, 1.5 Hz, 1 H), 2.05–1.82 (m, 3 H), 1.76–1.61 (m, 1 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.6, 198.0, 152.5, 129.5, 81.3, 57.2, 54.1, 44.7, 39.0, 33.4, 33.0, 25.7 (3 C), 23.8, 18.0, –4.7, –4.8; MS *m/z* (M^+) calcd 320.1808, obsd 320.1788.

Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.06; H, 8.93.

(1*R,3a*S**,4*R**,5a*R**,7*S**,9a*R**)-1-(*tert*-Butyldimethylsiloxy)-2,3,-3a,4,5,5a,6,7-octahydro-1*H*-cyclopent[*c*]indene-4,7-diol (10).** Diisobutylaluminum hydride (6.8 mL of 1 M solution in hexanes, 6.8 mmol) was added dropwise to a solution of **9** (990 mg, 3.1 mmol) in CH_2Cl_2 (20 mL) at –78 °C under N_2. After 30 min, a 1:1 mixture of water and methanol (5 mL) was added, the biphasic mixture was warmed to 20 °C, and 2 N HCl (5 mL) was introduced. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were washed with water (10 mL) and brine (10 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether) gave **10** (410 mg, 40%) and a mixture of three other diastereomeric diols (460 mg). The latter material was dissolved in dry CH_2Cl_2 (30 mL) and stirred at 20 °C in the presence of pyridinium chlorochromate on alumina (8.5 g, 1 mmol/g, 8.5 mmol) for 20 min. The resultant brown mixture was diluted with ether (100 mL) and filtered through a Celite pad. The filtrate was concentrated in vacuo to return 450 mg (100%) of diketone **9**, which was resubmitted to Dibal-H reduction as described above. The yield of **10** based on recovered unwanted diastereomers was 76%, colorless solid, mp 127–129 °C: IR (KBr, cm^{-1}) 3500–3100; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddd, J = 10, 2.5, 1 Hz, 1 H), 5.46 (br dd, J = 10, 0.5 Hz, 1 H), 4.20–4.15 (br m, 1 H), 3.95 (dt, J = 4.5, 4.5 Hz, 1 H), 3.76 (t, J = 4.5 Hz, 1 H), 2.22–2.14 (m, 1 H), 2.04–1.82 (m, 3 H), 1.80–1.52 (m, 5 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 129.9, 78.6, 71.6, 63.8, 56.6, 56.1, 41.9, 36.1, 34.3, 30.8, 25.8 (3 C), 20.1, 18.1, –4.7, –4.8; MS *m/z* (M^+ – *t*-Bu) calcd 267.1416, obsd 267.1406.

Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.24; H, 9.87.

(3a*R,4*S**,5a*S**,7*R**,9a*S**)-2,3,3a,4,5,5a,6,7-Octahydro-4,7-bis(methoxymethoxy)-1*H*-cyclopent[*c*]inden-1-one (11).** Chloromethyl methyl ether (0.52 mL, 6.8 mmol) was added dropwise to a solution of **10** (440 mg, 1.36 mmol) and diisopropylethylamine (1.42 mL, 8.2 mmol) in dry CH_2Cl_2 (15 mL) under N_2 at room temperature. After 8 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated NH_4Cl solution (2 × 20 mL) and brine (20 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in petroleum ether) provided the bis(MOM) ether (490 mg, 88%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (br dd, J = 10, 1.5 Hz, 1 H), 5.41 (br d, J = 10 Hz, 1 H), 4.69 (ABq, J = 7 Hz, $\Delta\nu$ = 9 Hz, 2 H), 4.62 (d, J = 7 Hz, 1 H), 4.56 (d, J = 7 Hz, 1 H), 4.10–3.96 (m, 2 H), 3.89 (dd, J = 9, 6 Hz, 1 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.59–2.51 (m, 1 H), 2.20–2.14 (m, 1 H), 1.93–1.55 (series of m, 7 H), 1.50–1.38 (m, 1 H), 0.87 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 128.4, 95.8, 95.2, 81.0, 78.4, 69.5, 55.4, 55.1, 54.8, 52.8, 36.9, 34.7, 32.8, 31.2, 25.9 (3 C), 21.1, 18.1, –4.6, –4.7; FAB MS *m/z* (M^+ + 1) calcd 411.26, obsd 411.28.

Anal. Calcd for $C_{22}H_{40}O_5Si$: C, 64.04; H, 9.77. Found: C, 64.36; H, 9.77.

Tetra-*n*-butylammonium fluoride (7 mL of 1 M solution in THF, 7 mmol) was added to the bis(MOM) ether (570 mg, 1.4 mmol) at 20 °C. After evaporation of the THF, the residue was dissolved in dry HMPA (40 mL), treated with 3-Å molecular sieves (0.1 g), stirred under N_2 for 30 min, and diluted with ethyl acetate (200 mL). After decantation, the organic solution was washed with saturated NH_4Cl solution (5 × 50 mL) and brine (50 mL), dried, and concentrated. Purification of the product by silica gel chromatography (elution with 50% ethyl acetate in petroleum ether) gave the deprotected alcohol (410 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 3600–3200; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dd, J = 10, 3.5 Hz, 1 H), 5.58 (br d, J = 10 Hz, 1 H), 4.68 (ABq, J = 7 Hz, $\Delta\nu$ = 8 Hz, 2 H), 4.62 (ABq, J = 7 Hz, $\Delta\nu$ = 21.5 Hz, 2 H), 4.10

(ddd, J = 7.5, 4, 4 Hz, 1 H), 3.99 (ddd, J = 6, 6, 6 Hz, 1 H), 3.87–3.81 (br m, 1 H), 3.37 (s, 3 H), 3.35 (s, 3 H), 2.72–2.57 (m, 2 H), 2.29 (ddd, J = 10, 6, 4 Hz, 1 H), 2.05–1.47 (series of m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 128.7, 95.7, 95.1, 79.0, 77.7, 68.7, 55.6, 55.5, 55.4, 53.8, 37.9, 34.1, 32.5, 30.1, 20.1; FAB MS m/z (M^+ + 1) calcd 299.19, obsd 299.22.

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.63; H, 8.87.

A mixture of the deprotected alcohol (0.40 g, 1.34 mmol) and pyridinium chlorochromate on alumina (5 g, 0.9 mmol/g, 4.5 mmol) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h, diluted with ether (100 mL), and filtered through Celite. The filtrate was concentrated and the residue subjected to chromatography on silica gel (elution with 40% ethyl acetate in petroleum ether) to provide **11** (0.35 g, 89%) as a white solid, mp 45–47 °C: IR (CCl_4, cm^{-1}) 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (br dd, J = 10, 2.5 Hz, 1 H), 5.44 (br dd, J = 10, 1.5 Hz, 1 H), 4.72 (s, 2 H), 4.62 (ABq, J = 6.5 Hz, $\Delta\nu$ = 15 Hz, 2 H), 4.19 (ddd, J = 6, 6, 5.5 Hz, 1 H), 4.14–4.08 (br m, 1 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 2.64–2.46 (m, 3 H), 2.33 (ddd, J = 18.5, 9, 6.5 Hz, 1 H), 2.08–1.69 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.6, 131.2, 128.6, 95.8, 95.2, 78.8, 68.5, 59.0, 55.5, 55.3, 52.3, 37.8, 36.4, 35.5, 30.8, 19.4; MS m/z (M^+) calcd 296.1624, obsd 296.1628.

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.59; H, 8.18.

(3a*R,4*S**,5a*S**,7*R**,9a*S**)-3a,4,5,5a,6,7-Hexahydro-4,7-bis(methoxymethoxy)-1*H*-cyclopent[*c*]inden-1-one (12).** *n*-Butyllithium (0.25 mL of 1.6 M solution in hexanes, 0.40 mmol) was added dropwise to a solution of hexamethyldisilazane (0.090 mL, 0.42 mmol) in THF (3 mL) under N_2 at 0 °C. After 30 min, the resultant mixture was cooled to –78 °C, and a solution of **11** (0.10 g, 0.34 mmol) in THF (0.3 mL) was introduced, followed 30 min later by a solution of phenylselenenyl chloride (78 mg, 0.40 mmol) in the same solvent (0.3 mL). The reaction mixture was stirred at –78 °C for 1 h and then warmed slowly to 20 °C before being diluted with ether (5 mL), washed with saturated NH_4Cl solution (5 mL) and brine (5 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in petroleum ether) provided the α-phenylseleno derivative (0.15 g, 100%) as a pale yellow oil.

Hydrogen peroxide (0.31 mL of 30% solution, 2.80 mmol) was added to a mixture of the above material (0.14 g, 0.31 mmol) and pyridine (0.064 mL, 0.79 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 30 min, more CH_2Cl_2 (10 mL) was added, and the organic phase was washed with saturated $NaHCO_3$ solution (5 mL), water (5 mL), and brine (5 mL) prior to drying and concentration. Chromatography of the residue on silica gel (elution with 40% ethyl acetate in petroleum ether) gave **12** (52 mg, 56%) as a colorless oil: IR (neat, cm^{-1}) 1705; ^{1}H NMR (300 MHz, C_6D_6) δ 7.26 (dd, J = 5.5, 3 Hz, 1 H), 6.04 (dd, J = 5.5, 2 Hz, 1 H), 6.03 (dd, J = 10, 4.5 Hz, 1 H), 5.23 (br d, J = 10 Hz, 1 H), 4.63 (ABq, J = 6.5 Hz, $\Delta\nu$ = 22 Hz, 2 H), 4.35 (s, 2 H), 4.03 (ddd, J = 8, 8, 5.5 Hz, 1 H), 3.94 (br ddd, J = 4.5, 4.5, 4 Hz, 1 H), 3.26 (s, 3 H), 3.07 (s, 3 H), 2.82 (ddd, J = 8, 3, 2 Hz, 1 H), 2.55 (br dddd, J = 10.5, 7, 5, 4.5 Hz, 1 H), 1.86 (ddd, J = 13, 5, 4.5 Hz, 1 H), 1.60 (ddd, J = 12.5, 8, 7 Hz, 1 H), 1.45 (ddd, J = 12.5, 5.5, 4.5 Hz, 1 H), 1.27 (ddd, J = 13, 10.5, 4 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 209.3, 162.2, 133.9, 129.9, 129.8, 96.1, 95.4, 77.2, 68.4, 58.0, 56.5, 55.2, 55.1, 36.3, 32.7, 31.9; MS m/z (M^+) calcd 294.1456, obsd 294.1488.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.91; H, 7.58.

(3*R,3a*S**,4*R**,5a*R**,7*S**,9a*R**)-2,3,3a,4,5,5a,6,7-Octahydro-4,7-bis(methoxymethoxy)-1-oxo-1*H*-cyclopent[*c*]indene-3-acetonitrile (13a).** *n*-Butyllithium (1.8 mL of 1.6 M solution in hexanes, 2.86 mmol) was added to a solution of (trimethylsilyl)acetonitrile (0.39 mL, 2.86 mmol) in THF (30 mL) under N_2 at –78 °C. After 30 min, HMPA (1.7 mL, 9.54 mmol) was introduced, followed 30 min later by a solution of **12** (0.70 g, 2.39 mmol) in THF (3 mL). The reaction mixture was stirred for 15 min before being quenched at –78 °C with saturated NH_4Cl solution (5 mL), diluted with ether (50 mL), washed with saturated NH_4Cl solution (20 mL) and water (20 mL), dried, and evaporated. The residue was dissolved in 10% aqueous acetonitrile (30 mL) and stirred at room temperature for 1 h in the presence of potassium fluoride (140 mg, 2.39 mmol). This mixture was diluted with ether (50 mL), washed with saturated $NaHCO_3$ solution (20 mL), water (20 mL), and brine (20 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether) afforded **13a** (0.66 g, 83%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 2440, 1735; ^{1}H NMR (300 MHz, C_6D_6) δ 5.96 (br dd, J = 10, 2.5 Hz, 1 H), 5.09 (ddd, J = 10, 1.5, 1 Hz, 1 H), 4.57 (s, 2 H), 4.24 (ABq, J = 6.5 Hz, $\Delta\nu$ = 10 Hz, 2 H), 3.94 (dddd, J = 9, 5, 2.5, 1.5 Hz, 1 H), 3.88 (ddd, J = 6.5, 6.5, 6 Hz, 1 H), 3.20 (s, 3 H), 3.04 (s, 3 H), 2.35 (dd, J = 17.5, 7.5 Hz, 1 H), 2.25–2.04 (m, 2 H), 2.00–1.76 (series of m, 5 H), 1.66 (br ddd, J = 13, 5.5, 5 Hz, 1 H), 1.47 (ddd, J = 13, 8, 5.5 Hz, 1 H), 1.40 (ddd, J = 13.5, 8, 7 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 213.3, 132.4, 128.7, 118.2, 96.0, 95.6, 78.3, 68.8, 59.7, 56.5, 55.2, 55.1, 43.4, 35.7, 35.6, 30.6, 30.0, 22.7; MS m/z (M^+) calcd 335.1733, obsd 335.1702.

Methyl (1*R,2*R**,3*S**,3a*S**,4*R**,5a*R**,7*S**,9a*R**)-3-(Cyanomethyl)-2,3,3a,4,5,5a,6,7-octahydro-1-hydroxy-4,7-bis(methoxymethoxy)-1*H*-cyclopent[*c*]indene-2-carboxylate (14a).** *n*-Butyllithium (1.48 mL of 1.6 M solution in hexanes, 2.4 mmol) was added dropwise to a solution of diisopropylamine (0.35 mL, 2.5 mmol) in dry THF (100 mL) at 0 °C under N_2. The solution was stirred at 0 °C for 45 min before being cooled to –78 °C and treated with a solution of **13a** (0.72 g, 2.2 mmol) in THF (2 mL). After 20 min, HMPA (0.38 mL, 2.2 mmol) was added, followed 20 min later by methyl cyanoformate (20 mL, 2.6 mmol). The reaction mixture was stirred at –78 °C for 30 min, slowly warmed to –20 °C, and quenched after 1 h with saturated NH_4Cl solution (2 mL). After dilution with ether (100 mL), the separated organic phase was washed with saturated NH_4Cl solution (20 mL), water (2 × 20 mL), and brine (20 mL) prior to drying and concentration. The remaining oil was taken up in methanol (30 mL), cooled to –20 °C, and treated with sodium borohydride (82 mg, 2.2 mmol). After 1 h, the reaction mixture was acidified with 1 N HCl (3 mL), diluted with CH_2Cl_2 (30 mL), washed with water (2 × 10 mL) and brine (10 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether) gave **14a** (0.42 g, 50%) as a colorless gum: IR ($CHCl_3$, cm^{-1}) 3610, 3500–3400, 2240, 1730; ^{1}H NMR (300 MHz, C_6D_6) δ 5.72 (dd, J = 10, 2.5 Hz, 1 H), 5.35 (br dd, J = 10, 1.5 Hz, 1 H), 4.58 (s, 2 H), 4.27 (d, J = 6.5 Hz, 1 H), 4.19 (d, J = 6.5 Hz, 1 H), 3.98 (br dddd, J = 8, 6, 2.5, 1.5 Hz, 1 H), 3.94 (dd, J = 9.5, 4 Hz, 1 H), 3.73 (ddd, J = 6, 4, 3.5 Hz, 1 H), 3.36 (s, 3 H), 3.21 (s, 3 H), 3.12–3.01 (m, 1 H), 3.04 (d, J = 9.5 Hz, 1 H), 3.04 (s, 3 H), 2.93 (dd, J = 11.5, 4 Hz, 1 H), 2.88–2.77 (m, 1 H), 2.13 (dd, J = 16.5, 4.5 Hz, 1 H), 2.02 (dd, J = 16.5, 6.5 Hz, 1 H), 1.83 (dd, J = 8.5, 6 Hz, 1 H), 1.79 (ddd, J = 12.5, 6.5, 3.5 Hz, 1 H), 1.75–1.65 (m, 2 H), 1.28 (ddd, J = 12.5, 10.5, 4 Hz, 1 H); ^{13}C NMR (62.5 MHz, C_6D_6) δ 171.7, 133.3, 128.5, 118.4, 95.5, 95.4, 78.7, 76.0, 69.1, 60.3, 56.6, 56.5, 55.5, 55.0, 51.4, 38.8, 33.9, 31.1, 30.6, 21.3; FAB MS m/z (M^+ + 1) calcd 396.20, obsd 396.21.

Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.75; H, 7.39. Found: C, 60.74; H, 7.41.

Methyl (2*R,3*R**,3a*R**,4*S**,5a*S**,7*R**,9a*R**)-3-(Cyanomethyl)-2,3,3a,4,5,5a,6,7-octahydro-4,7-bis(methoxymethoxy)-1*H*-cyclopent[*c*]indene-2-carboxylate (15).** Phosgene (0.30 mL of 1.93 M solution in toluene, 0.58 mmol) was added to a solution of **14a** (42 mg, 0.106 mmol) and pyridine (0.2 mL) in THF (5 mL). After 1 h at room temperature, the reaction mixture was concentrated to approximately 10% of its volume to remove the excess phosgene. THF (4 mL), benzene (4 mL), and pyridine (0.2 mL) were then added, followed by benzeneselenol (0.06 mL, 0.57 mmol). After the mixture was stirred for 2 h at room temperature, ether was added, and the organic layer was washed with 5% HCl, water, and brine prior to drying and solvent evaporation. Purification of the residue by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) afforded selenocarbonate **14b** (58 mg, 95%) as a colorless gum: IR (CCl_4, cm^{-1}) 2230, 1740, 1715, 1430, 1100, 1040, 915, 680; ^{1}H NMR (300 MHz, C_6D_6) δ 7.52–7.44 (m, 2 H), 6.98–6.91 (m, 3 H), 5.73 (dd, J = 10, 3.5 Hz, 1 H), 5.54 (d, J = 5 Hz, 1 H), 5.12 (br d, J = 10 Hz, 1 H), 4.49 (ABq, J = 6.5 Hz, $\Delta\nu$ = 8.5 Hz, 2 H), 4.31 (ABq, J = 6.5 Hz, $\Delta\nu$ = 7.5 Hz, 2 H), 3.93–3.86 (br m, 1 H), 3.81 (ddd, J = 7, 6, 6 Hz, 1 H), 3.38 (s, 3 H), 3.16 (s, 3 H), 3.09 (s, 3 H), 3.09 (dddd, J = 12, 9, 5, 4 Hz, 1 H), 3.00 (dd, J = 12, 5 Hz, 1 H), 2.57 (br dddd, J = 7, 7, 7, 5 Hz, 1 H), 2.40 (dd, J = 17, 5 Hz, 1 H), 2.28 (dd, J = 17, 4 Hz, 1 H), 1.95 (br dd, J = 9, 7 Hz, 1 H), 1.81–1.69 (m, 2 H), 1.56–1.41 (m, 2 H); ^{13}C NMR (62.5 MHz, C_6D_6) δ 170.1, 165.4, 135.9 (2 C), 132.2, 129.4 (2 C), 129.1, 128.8, 126.2, 118.0, 95.9, 95.4, 83.9, 76.0, 68.5, 57.6, 55.4, 55.2, 55.0, 53.1, 51.8, 37.8, 35.9, 32.4, 31.2, 20.6; FAB MS m/z (M^+ + 1) calcd 580.14, obsd 580.26.

A mixture of **14b** (298 mg, 0.52 mmol), tris(trimethylsilyl)silane (0.35 mL, 1.13 mmol), and AIBN (10 mg) was heated at reflux in benzene (30 mL) under N_2 for 2 h. After the mixture was cooled, the solvent was evaporated, and the residue was subjected to flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether). There was obtained 179 mg (92%) of **15** as a colorless gum: IR (CCl_4, cm^{-1}) 2250, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (dd, J = 10, 3 Hz, 1 H), 5.70

(d, J = 10 Hz, 1 H), 4.66 (s, 2 H), 4.62 (d, J = 6.5 Hz, 1 H), 4.59 (d, J = 6.5 Hz, 1 H), 4.17 (ddd, J = 7, 7, 6 Hz, 1 H), 4.05 (ddd, J = 5.5, 5.5, 3 Hz, 1 H), 3.70 (s, 3 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 2.88 (ddd, J = 11, 10.5, 7.5 Hz, 1 H), 2.84–2.72 (m, 1 H), 2.65 (m, 2 H), 2.25–2.17 (m, 2 H), 2.06 (dd, J = 13, 7 Hz, 1 H), 1.98 (ddd, J = 13, 7, 7 Hz, 1 H), 1.90 (dd, J = 13, 10.5 Hz, 1 H), 1.82 (ddd, J = 13, 6, 6 Hz, 1 H), 1.77–1.63 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.6, 135.8, 126.1, 118.2, 96.0, 95.4, 77.1, 68.7, 57.7, 55.1, 55.0, 51.7, 51.4, 48.9, 43.4, 39.7, 38.1, 36.6, 31.5, 21.1; FAB MS m/z (M^+ + 1) calcd 380.21, obsd 380.20.

Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.31; H, 7.70. Found: C, 62.89; H, 7.93.

(3*R,4a*S**,6*S**,6a*R**,6b*R**,10a*R**,11a*R**)-3,4,4a,5,6,6a,6b,7,8,9,10a,-11-Dodecahydro-3,6-bis(methoxymethoxy)-9-methyl-10*H*-benzo[3a,4]-pentaleno[2,1-*c*]pyridin-10-one (16b).** Sodium borohydride (500 mg, 13.2 mmol) was added in small portions to a solution of **15** (175 mg, 0.46 mmol) and anhydrous cobalt(II) chloride (180 mg, 1.39 mmol) in methanol (30 mL) during 3 h at room temperature. Since the starting material was completely consumed at this point (TLC analysis), a solution of KOH in methanol (10 mL of 10% w/v) was introduced, and stirring was continued for 4 h. The reaction mixture was partitioned between $CHCl_3$ and 5% HCl in brine, and the organic phase was dried and evaporated to afford lactam **16a** (130 mg). This material could be purified by flash chromatography on silica gel (elution with 10% methanol in $CHCl_3$) to give **16a** as a colorless solid, mp 109–110 °C (from ether), but was routinely carried forward without purification since it contained variable amounts of the (chromatographically unseparable) fully saturated analog formed by overreduction: IR ($CHCl_3$, cm^{-1}) 3400, 1660; ^{1}H NMR (300 MHz, C_6D_6) δ 5.74 (dd, J = 10, 4 Hz, 1 H), 5.39 (br d, J = 10 Hz, 1 H), 5.25 (br s, 1 H), 4.58 (ABq, J = 6.5 Hz, $\Delta\nu$ = 11 Hz, 2 H), 4.37 (ABq, J = 6.5 Hz, $\Delta\nu$ = 12 Hz, 2 H), 4.02 (ddd, J = 7.5, 7.5, 6 Hz, 1 H), 3.95 (br ddd, J = 5.5, 4.5, 4.5 Hz, 1 H), 3.20 (s, 3 H), 3.10 (s, 3 H), 2.75–2.60 (m, 2 H), 2.26 (dd, J = 12, 5.5 Hz, 1 H), 2.14–1.94 (m, 3 H), 1.90–1.50 (m, 5 H), 1.53 (ddd, J = 12.5, 6, 5 Hz, 1 H), 1.43 (ddd, J = 13.5, 9, 4.5 Hz, 1 H), 1.14–1.00 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.7, 137.8, 124.7, 95.7, 95.4, 76.6, 68.8, 58.7, 55.0, 54.9, 51.6, 48.8, 42.2, 41.6, 41.5, 38.2, 36.6, 32.1, 28.7; MS m/z (M^+) calcd 351.2046, obsd 351.2047.

Unpurified **16a** from above (130 mg) in THF (40 mL) was stirred with sodium hydride (60 mg, 2.5 mmol) for 1 h at room temperature, at which point methyl iodide (1.0 mL) was introduced. Stirring was continued until TLC analysis indicated complete consumption of starting material. Saturated NH_4Cl solution was added, and the reaction mixture was partitioned between $CHCl_3$ and 5% HCl in brine. The organic layer was dried and evaporated, and the crude product (123 mg) was purified by flash chromatography on silica gel (elution with 10% methanol in $CHCl_3$) to afford **16b** (91 mg, 54% from **15**) as a colorless gum. Like its precursor, this material contained variable amounts of the saturated congener: IR ($CHCl_3$, cm^{-1}) 1630; ^{1}H NMR (300 MHz, C_6D_6) δ 5.75 (dd, J = 10, 4 Hz, 1 H), 5.45 (br d, J = 10 Hz, 1 H), 4.58 (ABq, J = 6.5 Hz, $\Delta\nu$ = 10 Hz, 2 H), 4.41 (ABq, J = 6.5 Hz, $\Delta\nu$ = 12 Hz, 2 H), 4.04 (ddd, J = 7.5, 7.5, 6 Hz, 1 H), 3.96 (br ddd, J = 6, 4.5, 4 Hz, 1 H), 3.21 (s, 3 H), 3.14 (s, 3 H), 2.78–2.69 (m, 2 H), 2.70 (s, 3 H), 2.31 (dd, J = 12.5, 5.5 Hz, 1 H), 2.15–1.97 (m, 3 H), 1.92–1.40 (series of m, 7 H), 1.20–0.98 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 171.3, 137.9, 124.6, 95.7, 95.4, 76.7, 68.8, 58.7, 55.0, 54.9, 52.0, 50.2, 49.1, 42.2, 41.7, 38.1, 36.7, 33.3, 32.2, 29.6; MS m/z (M^+) calcd 365.2202, obsd 365.2203.

(4a*R,6*S**,6a*R**,6b*R**,10a*S**,11a*R**)-4a,5,6,6a,6b,7,8,9,10a,11-Decahydro-6-hydroxy-9-methyl-3*H*-benzo[3a,4]pentaleno[2,1-*c*]pyridine-3,10-dione (18).** A solution of lithium diisopropylamide in THF (5 mL of 0.5 M, 2.5 mmol) was added at –78 °C to a solution of **16b** (90 mg, 0.246 mmol) in THF (20 mL). The reaction mixture was stirred at –10 °C for 30 min, returned to –78 °C, and quenched by rapid introduction of H_2O–THF (5 mL of 1:4 v/v) with vigorous stirring. Partitioning between $CHCl_3$ and 5% HCl in brine followed by drying and evaporation of the organic phase led to quantitative recovery of cis lactam **17a** as a colorless solid, which was carried forward without purification: IR ($CHCl_3$, cm^{-1}) 1620; ^{1}H NMR (300 MHz, C_6D_6) δ 5.74 (ddd, J = 10, 2, 1 Hz, 1 H), 5.30 (ddd, J = 10, 1.5, 1 Hz, 1 H), 4.60 (ABq, J = 6.5 Hz, $\Delta\nu$ = 8.5 Hz, 2 H), 4.43 (d, J = 6.5 Hz, 1 H), 4.35 (d, J = 6.5 Hz, 1 H), 4.06 (dddd, J = 9.5, 5.5, 2, 1.5 Hz, 1 H), 3.87 (ddd, J = 6.5, 4.5, 3 Hz, 1 H), 3.22 (s, 3 H), 3.12 (s, 3 H), 2.75–2.65 (m, 1 H), 2.70 (s, 3 H), 2.53 (ddd, J = 12, 5, 3 Hz, 1 H), 2.40–2.24 (m, 3 H), 2.10–1.10 (series of m, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 171.1, 137.6, 127.1, 95.9, 95.5, 78.4, 69.6, 61.8, 55.2, 55.0, 52.0, 49.0, 46.9, 43.1, 39.9, 38.8, 36.6, 34.3, 30.4, 26.6; MS m/z (M^+) calcd 365.2202, obsd 364.2207.

Lactam **17a** from above was dissolved in THF (20 mL), treated with 10% HCl (10 mL), and stirred overnight. After neutralization with aqueous NaOH and exhaustive extraction of diol **17b** into $CHCl_3$, the combined organic layers were dried and evaporated. The residue (65 mg) was stirred with activated manganese dioxide (1.0 g) in $CHCl_3$ (15 mL) for 2 h, filtered though a pad of Celite, and evaporated. Purification of the residue by flash chromatography on silica gel (elution with 10% methanol in $CHCl_3$) afforded **18** (32 mg, 47% from **16b**) as a colorless solid, mp 268 °C (from methanol): IR (film, cm^{-1}) 3500–3200, 1665, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, J = 10, 1.5 Hz, 1 H), 5.84 (dd, J = 10, 1 Hz, 1 H), 4.32 (ddd, J = 6.5, 4, 1 Hz, 1 H), 3.40 (ddd, J = 12, 9, 6.5 Hz, 1 H), 3.24 (ddd, J = 12, 4, 3.5 Hz, 1 H), 3.05 (br ddd, J = 12, 7, 7 Hz, 1 H), 2.95 (s, 3 H), 2.72–2.58 (m, 2 H), 2.69 (dd, J = 15, 6 Hz, 1 H), 2.44 (br d, J = 15 Hz, 1 H), 2.39 (dd, J = 13, 7.5 Hz, 1 H), 2.21 (dd, J = 6.5, 1 Hz, 1 H), 1.85–1.70 (m, 3 H), 1.83 (dd, J = 13, 12 Hz, 1 H), 1.68 (ddd, J = 13, 13, 4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 171.4, 155.7, 126.0, 72.0, 63.4, 52.9, 49.5, 46.8, 41.7, 40.2, 39.7, 38.3, 37.6, 34.7, 26.2; MS m/z (M^+) calcd 275.1521, obsd 275.1520.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.98; H, 7.71.

Magellaninone (2). Ethereal methyllithium (0.30 mL of 1.5 M, 0.45 mmol) was added dropwise at –78 °C to a solution of **18** (25 mg, 0.092 mmol) in THF (20 mL). After 30 min, the reaction mixture was quenched with saturated NH_4Cl solution at –78 °C and worked up by partitioning between $CHCl_3$ and brine. The organic phase was dried and evaporated to leave the diol as a colorless gum (23 mg, 87%), which proved to be a single isomer by ^{1}H NMR. This material was carried forward without purification: IR ($CHCl_3$, cm^{-1}) 3600, 3500–3200, 1620; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (d, J = 10 Hz, 1 H), 5.40 (d, J = 10 Hz, 1 H), 4.35 (ddd, J = 7, 5.5, 5.5 Hz, 1 H), 3.40–3.30 (m, 1 H), 3.22 (ddd, J = 12, 4.5, 4 Hz, 1 H), 2.92 (s, 3 H), 2.92–2.83 (m, 1 H), 2.65–2.55 (m, 1 H), 2.22–1.95 (m, 6 H), 1.86–1.63 (m, 6 H), 1.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 135.8, 131.5, 72.6, 67.8, 61.6, 51.9, 49.3, 46.6, 43.7, 40.9, 40.1, 39.7, 37.8, 34.7, 30.1, 26.5; MS m/z (M^+) calcd 291.1834, obsd 291.1834.

To a solution of the diol from above (23 mg) in THF (5 mL) was added lithium aluminum hydride (20 mg, 0.53 mmol). This mixture was refluxed for 2 h, cooled to 0 °C, and hydrolyzed with 10% NaOH. After the further addition of brine, the product was extracted into $CHCl_3$, and the combined organic layers were dried and evaporated to leave 18 mg of the amino diol. This material was dissolved in acetone (1 mL) and treated at 0 °C with small portions of Jones' reagent (2.5 M CrO_3 in 20% aqueous H_2SO_4) until a yellow color persisted. Isopropyl alcohol was added to destroy the excess oxidant, the mixture was diluted with brine and $CHCl_3$, and neutralization was effected with aqueous NaOH. The acetone was removed under reduced pressure, and the product was extracted into $CHCl_3$ after the addition of brine containing NaOH. The organic phase was dried and evaporated, and the residue was passed through a plug of basic alumina (activity I) with $CHCl_3$ to deliver **2** (17 mg, 67%) as a faintly yellow gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (br s, 1 H), 3.02 (br d, J = 7 Hz, 1 H), 2.75 (dddd, J = 19, 6.5, 2.5, 1 Hz, 1 H), 2.65–1.70 (series of m, 14 H), 2.27 (s, 3 H), 1.98 (br s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 200.6, 158.3, 125.7, 60.1, 58.5, 56.3, 52.7, 46.4, 44.9, 40.6, 40.0, 39.5, 39.3, 29.8, 25.9, 24.6; MS m/z (M^+) calcd 273.1729, obsd 273.1726.

5-Epimagellanine (19). To a solution of **2** (12.4 mg) in ethanol (1 mL) was added solid sodium borohydride at 0 °C in very small portions with close monitoring of reaction progress by TLC. As soon as all of **2** had been consumed, the excess hydride was destroyed by the addition of a few drops of 5% HCl. The reaction mixture was partitioned between $CHCl_3$ and brine containing some NaOH, and the organic phase was dried and evaporated to give 9.4 mg (76%) of **19** as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (br s, 1 H), 3.81 (ddd, J = 9.5, 6, 6 Hz, 1 H), 2.72–2.57 (br m, 3 H), 2.55 (br d, J = 7 Hz, 1 H), 2.36 (dd, J = 5.5, 3.5 Hz, 1 H), 2.27–1.77 (series of m, 7 H), 2.21 (s, 3 H), 1.93 (br s, 3 H), 1.72–1.50 (m, 3 H), 1.54 (ddd, J = 13.5, 11.5, 9.5 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.7, 157.7, 125.3, 78.0, 63.0, 60.0, 56.6, 54.6, 46.8, 42.2, 41.3, 40.9, 39.9, 38.2, 30.3, 26.6, 24.5; MS m/z (M^+) calcd 275.1885, obsd 275.1879.

Magellanine (1). To a solution of **19** (6.5 mg, 0.024 mmol), triphenylphosphine (25 mg, 0.095 mmol), and formic acid (20 mg, 18.5 equiv) in THF (3 mL) was added diethyl azodicarboxylate (16 mg, 0.092 mmol) dropwise during 5 min. With TLC monitoring of reaction progress, sequential addition of triphenylphosphine and diethyl azodicarboxylate was repeated several times during the course of 3 h, during which time a less polar product was being formed. Once the conversion was complete, the mixture was diluted with methanol (5 mL) and treated with a few

drops of 10% aqueous KOH until strongly alkaline. After being stirred for several minutes, the mixture was neutralized by dropwise addition of 5% HCl, concentrated to remove the methanol and THF, and partitioned between $CHCl_3$ and brine containing some NaOH. The dried organic layer was evaporated, and the residue was flash chromatographed first on basic alumina (activity I; elution with $CHCl_3$) and then on silica gel with gradient elution from $CHCl_3$ to $CHCl_3$–CH_3OH–25% NH_4OH (6:3:1) to give 4.7 mg (72%) of **1** as a colorless gum: ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (br s, 1 H), 4.23–4.18 (m, 1 H), 2.80–2.57 (m, 5 H), 2.51 (ddd, J = 12, 7, 7 Hz, 1 H), 2.30–1.50 (series of m, 10 H), 2.20 (br s, 3 H), 1.92 (br s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.2, 158.0, 125.7, 72.1, 61.0, 59.6, 56.5, 55.4, 46.9, 41.9, 41.4, 40.2, 37.3, 37.0, 30.4, 27.0, 24.5; MS m/z (M^+) calcd 275.1885, obsd 275.1892.

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