Use of an Axial β-Face Thiomethyl Control Element in Intramolecular Conjugate Additions. Synthesis of a Tricyclic Bruceantin Precursor[1]

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An ABC ring intermediate for the synthesis of the quassinoidal antileukemia agent bruceantin has been prepared. Control of stereochemistry at C-8 was achieved by intramolecular conjugate addition of a nucleophile bound to the axial C-10 methyl group by a sulfide linkage. Conditions for the control of stereochemistry at C-9 in this conjugate addition approach have been developed. In the preparation of the sulfide intermediate, an inhibition of Birch reduction by a proximate mercaptide was observed. Studies on Birch reduction of analogous alcohol- and ether-bearing compounds gave overreduction and normal reduction modes, respectively. The effects of this intramolecular interaction of the mercaptide in the reduction intermediates were overcome by use of Benkeser reduction conditions. Stereospecific introduction of the C-7 oxygen functionality was accomplished by γ-oxidation of dienol ethers. Persulfate oxidation gave γ-hydroxy enone with competitive oxidation of sulfide to sulfoxide while light-induced autoxidation gave chemospecific oxidation of dienol ether in the presence of sulfide.

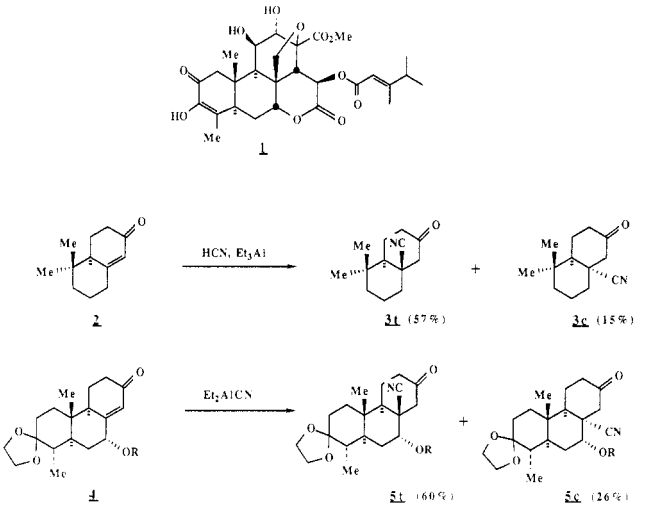
One of the goals of this laboratory has been the stereocontrolled synthesis of bruceantin **1**.[1-4] In the course of model studies on the BCE ring system, it was found that conjugate addition of cyanide ion to octalone **2**, a process intended to mimic the introduction of the axial carbon substituent at C-8 of the ring system, gave a mixture of the cis and trans isomers (**3t**,**3c**) (Scheme I).[3] When this process was carried out on enone **4**, the substrate needed for the actual synthesis, a similar mixture (**5t**/**5c** = 2.3) of epimers was formed.[1]

To incorporate such a step at an early stage of the synthesis would apparently mandate a tedious separation, resulting in the loss of significant amounts of material to an unusable isomer. To avoid this serious bottleneck, an alternate approach was developed which would allow *complete* control of the stereochemistry of the conjugate addition. Specifically, the carbon nucleophile was to be bound covalently to the β-face of the molecule so that α-face addition would be precluded. The use of a sulfide linkage (Scheme II) would accomplish this and, yet, be removable by reduction with Raney nickel at a later point to allow elaboration toward bruceantin. In the course of this investigation, a number of problems in stereochemical control and selectivity of oxidation and reduction were addressed.

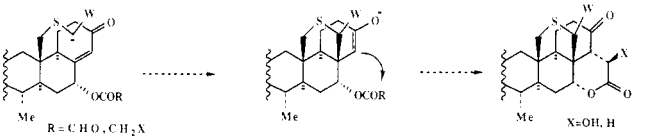
Results and Discussion

Synthesis of the desired sulfide intermediate began with β-keto ester **6**.[5] Robinson annulation was performed with ethyl vinyl ketone, generated in situ by treatment of 1-chloro-3-pentanone[6] with potassium carbonate, to give enone **7** in 84% yield. Hydrogenation[7] of **7** using 10% palladium on carbon catalyst in ethanol/pyridine gave a mixture of all possible ketone diastereoisomers, with the desired isomer **8** as the major product (82% isolated yield). (The other isomers were isolated by fractional crystallization and their properties are reported in the Experimental Section.) Ketalization of **8** under standard conditions gave ketal **9** in 80% yield after recrystallization. The low yield was due to the formation of a small amount of the C-4 epimer of **9** during the reaction. Hydrolysis of the mother liquors gave an almost complete recovery of ketone **8** (17%). LAH reduction of the ester moiety gave alcohol **10** in 94% yield. The mesylate **11** proved to be quite unstable. Treatment of **10** with methane sulfonyl

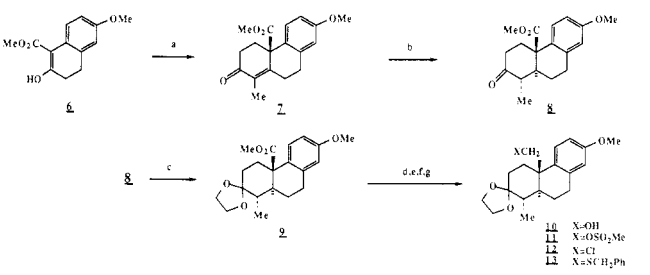
Scheme I



Scheme II



Scheme III[a]



[a] (a) $EtCOC_2H_4Cl$, K_2CO_3; (b) H_2, Pd/C; (c) HOC_2H_4OH, TsOH; (d) LAH; (e) $MeSO_2Cl$, Et_3N; (f) LiCl, NMP; (g) $NaSCH_2Ph$, NMP.

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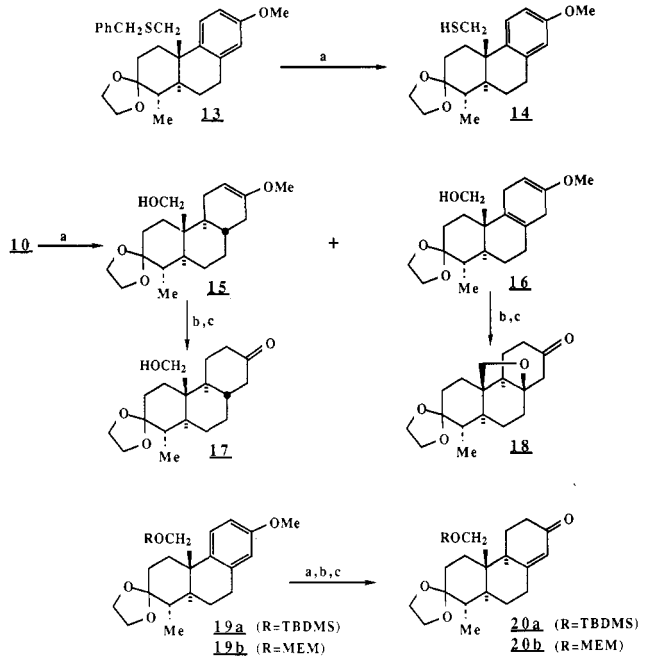
(1) Bruceantin Support Studies. 10. For previous papers in this series see: Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902.

0022-3263/87/1952-0592$01.50/0

Scheme IV[a]

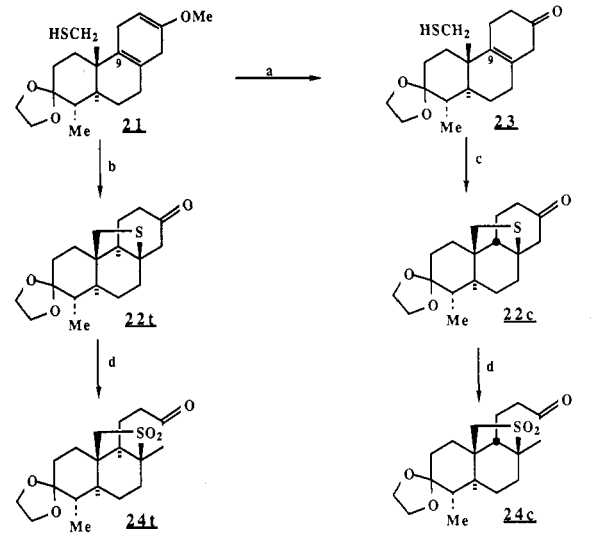


[a] (a) Li/NH_3, *t*-BuOH; (b) HOAc, H_2O; (c) MeOK, MeOH.

chloride and triethylamine in CH_2Cl_2 at 0 °C gave a complex mixture. At −20 °C or −78 °C, mesylate **11** could be formed cleanly, but extensive decomposition occurred upon attempted isolation. Therefore, the mesylate was converted to chloride **12** without isolation. After formation of **11** in CH_2Cl_2 at −78 °C, lithium chloride and *N*-methylpyrrolidinone[8] (NMP) were added to the reaction mixture. After one day at room temperature, the crystalline chloride **12** could be isolated in 91% yield. Nucleophilic displacement of the neopentyl chloride could be accomplished with alkyl mercaptides in HMPA or NMP. Reaction with sodium benzylthiolate in NMP gave benzyl sulfide **13** in 96% yield (Scheme III).

The next step in the planned synthesis called for a one-pot reductive cleavage of the benzyl group,[9] freeing the mercaptan for attachment of the carbon–nucleophile fragment mentioned above, concomitant with reduction of the aromatic nucleus, allowing for construction of the requisite C-ring enone. Under Birch reduction conditions known to be effective for aryl alkyl ethers,[10] there was rapid

Scheme V[a]



[a] (a) HOAc, H_2O; (b) Pyr–HOTs; (c) MeOK, MeOH; (d) MCPBA.

cleavage of the benzyl sulfide. Surprisingly, however, in repeated attempts which employed large excesses of lithium and extended reaction times, the C-ring proved to be resistant to reduction giving mercaptan **14** as the product. This may be contrasted with reports[11] of overreduction rather than lack of reduction in molecules with similar ring systems bearing an unprotected functionality.

To probe the cause of this difficulty, alcohol **10** was used as a model compound with an identical ring system and similar functionality to **14**. Under reduction conditions similar to those employed on **13**, overreduction of **10** to give **15** and **16** (1:1 mixture as indicated by the NMR spectrum of the crude product). Identities of the products were confirmed by hydrolysis of the enol ethers and isolation of the derivatives **17** and **18**, respectively. Deprotonation of the alcohol by treatment with lithium amide prior to the addition of the lithium to the reduction medium led to enhanced overreduction (2:1 ratio of **15**:**16**). Finally, reduction of alcohol-protected[12] derivatives of **10** (**19a,b**) showed no overreduction under similar conditions, giving **20a,b**, respectively (Scheme IV).

These results indicate that there is nothing inherent to the ring system that makes reduction difficult. The presence of a negative charge as an alkoxide does not inhibit reduction, so the presence of a charged group inhibiting the addition of an electron to the mercaptide analogue is unlikely. Beyond this simple electrostatic effect, one may speculate about orbital interactions between the sulfur atom and aromatic ring as a cause for destabilization of the radical anion reduction intermediate. In this case, either the electron transfer from lithium to the aromatic nucleus is slow or the rate of electron transfer from the radical anion intermediate to the proton source is enhanced.

In any event, the solution to this problem was to use more forcing conditions for the reduction. Reduction[13] with lithium in methyl amine with *tert*-butyl alcohol as

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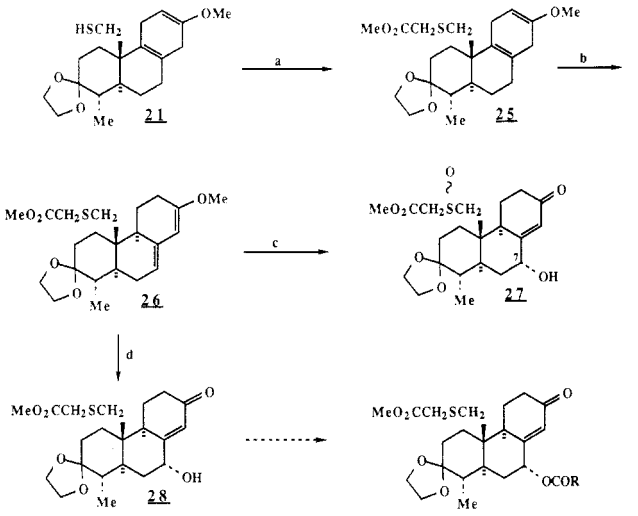
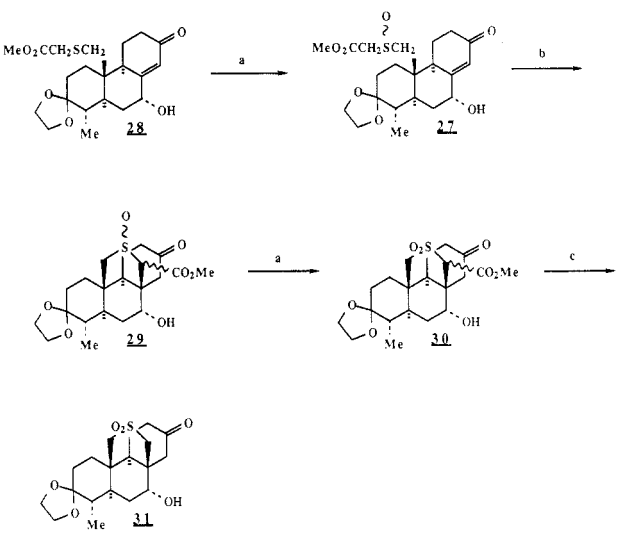
Scheme VI[a]



[a] (a) MeO_2CCH_2Br $(i\text{-}Pr)_2NEt$; (b) Pyr–HOTs; (c) oxone, $NaHCO_3$; (d) light, O_2, sensitizer, MeOH.

Scheme VII[a]



[a] (a) MCPBA; (b) MeOK, MeOH; (c) Me_4NOAc, HMPA, 125 °C.

a proton source gave rapid reduction at both reflux and dry ice temperatures. However, desulfurization products were formed in addition to the desired mercaptan **21**. Therefore, maintaining a temperature below −85 °C was necessary to give good yields (>90%) of **21**.

In the course of the optimization of these reduction conditions, **21** was hydrolyzed and converted to a pair of cyclic sulfides in contrast to the **16** → **18** conversion. In model systems such as **4** or **18**, the stereochemistry established at C-9 by the equilibration of the C-ring enone strongly favors the trans-ring fusion (α-protonation), the stereochemistry required for bruceantin. However, two isomeric cyclic sulfides (**22c,t**) were formed on hydrolysis of **21** (Scheme V), with a ratio that depended upon the hydrolysis method used. When **21** was treated with aqueous acid, β,γ enone **23** could be isolated. Treatment of **23** with base gave predominantly **22c**. On the other hand, treatment of **21** with anhydrous acid, followed by aqueous workup, gave mainly **22t**. Thus, the stereochemistry of **22c** is favored by base-catalyzed equilibration of the enone, and **22t** is favored by acid-catalyzed equilibration[14] of the dienyl ether. Initially, the stereochemistries of the two sulfides were assigned from ^{13}C NMR chemical shift data for **22c** and **22t** and the derived sulfones **24c** and **24t** (see Supplementary Material). However, the need for an unequivocal assignment of the C-9 stereochemistry prompted the determination of the X-ray crystal structures for both sulfones **24c** and **24t** (see Supplementary Material).

The control of stereochemistry at C-9 by acid-catalyzed equilibration of the dienyl ether was used to advantage in further development of the synthesis. Alkylation of mercaptan **21** with methyl bromoacetate gave sulfide **25** in quantitative yield. Isomerization in anhydrous acetic acid or CH_2Cl_2 containing pyridinium tosylate gave dienyl ether **26** in 50% overall yield from benzyl sulfide **13** as a pure crystalline product.

The dienyl ether of **26** is poised for γ-oxidation to introduce the C-7 oxygen functionality necessary for bruceantin. Oxone (Du Pont) has been shown to be the reagent of choice for this type of oxidation in an analogous compound.[15] However, in this instance, oxidation at sulfur was competitive with dienyl ether oxidation, producing several additional products as well as the C-7 oxygenated product sulfoxide **27** (57%). Unfortunately this reaction was not highly reproducible and yields of 20–45% were more generally the norm.

An alternative oxidation method with superior reproducibility was light-initiated autoxidation. Irradiation of a methanol solution of **26** under an oxygen atmosphere, either without sensitizer[16] or in the presence of biacetyl[17] or sulfur dioxide,[18] gave up to 50% yields of sulfide, γ-hydroxyenone **28** (Scheme VI). This intermediate was more useful than **27** due to ease of purification (the sulfide is less polar and is not a mixture of diastereomers) and the ability to form esters at C-7 without the possibility of causing a Pummerer rearrangement of the sulfoxide. This gave some hope for flexibility in attaching an appropriate ester moiety to form the D-ring lactone of bruceantin.

Finally, the concept of sulfur-directed intramolecular conjugate addition could be tested. Oxidation of **28** with MCPBA gave sulfoxide **27** in 90% yield. Treatment of this material with methanolic potassium methoxide caused rapid cyclization to give **29** as a mixture of diastereoisomers. From this mixture, a single isomer could be crystallized in 14% yield. This material was subjected to X-ray crystallographic analysis as a final verification of C-9 stereochemistry. While the results of the X-ray study supported the assigned stereochemistry, a refinement beyond the level of $R = 0.18$ could not be obtained. Therefore, this data cannot be considered as definitive.

Oxidation of the mixture **29** with *m*-CPBA simplified isolation of cyclized products by removal of the polar diastereomeric sulfoxide center giving sulfone products which were easier to purify by chromatography. Thus, the sulfone **30** could be isolated as a mixture of two diastereoisomers in 76% overall yield from sulfide **28**. Removal of the last diastereomeric center by decarboxmethoxylation[19] with tetramethyl ammonium acetate in HMPA gave sulfone **31** in 35% yield (Scheme VII). This material was a single isomer as determined by 470-MHz NMR spectroscopy. Thus, barring the unlikely event that *complete* epimerization of the C-9 center occurred prior to cyclization or *complete* destruction of a C-9 epimer took place

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during this sequence of reactions, the C-9 stereochemistry established for **26** has been maintained through the cyclization process.

In conclusion, the viability of the use of a covalently bound nucleophile for the stereoselective introduction of a carbon group at C-8 has been demonstrated. However, the difficulties involved in the oxidation of a dienyl ether in the presence of sulfide are a bottleneck in the further development of the synthesis. Therefore, an alternative strategy that establishes the C-7 oxygen functionality prior to arene reduction and also utilizes the concept of stereocontrol via an axial heteroatom control element is worthy of investigation.

Experimental Section

General: All reactions were run under a nitrogen atmosphere with magnetic stirring unless otherwise noted. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone. Benzene, toluene, CH_2Cl_2, *tert*-butyl alcohol, ethylene glycol, triethylamine, and hexamethylphosphonic triamide (HMPA) were distilled from CaH_2 and stored over molecular sieves. Anhydrous acetic acid was prepared by distillation from P_2O_5. Flash chromatography was carried out as described by Still[20] using silica gel 60 (230–400 mesh). Other preparative chromatography was carried out on open columns of silica gel 60 (60–200 mesh).

Proton NMR spectra were recorded on Perkin-Elmer R-32 or Nicolet NT-470 spectrometers in $CDCl_3$ solutions with Me_4Si as internal standard. Carbon NMR spectra were recorded on Varian CFT-20 or XL-200 spectrometers. The carbon multiplicities were determined from single-frequency off-resonance decoupled or APT[21] spectra (τ = 8 ms). The APT data are represented by E for methylene and quaternary carbons, and O for methyl and methine carbons.

Mass spectra were recorded on a CRC-21-110-B high resolution mass spectrometer or a Finnigan 4000 mass spectrometer.

Infrared spectra were recorded in $CHCl_3$ solution on a Perkin-Elmer 137 or 267 spectrometer.

Melting points were measured on a Fisher-Johns apparatus and are uncorrected.

2,3,4,4a,9,10-Hexahydro-7-methoxy-4a-(methoxycarbonyl)-1-methyl-2-phenanthrone (7): A 2-L 3-neck flask, equipped with a mechanical stirrer and septum inlet, was charged with K_2CO_3 (200 g, 1.4 mmol) and methanol (150 mL), thoroughly flushed with N_2, and cooled in an ice bath. A solution of 1-carbomethoxy-6-methoxy-2-tetralone (**6**)[5] (150 g, 0.64 mmol) in methanol (500 mL) was added via cannula. An additional 100 mL of methanol was used to flush the flask and cannula to ensure complete transfer of the tetralone. A solution of 1-chloro-3-pentanone (80 g, 0.66 mmol) in methanol (150 mL) was added *via* cannula. The flask was allowed to warm to room temperature, and stirring was continued at room temperature for 3 days. The reaction mixture was filtered, and the precipitate was shaken with a mixture of CH_2Cl_2 and water until completely dissolved. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated in vacuo. Crystallization of the residue from ether/$CHCl_3$ gave enone **7** (161 g, 84%): mp 114–115 °C; MS, $C_{18}H_{20}O_4$ calcd 300.136, found 300.133; ^{1}H NMR δ 1.85 (3 H, s), 2.0–3.1 (8 H, m), 3.64 (3 H, s), 3.80 (3 H, s), 6.65–6.90 (2 H, m), 7.40 (1 H, d); ^{13}C NMR δ 11.2 (CH_3), 29.0 (CH_2), 29.2 (CH_2), 33.9 (CH_2), 35.0 (CH_2), 50.6 (C), 52.6 (OCH_3), 55.1 (OCH_3), 112.8 (CH), 113.3 (CH), 127.4 (CH), 129.6 (C), 131.3 (C), 139.0 (C), 155.2 (C), 159.7 (C), 172.7 (C), 196.9 (C); IR 3.42, 5.85, 6.06, 6.24, 6.71. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found C 71.74, H 6.87.

1β,2,3,4,4a,9,10,10aα-Octahydro-7-methoxy-4aβ-(methoxycarbonyl)-1α-methyl-2-phenanthrone (8): Enone **7** (150 g, 0.5 mmol) was placed in a 2-L Brown flask. A suspension of 10% palladium on carbon (1.5 g) in 100 mL of ethanol was added, followed by an additional 900 mL of ethanol and 5 mL of pyridine. The flask was attached to a Brown[2] hydrogenator, and hydrogenation was allowed to continue for 3 days. The solution was filtered through Celite, and the filter cake was washed with CH_2Cl_2 to dissolve some material that had crystallized during the reaction. The filtrate was concentrated in vacuo and the residue dissolved in CH_2Cl_2. The solution was washed with 10% HCl and saturated $NaHCO_3$ and then dried with Na_2SO_4. The solution was concentrated in vacuo and the residue crystallized from ether. Recrystallization from ether/$CHCl_3$ gave ketone **8** (124 g, 82%): mp 102–103 °C; MS, $C_{18}H_{22}O_4$ calcd 302.152, found 302.151; ^{1}H NMR δ 1.12 (3 H, d), 1.5–3.3 (10 H, m), 3.69 (3 H, s), 3.78 (3 H, s), 6.7 (2 H, m), 7.38 (1 H, d); ^{13}C NMR δ 11.8 (CH_3), 22.8 (CH_2), 29.7 (CH_2), 36.1 (CH_2), 38.9 (CH_2), 46.1 (CH), 48.8 (CH), 49.1 (C), 51.9 (OCH_3), 54.9 (OCH_3), 112.3 (CH), 113.6 (CH), 127.8 (CH), 130.0 (C), 138.4 (C), 158.6 (C), 174.0 (C), 210.6 (C); IR 3.4, 5.8, 5.85, 6.2, 6.7. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H 7.33. Found C, 71.64; H, 7.42. In the process of fractional crystallization of mother liquors from several hydrogenation runs, the other isomers of ketone **8** were isolated.

1α,2,3,4,4a,9,10,10aα-Octahydro-7-methoxy-4aβ-(methoxycarbonyl)-1β-methyl-2-phenanthrone: mp 89–92 °C; MS, $C_{18}H_{22}O_4$ calcd 302.152, found 302.152; ^{1}H NMR δ 1.04 (3 H, d), 1.3–3.3 (10 H, m), 3.63 (3 H, s), 3.78 (3 H, s), 6.7 (2 H, m), 7.19 (1 H, d); ^{13}C NMR δ 11.9 (CH_3), 23.3 (CH_2), 30.2 (CH_2), 35.8 (CH_2), 36.3 (CH_2), 45.5 (CH), 45.5 (C), 49.6 (CH), 51.9 (OCH_3), 55.1 (OCH_3), 112.4 (CH), 114.3 (CH), 127.0 (CH), 131.0 (C), 138.0 (C), 158.6 (C), 175.6 (C), 213.9 (C); IR 3.4, 5.8, 5.85, 6.2, 6.7 cm^{-1}.

1β,2,3,4,4a,9,10,10aβ-Octahydro-7-methoxy-4aβ-(methoxycarbonyl)-1α-methyl-2-phenanthrone: mp 130–132 °C; MS, $C_{18}H_{22}O_4$ calcd 302.152, found 302.156; ^{1}H NMR δ 1.10 (3 H, d), 1.6–3.0 (10 H, m), 3.77 (3 H, s), 3.81 (3 H, s), 6.7 (2 H, m), 7.00 (1 H, d); ^{13}C NMR δ 11.7 (CH_3), 19.3 (CH_2), 30.0 (CH_2), 35.4 (CH_2), 39.4 (CH_2), 45.4 (CH), 46.5 (CH), 51.9 (C), 52.6 (OCH_3), 55.1 (OCH_3), 112.8 (CH), 114.0 (CH), 127.4 (CH), 130.7 (C), 136.1 (C), 158.4 (C), 175.9 (C), 211.7 (C); IR 3.4, 5.8, 5.85, 6.2, 6.7 cm^{-1}.

1α,2,3,4,4a,9,10,10aβ-Octahydro-7-methoxy-4aβ-(methoxycarbonyl)-1β-methyl-2-phenanthrone: mp 137–138 °C; MS, $C_{18}H_{22}O_4$ calcd 302.152, found 302; ^{1}H NMR δ 1.11 (3 H, d), 1.8–2.9 (10 H, m), 3.66 (3 H, s), 3.80 (3 H, s), 6.7 (2 H, m), 7.33 (1 H, d); ^{13}C δ NMR 12.4 (CH_3), 23.5 (CH_2), 25.6 (CH_2), 33.9 (CH_2), 36.9 (CH_2), 44.3 (CH), 45.2 (CH), 50.0 (C), 52.5 (OCH_3), 55.1 (OCH_3), 112.9 (CH), 113.8 (CH), 126.7 (CH), 128.9 (C), 138.0 (C), 158.5 (C), 176.3 (C), 212.1 (C); IR 3.4, 5.8, 6.2, 6.7 cm^{-1}.

1β,2,3,4,4a,9,10,10aα-Octahydro-7-methoxy-4aβ-(methoxycarbonyl)-1α-methyl-2-phenanthrone 2-(Ethylene Acetal) (9). A 2-L flask was charged with ketone **8** (151 g, 0.5 mmol), benzene (1 L), *p*-toluenesulfonic acid (0.5 g), and ethylene glycol (42 mL, 0.7 mmol). The flask was fitted with a Dean–Stark trap and the mixture heated at reflux for 2 days. Most of the benzene (700 mL) was removed by distillation. The residue was diluted with ether, then washed with saturated $NaHCO_3$, and dried (Na_2SO_4). Concentration in vacuo, crystallization from ether, and recrystallization from ether/$CHCl_3$ gave ketal **9** (138 g, 80%): mp 110–112 °C; MS, $C_{20}H_{26}O_5$ calcd 346.178, found 346.180; ^{1}H NMR δ 0.93 (3 H, d), 1.5–2.4 (7 H, m), 2.7–2.9 (3 H, m), 3.60 (3 H, s), 3.77 (3 H, s), 3.95 (4 H, br s), 6.6–6.8 (2 H, m), 7.41 (1 H, d); ^{13}C NMR δ 10.7 (CH_3), 22.0 (CH_2), 29.7 (CH_2), 33.0 (CH_2), 33.9 (CH_2), 40.8 (CH), 45.4 (CH), 49.2 (C), 51.5 (OCH_3), 54.9 (OCH_3), 65.0 (OCH_2), 65.0 (OCH_2), 110.2 (C), 111.9 (CH), 113.4 (CH), 127.8 (CH), 131.2 (C), 138.7 (C), 158.3 (C), 174.3 (C); IR 3.4, 5.8, 6.2, 6.7 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found C, 69.13; H, 7.80. The residue from the mother liquors was hydrolyzed ($CHCl_3$, 10% HCl—two-phase reaction). Workup and crystallization from ether gave ketone **8** (25.6 g, 17%).

1β,2,3,4,4a,9,10,10aα-Octahydro-4aβ-(hydroxymethyl)-7-methoxy-1α-methyl-2-phenanthrone 2-(Ethylene Acetal) (10). To a solution of LAH (1.25 g, 33 mmol) in THF (50 mL) at 0 °C was added a solution of ketal **9** (10.4 g, 30 mmol) in THF (100 mL). The solution was warmed to room temperature and stirred overnight. The flask was cooled in an ice bath, and then water (1.25 mL) and 10% NaOH (1.25 mL) were added to destroy excess hydride. After 15 min, water (4 mL) was added. Stirring was continued until the precipitate was white. The precipitated aluminum salts were removed by filtration, and the filtrate was concentrated in vacuo Crystallization of the residue from ether gave alcohol **10** (9.0 g, 94%): mp 110–112 °C; MS, $C_{19}H_{26}O_4$ calcd 318.183, found 318.184; ^{1}H NMR δ 0.90 (3 H, d), 0.98–1.12 (1 H,

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m, exchanges with D_2O), 1.5–2.0 (7 H, m), 2.4–2.6 (1 H, m), 2.8–3.0 (2 H, m), 3.75 (3 H, s), 3.92 (4 H, br s), 3.6–3.9 (2 H, m), 6.6–6.8 (2 H, m), 7.22 (1 H, d); ^{13}C NMR δ 11.0 (CH_3), 21.2 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 31.0 (CH_2), 39.6 (CH), 40.4 (C), 44.6 (CH), 54.9 (OCH_3), 63.2 (OCH_2), 64.9 (OCH_2), 64.9 (OCH_2), 110.4 (C), 111.0 (CH), 113.9 (CH), 127.2 (CH), 135.0 (C), 137.6 (C), 157.8 (C); IR 2.8, 3.4, 6.2, 6.7 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found C, 71.56; H, 8.33.

1β,2,3,4,4a,9,10,10aα-Octahydro-4aβ-(chloromethyl)-7-methoxy-1α-methyl-2-phenanthrone 2-(Ethylene Acetal) (12). A solution of alcohol **10** (20 g, 63 mmol) in dry CH_2Cl_2 (180 mL) was cooled in a dry ice–isopropanol bath. Triethylamine (20 mL, 140 mmol) was added. Methanesulfonyl chloride (8 mL, 100 mmol) was added dropwise over 1 h. After 1.5 h at −78°C, LiCl (15 g, 350 mmol) and NMP (200 mL) were added. The mixture was allowed to warm to room temperature overnight. The mixture was diluted with ether and washed several times with water. After drying (Na_2SO_4), the solvent was removed in vacuo and the residue crystallized from ether/$CHCl_3$ to give chloride **12** (19.3 g, 91%): mp 116–117 °C; MS, $C_{19}H_{25}ClO_3$ calcd 336.149, found 336.150; ^1H NMR δ 0.90 (3 H, d), 1.5–2.0 (7 H, m), 2.7 (1 H, m), 2.8–3.0 (2 H, m), 3.78 (3 H, s), 3.97 (4 H, br s), 3.5–4.1 (2 H, AB, J = 11 Hz), 6.6–6.8 (2 H, m), 7.30 (1 H, d); ^{13}C NMR δ 11.0 (CH_3), 21.2 (CH_2), 28.5 (CH_2), 29.5 (CH_2), 30.7 (CH_2), 39.5 (C), 40.0 (CH), 45.5 (CH), 48.8 (CH_2Cl), 55.0 (OCH_3), 65.0 (OCH_2), 65.0 (OCH_2), 110.0 (C), 110.7 (CH), 113.7 (CH), 128.1 (CH), 134.5 (C), 136.6 (C), 158.1 (C); IR 3.4, 6.2, 6.7. Anal. Calcd for $C_{19}H_{25}ClO_3$: C, 67.74; H, 7.48; Cl 10.52. Found C, 67.86; H, 7.40; Cl, 10.34.

1α,2,3,4,4a,9,10,10aα-Octahydro-7-methoxy-1α-methyl-4aβ-(3-phenyl-2-thiapropyl)-2-phenanthrone 2-(Ethylene Acetal) (13). A 500-mL flask was charged with NMP (300 mL) and NaH (4.4 g, 180 mmol) and then flushed with N_2. Benzyl mercaptan (22 mL, 190 mmol) was added over 30 min. After 1 h at room temperature, solid chloride **12** (34 g, 100 mmol) was added rapidly, and the flask was resealed. The mixture was heated at 55–60 °C for 9 days and then poured into water (2.5 L). The aqueous solution was extracted with ether (3 × 600 mL). The ether solution was washed with water (3×) and saturated NaCl (1×) and then dried (Na_2SO_4). Concentration in vacuo gave a residue that was chromatographed on silica gel (10% CH_2Cl_2/hexane, CH_2Cl_2) to give benzyl sulfide **13** (41.2 g, 96%): oil; MS, $C_{26}H_{32}O_3S$ calcd 424.207, found 424.206; ^1H NMR δ 0.85 (3 H, d), 1.4–1.8 (7 H, m), 2.5–3.0 (3 H, m), 2.4–2.9 (2 H, AB, J = 14 Hz), 2.9–3.4 (2 H, AB, J = 13 Hz), 3.75 (3 H, s), 3.90 (4 H, br s), 6.6–6.8 (2 H, m), 7.0–7.4 (6 H, m); ^{13}C NMR δ 10.8 (CH_3), 21.2 (CH_2), 28.1 (CH_2), 30.6 (CH_2), 30.6 (CH_2), 34.2 (CH_2), 37.3 (CH_2), 38.8 (C), 39.7 (CH), 45.5 (CH), 54.9 (OCH_3), 64.8 (OCH_2), 64.8 (OCH_2), 110.1 (C), 110.5 (CH), 113.5 (CH), 126.6 (CH), 127.5 (CH), 128.1 (2 × CH), 128.8 (2 × CH), 135.9 (C), 136.9 (C), 138.3 (C), 157.9 (C); IR 3.4, 6.2, 6.7 cm^{-1}.

Birch Reduction of Alcohol 10. Ammonia (50 mL) was distilled into a 100 mL flask, equipped with a dry ice condenser and septum inlet. To the flask were added a solution of alcohol **10** (480 mg, 1.5 mmol) in THF (15 mL), *tert*-butyl alcohol (2 mL, 20 mmol), and lithium wire (110 mg, 16 mmol). The mixture was maintained at reflux for 30 min, then the excess reducing agent was destroyed by addition of isoprene (0.35 mL). Ammonium chloride (1 g) was added and the NH_3 allowed to evaporate. The residue was dissolved in ether and the solution was washed with water. Drying (Na_2SO_4) and removal of the solvent in vacuo gave an oil. The ^1H NMR of the oil showed two methyl enol-ether methyl singlets at 3.47 and 3.52 ppm with equal intensity. The mixture was hydrolyzed in 1:9 H_2O/HOAc for 30 min at room temperature. The solvent was removed in vacuo and the residue was dissolved in ether. The ether solution washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in methanol and $KOCH_3$ added. After a few minutes NH_4Cl was added, and the solvent was removed in vacuo. The residue was dissolved in ether, and the solution was washed with saturated $NaHCO_3$. Drying (Na_2SO_4), concentration in vacuo, and flash chromatography (1:4 ether/CH_2Cl_2) gave cyclic ether **18** (117 mg, 25%) and alcohol **17** (123 mg, 26%).

The reaction was repeated as above except that *n*-butyllithium (3 mmol) was added to the NH_3 prior to addition of the other reagents. The ^1H NMR of intermediate enol-ether mixture showed a 3.47 ppm singlet twice as intense as the 3.52 ppm singlet. Hydrolysis, cyclization and chromatography as above gave cyclic ether **18** (80 mg, 17%) and alcohol **17** (130 mg, 28%).

1β,2,3,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-Tetradecahydro-4aβ-(hydroxymethyl)-1α-methyl-2,7-phenanthradione 2-(Ethylene Acetal) (17): mp 160–163 °C; MS, $C_{18}H_{28}O_4$ calcd 308.199, found 308.199; ^1H NMR δ 0.81 (3 H, d), 1.0–2.5 (m), 3.78 (2 H, br s), 3.94 (4 H, br s); ^{13}C NMR δ 11.1 (CH_3), 23.7 (CH_2), 27.6 (CH_2), 29.8 (CH_2), 31.2 (CH_2), 35.1 (CH_2), 38.1 (CH), 39.2 (CH), 40.0 (C), 42.2 (CH_2), 49.2 (CH_2), 49.4 (CH), 52.3 (CH), 59.8 (OCH_2), 64.9 (OCH_2), 65.0 (OCH_2), 110.7 (C), 211.8 (C).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9,10,10aα-Tetradecahydro-8aβ,4aβ-(epoxymethano)-1α-methyl-2,7-phenanthradione 2-(Ethylene Acetal) (18): mp 200–205 °C; MS, $C_{18}H_{26}O_4$ calcd 306.183, found 306.183; ^1H NMR 0.86 (3 H, d), 1.0–2.6 (m), 3.5–4.1 (2 H, AB, J = 9 Hz), 3.92 (4 H, br s); ^{13}C NMR 10.4 (CH_3), 23.6 (CH_2), 25.4 (CH_2), 27.8 (CH_2), 32.6 (CH_2), 39.3 (CH_2), 39.8 (CH_2), 42.1 (CH), 46.5 (CH), 47.6 (CH_2), 48.3 (C), 51.5 (CH), 64.8 (OCH_2), 65.3 (OCH_2), 71.9 (OCH_2), 85.4 (C), 109.9 (C), 209.6 (C).

1β,2,3,4,4a,4bα,5,6,7,9,10,10aα-Dodecahydro-1α-methyl-4aβ-(3,3,4,4-tetramethyl-2-oxa-3-sila-1-pentyl)-2,7-phenanthradione 2-(Ethylene Acetal) (20a). Alcohol **10** (1.0 g, 3.1 mmol) was dissolved in DMF (20 mL). Imidazole (.53 g, 7.8 mmol) and TBDMS–Cl (0.52 g, 3.4 mmol) were added. After 18 h at room temperature, the mixture was diluted with ether and washed with saturated $NaHCO_3$ and water. Drying (Na_2SO_4) and solvent removal gave the crude silyl ether **19a** as an oil.

The crude silyl ether was dissolved in THF (20 mL) and added to a flask containing ammonia (40 mL) at −78 °C. *tert*-Butyl alcohol (2 mL, 20 mmol) and lithium wire (105 mg, 15 mmol) were added, and the mixture was warmed to reflux. After 2 h, the excess reducing agent was quenched with isoprene (0.2 mL) and the mixture poured into NH_4Cl solution (200 mL). The aqueous solution was extracted with ether. The ether solution was washed with water and dried (Na_2SO_4). Solvent removal in vacuo gave crude diene.

The crude diene was dissolved in 10 mL of 1:9 water/acetic acid. After 15 min, the mixture was diluted with ether and washed with water and saturated $NaHCO_3$. Drying and solvent removal gave crude β,γ-enone.

The crude β,γ-enone was dissolved in methanol (20 mL) and $KOCH_3$ (100 mg) was added. After 18 h, the base was neutralized with NH_4Cl and the solvent removed in vacuo. The residue was dissolved in ether and washed with saturated $NaHCO_3$. Drying and solvent removal, followed by flash chromatography (1:9 ether/CH_2,cl_2) gave enone **20a** (437 mg, 33%): oil; ^1H NMR δ 0.85 (12 H, m), 1.1–2.6 (m), 3.61 (2 H, s), 3.96 (4 H, br s), 5.87 (1 H, br s); ^{13}C NMR δ −5.8 ($SiCH_3$), −5.7 ($SiCH_3$), 11.1 (CH_3), 18.1 (SiC), 22.1 (CH_2), 24.0 (CH_2), 25.8 (3 × CH_3), 30.5 (CH_2), 31.2 (CH_2), 35.1 (CH_2), 37.2 (CH_2), 39.6 (CH), 41.8 (C), 48.3 (CH), 49.4 (CH), 61.4 (OCH_2), 65.0 (OCH_2), 65.2 (OCH_2), 110.4 (C), 125.6 (CH), 165.8 (C), 199.7 (C); IR 3.4, 6.0 cm^{-1}.

1β,2,3,4,4a,4bα,5,6,7,9,10,10aα-Dodecahydro-1α-methyl-4aβ-(2,4,7-trioxaoctyl)-2,7-phenanthradione 2-(Ethylene Acetal) (20b). Alcohol **10** (3.18 g, 10 mmol) was dissolved CH_2Cl_2 (70 mL). Diisopropylethylamine (3 mL, 17 mmol) and MEM–Cl (1.7 mL, 15 mmol) were added. After 18 h at room temperature, the solution was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). Solvent removal in vacuo gave crude MEM ether **19b**.

The crude MEM ether was dissolved in THF (10 mL) and ammonia (50 mL) was added at −78 °C. *tert*-Butyl alcohol (5 mL, 50 mmol) and lithium wire (220 mg, 39 mmol) were added, and the mixture was warmed to reflux. The lithium was consumed within 30 min. The mixture was neutralized with NH_4Cl and the NH_3 allowed to evaporate. The residue was dissolved in ether and the solution washed with saturated $NaHCO_3$. Drying (Na_2SO_4) and solvent removal grave crude diene (4.2 g).

The crude diene was dissolved in 1:9 water/acetic acid. After 30 min at room temperature, the mixture was diluted wtih ether and washed with water and saturated $NaHCO_3$. Drying and solvent removal gave crude β,γ-enone (3.8 g).

The crude β,γ-enone was dissolved in methanol (20 mL) and $KOCH_3$ (100 mg) added. After 18 h, the base was neutralized with NH_4Cl and the solvent removed in vacuo. The residue was dissolved in ether and the solution was washed with water. Drying and solvent removal gave crude α,β-enone (3.7 g). Purification by chromatography (3:7 EtOAc/$CHCl_3$) gave enone **20b** (3.2 g,

81%): waxy solid; MS, $C_{22}H_{34}O_6$ calcd 394.236, found 394.237; ^{1}H NMR δ 0.88 (3 H, d), 1.1–2.6 (m), 3.36 (3 H, s), 3.5–3.7 (6 H, m), 3.98 (4 H, br s), 4.62 (2 H, s), 5.90 (1 H, br s); ^{13}C NMR δ 11.0 (CH_3), 22.0 (CH_2), 23.9 (CH_2), 30.2 (CH_2), 31.1 (CH_2), 34.9 (CH_2), 37.0 (CH_2), 39.5 (CH), 41.1 (C), 48.4 (CH), 49.3 (CH), 58.9 (OCH_3), 64.9 (OCH_2), 65.1 (OCH_2), 66.9 (OCH_2), 67.3 (OCH_2), 71.7 (OCH_2), 96.0 (OCH_2O), 110.2 (C), 125.5 (CH), 165.1 (C), 199.5 (C); IR 3.4, 6.0 cm^{-1}.

1β,2,3,4,4a,5,8,9,10,10aα-Decahydro-4aβ-(mercaptomethyl)-7-methoxy-1α-methyl-2-phenanthrone 2-(Ethylene Acetal) (21). Methyl amine (300 mL) was distilled into a 500-mL 3-neck flask (equipped with a dry ice condenser, thermometer, and mechanical stirrer). The flask was cooled in a dry ice/ether bath. At −70 °C, lithium wire (1.3 g, 180 mmol) was added. The solution was stirred rapidly for 1 h to ensure complete dissolution of the metal. Liquid N_2 was added to the bath to cool the solution to −95 °C. A solution of benzyl sulfide **13** (6.0 g, 14 mmol) in ether (25 mL) was added via syringe at a rate such that the temperature remained below −90 °C. An additional 10 mL of ether was used to rinse the syringe and complete the addition. Under the same temperature restriction, *tert*-butyl alcohol (18 mL, 180 mmol) was added. With liberal addition of liquid N_2 to the bath and vigorous stirring, both additions were completed in 10 min. The mixture was warmed slowly. The blue color dissipated at −50 °C to reveal a cloudy white suspension of lithium salts. Neutralization with NH_4Cl (11 g, 210 mmol) gave a clear, colorless solution. The methyl amine was allowed to evaporate under a stream of N_2. The residue was dissolved in ether, and the solution was washed several times with water and once with saturated NaCl. Drying (Na_2SO_4) and solvent removal in vacuo gave mercaptan **21** (4.9 g, 100%) as a colorless oil, pure enough for further transformation: oil; ^{1}H NMR δ 0.85 (3 H, d), 1.2–2.2 (m), 2.4–3.1 (m), 3.50 (3 H, s), 3.91 (4 H, br s), 4.59 (1 H, m).

1β,2,3,4,4α,4bβ,5,6,7,8,8a,9,10,10aα-Tetradecahydro-8aβ,4aβ-(epithiomethano)-1α-methyl-2,7-phenanthradione 2-(Ethylene Acetal) (22c). Mercaptan **21** (425 g, 1.3 mmol) was dissolved in 1:9 water/acetic acid (3 mL). After 30 min at room temperature, the mixture was diluted with ether, and the solution was washed with water and saturated $NaHCO_3$. Drying (Na_2SO_4) and solvent removal in vacuo gave crude mercaptan **23** (375 mg). The crude mercaptan was dissolved in methanol (15 mL) and $KOCH_3$ (100 mg) added. After 18 h at room temperature, NH_4Cl (0.5 g) was added, and the solvent was removed in vacuo. The residue was dissolved in ether, and the solution was washed with water. Drying (Na_2SO_4) and concentration in vacuo, followed by crystallization from ether gave sulfide **22c** (76 mg, 20%): mp 218–222 °C; MS, $C_{18}H_{26}O_3S$ calcd 322.160, found 322.161; ^{1}H NMR δ 0.82 (3 H, d), 1.2–2.5 (m), 2.57, 2.81 (2 H, AB, J = 15 Hz), 2.64, 3.22 (2 H, AB, J = 11 Hz), 3.91 (4 H, br s); ^{13}C NMR (APT) δ 10.4 (O), 21.0 (E), 25.3 (E), 32.4 (E), 33.0 (E) 33.9 (E), 37.1 (E), 39.1 (O), 39.4 (E), 41.1 (O), 46.0 (E), 53.6 (E), 55.2 (O), 57.0 (E), 64.9 (E), 65.3 (E), 110.2 (E), 209.1 (E); IR 3.4, 5.8 cm^{-1}.

1β,2,3,4,4α,4bα,5,6,7,8,8a,9,10,10aα-Tetradecahydro-8aβ,4aβ-(epithiomethano)-1aα-methyl-2,7-phenanthradione 2-(Ethylene Acetal) (22t). Mercaptan **21** (2.5 g, 7.4 mmol) was dissolved in CH_2Cl_2 (100 mL). Pyridinium tosylate (100 mg) was added. After 1 h at room temperature, water was added to effect hydrolysis. The mixture was washed with water and saturated $NaHCO_3$. Drying (Na_2SO_4) and solvent removal in vacuo gave an oil. The oil was treated with $KOCH_3/CH_3OH$ as in the procedure for **22c** to cyclize any mercaptoenone present. Crystallization of the product from ether and recrystallization from ether/$CHCl_3$ gave sulfide **22t** (650 mg, 27%): mp 212–214 °C; MS $C_{18}H_{26}O_3S$ calcd 322, found 322; ^{1}H NMR δ 0.88 (3 H, d), 1.2–2.5 (m), 2.52, 2.98 (2 H, AB, J = 11 Hz), 3.96 (4 H, br s); ^{13}C NMR δ (APT) 10.4 (O), 24.8 (E), 25.3 (E), 31.2 (E), 32.0 (E), 34.9 (E), 40.1 (E), 40.9 (O), 43.1 (E), 47.9 (O), 48.4 (E), 50.0 (E), 56.8 (O), 60.5 (E), 64.9 (E), 65.2 (E), 109.9 (E), 208.5 (E); IR 3.4, 5.8 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H 8.13; S 9.94. Found C, 66.88; H, 8.43; S, 9.67.

1β,2,3,4,4a,4bβ,5,6,7,8,8a,9,10,10aα-Tetradecahydro-8aβ,4aβ-(epithiomethano)-1α-methyl-2,7-phenanthradione 1,1-Dioxide 2-(Ethylene Acetal) (24c). Sulfide **22c** (100 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (5 mL) and *m*-CPBA (135 mg, 0.62 mmol) added. After 2 h at room temperature, the solution was washed with 10% Na_2SO_3 and saturated $NaHCO_3$. Drying (Na_2SO_4), solvent removal in vacuo, and crystallization of the residue from ether/$CHCl_3$ gave sulfone **24c** (80 mg, 73%): mp 240–250 °C dec; MS, $C_{18}H_{26}O_5S$ calcd 354, found 354; ^{1}H NMR δ 0.83 (3 H, d), 1.2–2.5 (m), 2.37, 2.97 (2 H, AB, J = 14 Hz), 2.93, 3.41 (2 H, AB, J = 13 Hz), 3.91 (4 H, br s); ^{13}C NMR δ 10.0 (O), 19.5 (E), 23.6 (E), 25.5 (E), 32.0 (E), 33.2 (E), 37.9 (O), 39.1 (E), 41.1 (O), 43.5 (E), 43.8 (E), 46.0 (O), 60.4 (E), 64.1 (E), 65.0 (E), 65.2 (E), 109.2 (E), 206.6 (E); IR 3.4, 5.8, 7.7, 9.2 cm^{-1}.

1β,2,3,4,4a,4bα,5,6,7,8,8a,9,10,10aα-Tetradecahydro-8aβ,4aβ-(epithiomethano)-1aα-methyl-2,7-phenanthradione 1,1-Dioxide 2-(Ethylene Acetal) (24t). Sulfide **22t** (100 mg, 0.31 mmol) was oxidized as **22c** above and crystallized to give sulfone **24t** (70 mg, 64%): mp 250–260 °C dec.; MS, $C_{18}H_{26}O_5S$ calcd 354, found 354; ^{1}H NMR δ 0.85 (3 H, d), 1.2–2.5 (m), 2.24, 2.82 (2 H, AB, J = 17 Hz), 2.98, 3.28 (2 H, AB, J = 15 Hz), 3.93 (4 H, br s); ^{13}C NMR (APT) δ 10.1 (O), 23.5 (E), 24.2 (E), 32.0 (E), 32.6 (E), 36.0 (E), 39.3 (E), 41.2 (O), 41.6 (E), 43.4 (E), 47.7 (O), 50.2 (O), 56.8 (E), 65.1 (E), 65.3 (E), 66.0 (E), 109.2 (E), 204.9 (E); iR 3.4, 5.8, 7.7, 9.2 cm^{-1}.

1β,2,3,4,4a,5,8,9,10,10aα-Decahydro-7-methoxy-1α-methyl-4aβ-[(((methoxycarbonyl)methyl)thio)methyl]-2-phenanthrone 2-(Ethylene Acetal) (25). Benzyl sulfide **13** (10.1 g, 24 mmol) was reduced to **21** as described above. Since this material rearomatizes easily, the crude product was carried on without complete removal of solvent. The crude intermediate was dissolved in CH_2Cl_2 (30 mL). Diisopropylethyl amine (8 mL, 46 mmol) and methyl bromoacetate (2.5 mL, 30 mmol) were added. After 24 h at room temperature, the solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. Drying (Na_2SO_4), solvent removal in vacuo, and chromatography (ether/hexane gradient) gave methyl ester **25** (9.8 g, 100%): oil; ^{1}H NMR δ 0.87 (3 H, d), 1.4–2.2 (m), 2.5–3.0 (m), 2.96 (2 H, br s), 3.13 (2 H, s), 3.50 (3 H, s), 3.70 (3 H, s), 3.91 (4 H, br s), 4.60 (1 H, m).

1β,2,3,4,4a,4bα,5,6,10,10aα-Decahydro-7-methoxy-1α-methyl-4aβ-[(((methoxycarbonyl)methyl)thio)methyl]-2-phenanthrone 2-(Ethylene Acetal) (26). Ester **25** (4.9 g, 12 mmol) was dissolved in ahydrous acetic acid (30 mL). After 4 h at room temperature, the solvent was removed in vacuo. The residue was dissolved in ether, and the solution was washed with water, saturated $NaHCO_3$, and saturated NaCl. The solution was dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the residue (ether/hexane gradient) followed by crystallization from ether/hexane gave ester **26** (2.5 g, 51%): mp 135–140 °C; MS, $C_{22}H_{32}O_5S$ calcd 408.197, found 408.199; ^{1}H NMR δ 0.84 (3 H, d), 1.5–2.4 (13 H, m), 2.8 (2 H, AB, J = 12 Hz), 3.13 (2 H, s), 3.54 (3 H, s), 3.69 (3 H, s), 3.91 (4 H, br s), 5.20 (1 H, br s), 5.30 (1 H, m); ^{13}C NMR δ 10.5 (CH_3), 24.5 (CH_2), 27.2 (CH_2), 29.0 (CH_2), 31.2 (CH_2), 31.6 (CH_2), 32.0 (CH_2), 35.3 (CH_2), 37.7 (C), 40.1 (CH), 46.3 (CH), 48.5 (CH), 52.2 (OCH_3), 54.2 (OCH_3), 64.8 (OCH_2), 65.1 (OCH_2), 99.4 (CH), 110.2 (C), 117.5 (CH), 134.2 (C), 157.7 (C), 170.7 (C); IR 3.4, 5.75, 6.04, 6.14 cm^{-1}.

1β,2,3,4,4a,4bα,5,6,7,9β,10,10aα-Dodecahydro-9α-hydroxy-1α-methyl-4aβ-[(((methoxycarbonyl)methyl)thio)methyl]-2,7-phenanthradione S-Oxide 2-(Ethylene Acetal) (27). Ester **26** (100 mg, 0.25 mmol) was dissolved in THF (5 mL) was added to a solution of Oxone[15] (200 mg, 0.33 eq) and $NaHCO_3$ (28 mg, 0.33 mmol) in water (5 mL). After 45 min at room temperature, the mixture was diluted with water and extracted with CH_2Cl_2. Drying (Na_2SO_4) and concentration of the CH_2Cl_2 solution in vacuo gave 110 mg of crude product. Flash chromatography (1:1 CH_3CN/EtOAc) gave sulfoxide **27** (60 mg, 57%) as a mixture of sulfoxide diastereoisomers: oil; ^{1}H NMR δ 0.85 (3 H, d), 1.2–3.1 (m), 3.65, 3.71 (3 H, s), 3.91 (4 H, br s), 4.29 (1 H, m), 6.00 (1 H, br s).

1β,2,3,4,4a,4bα,5,6,7,9β,10,10aα-Dodecahydro-9α-hydroxy-1α-methyl-4aβ-[(((methoxycarbonyl)methyl)thio)methyl]-2,7-phenanthradione 2-(Ethylene Acetal) (28). (a) **Sulfur Dioxide Sensitized[18] Oxidation.** Ester **26** (50 mg, 0.12 mmol), NaOAc (30 mg), THF (5 mL), and methanol (20 mL) were placed in a quartz tube. The tube was cooled to −20 °C and SO_2 (2 mL) was distilled into the tube. The solution turned bright yellow. The solution was irradiated (Rayonet reactor, 350 nm) under O_2 (1 atm) for 30 min to give a colorless solution. Addition of $KHCO_3$ (0.5 g) followed by removal of the solvent in vacuo gave a residue that was dissolved in ether. The ether solution was washed with

saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography with EtOAc gave sulfide **28** (20 mg, 40%).

(b) Biacetyl Sensitized Oxidation.[17] Ester **26** (200 mg, 0.49 mmol), pyridine (1 mL), biacetyl (0.1 mL), and methanol (25 mL) were placed in a quartz tube. The tube was cooled to −20 °C and the solution irradiated (Rayonet reactor, 350 nm) under O_2 (1 atm) for 3 h. The mixture was diluted with water and extracted with CH_2Cl_2 and ether. The combined organic solution was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. Drying (Na_2SO_4), concentration in vacuo, and flash chromatography (EtOAc) gave sulfide **28** (96 mg, 48%): oil; MS, $C_{21}H_{30}O_6S$ calcd 410.176, found 410.178; ^1H NMR δ 0.90 (3 H, d), 1.2–2.9 (m), 3.15 (2 H, s), 3.69 (3 H, s), 3.97 (4 H, br s), 4.35 (1 H, m), 6.05 (1 H, d); ^{13}C NMR δ 10.8 (CH_3), 22.0 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 31.6 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 36.9 (CH_2), 39.2 (CH), 41.8 (C), 43.4 (CH), 45.6 (CH), 52.5 (OCH_3), 65.0 (OCH_2), 65.2 (OCH_2), 70.8 (CH), 110.1 (C), 128.4 (CH), 163.1 (C), 170.4 (C), 200.7 (C); IR 2.9, 3.4, 5.8, 6.0.

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10aα-Tetradecahydro-9α-hydroxy-8aβ,4aβ-(1-(methoxycarbonyl)-2-thiapropano)-1α-methyl-2,7-phenanthradione 2-Oxide 2-(Ethylene Acetal) (29). Ester **26** (200 mg, 0.49 mmol) was oxidized via biacetyl sensitization as described above. The crude product (260 mg) was dissolved in CH_2Cl_2 (20 mL), and the mixture was cooled to 0 °C. *m*-CPBA (80%, 100 mg, 0.47 mmol) was added over 15 min. After 15 min, the solution was diluted with ether and washed with 10% Na_2SO_3 and saturated $NaHCO_3$. Drying (Na_2SO_4) and solvent removal in vacuo gave 150 mg of crude sulfoxide **27**. Back extraction of the aqueous washes, followed by drying and concentration in vacuo gave an additional 85 mg of crude sulfoxide **27**.

Each sample of **27** was dissolved in methanol (25 mL) and $KOCH_3$ (20 mg) added. After 15 min at room temperature, NH_4Cl (100 mg) was added to the mixtures and the solvent removed in vacuo. The residues were dissolved in CH_2Cl_2, and the solutions were washed with water. Drying (Na_2SO_4) and concentration in vacuo gave oils (102 and 70 mg, respectively). The latter oil crystallized from $CHCl_3$ to give a single sulfoxide **29** (30 mg, 14%). (The former oil gave no crystalline product): mp 250 °C dec; MS, $C_{20}H_{30}O_7S$ calcd 426, found 426; ^1H NMR δ 0.87 (3 H, d), 1.5–2.5 (m), 2.01, 3.03 (2 H, AB, J = 15 Hz), 2.50, 3.78, (2 H, AB, J = 13 Hz), 3.60 (1 H, s), 3.84 (3 H, s), 3.95 (4 H. m), 4.11 (1 H, br s).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10aα-Tetradecahydro-9α-hydroxy-8aβ,4aβ-(1-(methoxycarbonyl)-2-thiapropano)-1α-methyl-2,7-phenanthradione 2,2-Dioxide 2-(Ethylene Acetal) (30). To a solution of sulfide **28** (340 mg, 0.83 mmol) in CH_2Cl_2 (25 mL) was added 80% *m*-CPBA (200 mg, 0.93 mmol). After 5 min at room temperature, the mixture was diluted with ether and washed with saturated $NaHCO_3$ and saturated NaCl. Drying (Na_2SO_4) and solvent removal in vacuo gave crude sulfoxide **27** (130 mg). Back extraction of the aqueous washes gave more sulfoxide **27** (180 mg, 88% total).

The combined sulfoxide **27** was dissolved in methanol (40 mL) and $KOCH_3$ (50 mg) added. After 1 h at room temperature, NH_4Cl (200 mg) was added and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and the solution washed with water. Drying (Na_2SO_4) and concentration in vacuo gave crude cyclic sulfoxide **29** (320 mg, 90%).

The crude sulfoxide **29** was dissolved in CH_2Cl_2 (30 mL) and 80% *m*-CPBA (200 mg, 0.93 mmol) added. After 3 h at room temperature, the solution was washed with 10% Na_2SO_3 and dried (Na_2SO_4). Removal of the solvent in vacuo and flash chromatography (EtOAc) gave sulfone **30** (280 mg, 76%) as a mixture of diastereoisomers (4:1). Attempted recrystallization from ether/$CHCl_3$ gave a mixture of isomers: amorphous solid; ^1H NMR (major isomer) δ 0.87 (3 H, d), 1.3–2.7 (m), 2.18, 3.18 (2 H, AB, J = 15 Hz), 3.12, 3.82 (2 H, AB, J = 15 Hz), 3.86 (3 H, s), 3.95 (4 H, m), 4.17 (1 H, s), 4.85 (1 H, br s); IR 3.4, 5.7, 5.8 cm^{-1}.

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10aα-Tetradecahydro-9α-hydroxy-1α-methyl-8aβ,4aβ-(2-thiapropano)-2,7-phenanthradione 2,2-Dioxide 2-(Ethylene Acetal) (31). The sulfone mixture **30** (50 mg, 0.11 mmol) was dissolved in HMPA (1 mL) and tetramethyl ammonium acetate (100 mg) added. After 2 h at 125 °C, the mixture was poured onto a plug of silica gel and eluted with EtOAc. Removal of the solvent in vacuo gave a residue (150 mg) that was purified by flash chromatography (EtOAc) to give sulfone **31** (15 mg, 35%): foam; ^1H NMR 0.88 (3 H, d), 1.2–2.8 (m), 1.89, 3.16 (2 H, AB, J = 14 Hz), 2.97, 3.18 (2 H, AB, J = 15 Hz), 2.99, 3.68 (2 H, AB, J = 15 Hz), 3.62 (1 H, br s), 3.95 (4 H, m); IR 3.4, 5.8 cm^{-1}.

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Registry No. 1, 41451-75-6; 6, 105619-37-2; (±)-7, 105619-38-3; (±)-8 (isomer 1), 105619-39-4; (±)-8 (isomer 2), 105619-34-9; (±)-8 (isomer 3), 105662-66-6; (±)-8 (isomer 4), 105619-35-0; (±)-9, 105619-41-8; (±)-10, 105619-41-8; (±)-11, 105619-42-9; (±)-12, 105619-43-0; (±)-13, 105619-44-1; (±)-14, 105639-31-4; (±)-15, 105619-45-2; (±)-16, 105619-46-3; (±)-17, 105619-47-4; (±)-18, 105619-48-5; (±)-19a, 105619-49-6; (±)-19a (dihydro deriv.), 105619-36-1; (±)-19a (enone), 105619-60-1; (±)-19b, 105619-61-2; (±)-19b (diene), 105619-62-3; (±)-19b (enone), 105619-63-4; (±)-20a, 105619-50-9; (±)-20b, 105619-64-5; (±)-21, 105619-51-0; (±)-22c, 105662-67-7; (±)-22t, 105619-52-1; (±)-23, 105619-53-2; (±)-24c, 105662-68-8; (±)-24t, 105619-54-3; (±)-25, 105619-55-4; (±)-26, 105619-56-5; (±)-27 (isomer 1), 105760-35-8; (±)-27 (isomer 2), 105619-65-6; (±)-28, 105619-57-6; 29, 105639-32-5; (±)-30 (isomer 1), 105619-58-7; (±)-30 (isomer 2), 105662-69-9; (±)-31, 105619-59-8; 1-chloro-3-pentanone, 32830-97-0.

Supplementary Material Available: Stereochemical assignment of **22c**, **22t**, **24c**, and **24t** by ^{13}C NMR chemical shifts, a tabular ^{13}C NMR comparison of **6**, **7**, **8**, **9**, **10**, **12**, **13**, **18**, **20a**, **20b**, **22c**, **22t**, **24c**, **24t**, **26**, and **28**, and X-ray crystallographic data for **24c** and **24t** (10 pages). Ordering information is given on any current masthead page.

Trichothecene Degradation Studies. 2. Synthesis of [13-^{14}C]Anguidine

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An efficient degradation and resynthesis of anguidine that pivots around norketone **4** is described. The sequence from anguidine to anguidine via **4** proceeds in 12 steps with an overall yield of 30%. This work has permitted for the first time the preparation of an enantiomerically pure, high specific activity ^{14}C-labeled epoxytrichothecene mycotoxin required for biological investigations. The radiolabel was introduced by the reaction of **4** with [^{14}C]CH_2PPh_3.

The epoxytrichothecene mycotoxins are a group of fungal metabolites that exhibit a range of significant biological properties including cyto- and phytotoxicity.[2] These mycotoxins are potent inhibitors of protein synthesis

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