Use of an Axial α-Face Control Element in Intramolecular Conjugate Additions: Synthesis of an ABCD Tetracyclic Bruceantin Precursor[1]

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An ABCD ring intermediate for the synthesis of the quassinoidal antileukemia agent bruceantin has been prepared. Control of stereochemistry of the C ring fusion has been established by a cesium fluoride mediated intramolecular conjugate addition of an α-face α-sulfonyl ester to an α-chloro enone (**49**); the product from this reaction is a pentacyclic cyclopropyl sulfone (**60**). Reductive silylation of this sulfone affords a regiospecific silyl enol ether (**64**) which can be converted to the natural BC ring stereochemistry by oxidative cleavage followed by intramolecular aldol reaction (**64** to **69**). A new method for the oxidative ring expansion of δ-lactones to α-keto δ-lactols is demonstrated. The procedure involves the conversion of a tertiary lactol to a β-methylthio exocyclic enol ether by the action of the Swern reagent (**74** to **75** and **84** to **85**); further oxidation of these β-methylthio enol ethers with osmium tetraoxide directly affords the ring-expanded α-keto lactols (**86**, **87**).

The potent cytotoxic properties[2] and dense array of functionality present in the quassinoid bruceantin (**1**), have elicited considerable medicinal and synthetic interest.[3] Based upon our success at transforming model enone **5t** to the BCE model system **6**[4] we initially elected to investigate approaches to the polycyclic bruceantin nucleus involving cyanation–alkylation (**2A** to **3A**) or cyanation–aldol (**2B** to **3B**) reactions (Scheme I).

Conversion of tricyclic enone **7**,[5] to the requisite pair of A-ring protected γ-hydroxy enones **11** and **14** was accomplished on large scale as described in Scheme II.[5,6] The major innovation in this sequence involves the use of buffered persulfate ("oxone") as a means of oxidation of dienyl ethers **10** and **13** to the γ-hydroxy enones **11** and **14**.[7,8]

Introduction of the requisite axial C-8 carbon residue was first examined by a hydrocyanation approach by analogy to the model system[4] (cf. **4** to **5t**, Scheme I). Although the parent tricyclic enone **15** underwent efficient and reasonably specific axial hydrocyanation with diethylaluminum cyanide or pyridinium hydrocyanide to afford β-cyano ketones **16t** and **16c** in excellent yields, *similar addition to the δ-silyloxy enone* **17** *was far more difficult*. Satisfactory yields were only achieved with the most reactive reagent, diethylaluminum cyanide. Unfortunately, under these conditions a much poorer trans/cis ratio (2.3) of the β-cyano ketones **18t** and **18c** was obtained. A similar rate retardation (of about 100) had previously been observed by Nagata[10] in the hydrocyanation of a pair of steroidal γ-acetoxy enones (**21** to **22t**/**22c**; **23** to **24t**/**24c**; Scheme III).

In a final attempt to secure a suitable intermediate for the conjugate addition/alkylation sequence (cf. **2A** to **3A**), we treated α-halo esters **25A,B** with trimethylsilyl cyanide and triethylaluminum under the conditions reported by Utimoto et al.[11] to yield β-cyano silyl enol ethers. The reactions each produced a single 1:1 adduct which we initially assumed to have structures **26A,B**, respectively. The products obtained from this reaction are, in fact, the 1,2-adducts **27A,B** (C-13 stereochemistry tentatively assigned). Assignment of structure **27** is based upon both spectral (see Experimental Section) and chemical evidence. Specific chemical observations indicative of **27A,B** include (1) hydrolysis of **27A,B** with 20% aqueous acetic acid to yield enones **25A,B** under conditions where β-cyano ketones **29A,B** do not yield **25A,B** and (2) transformation of **25A,B** to **27A,B** using conditions (ZnI_2/Me_2Si–CN[12]) known to produce 1,2-adducts with similar enones.

Treatment of **27A,B** (while still laboring under the delusion that they possessed structures **26A,B**) with cesium fluoride[13] in anhydrous acetonitrile afforded in a low yield a 1:1 mixture of tetracyclic nitriles **30**, which were diastereomeric at the nitrile-bearing carbon. This same mixture was also produced by treatment of β-cyano ketones **29A,B** under various basic conditions. Syntheses of **29A,B** were smoothly accomplished in >90% overall yields by sequential treatment of **18t** with tetrabutylammonium fluoride and bromoacetyl bromide or chloroacetyl chloride, respectively.

This intramolecular Michael reaction apparently occurred via cyclization of α-cyano ester **31**, produced in situ by the reaction of liberated cyanide ion on α-halo esters **25A,B**. Support for the feasibility of this scenario was provided by the observation that treatment of authentic **31** (prepared in 95% yield from the DCC coupling of γ-hydroxy enone **11** and cyanoacetic acid) with cesium

(1) Bruceantin Support Studies. 10. (a) For paper 9, see: Hedstrand, D. M.; Bryn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Org. Chem.*, submitted for publication. (b) For paper 7, see: Suryawanshi, S. N.; Swenson, C. J.; Jorgensen, W. L.; Fuchs, P. L. *Tetrahedron Lett.* **1984**, *25*, 1859.

(2) (a) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Siegel, C. W. *J. Org. Chem.* **1973**, *38*, 178. (b) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; M. Ziegler, M. F. Siegel, C. W. *J. Org. Chem.* **1975**, *40*, 648.

(3) For studies directed toward the synthesis of bruceantin and other quassinoids, see: (a) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943. (b) Voyle, M.; Dunlap, N. K.; Watt, D. S.; Anderson, O. P. *J. Org. Chem.* **1983**, *48*, 3242. (c) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. (d) Shishido, K.; Saitoh, T.; Fukumato, K.; Kametani, T.; *J. Chem. Soc., Chem. Commun.* **1983**, 852. (e) Kraus, G. A.; Taschner, M.; Shimagaki, M. *J. Org. Chem.* **1982**, *47*, 4271 and references cited therein.

(4) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216.

(5) Stork, G.; Meisels, A.; Davis, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 3419.

(6) For related functionalizations of enone **7**, see: (a) Hanth, H.; Stauffacher, D. *Helv. Chim. Acta* **1972**, *55*, 1532. (b) ApSimon, J. W.; Baker, P.; Hooper, J. W.; Macauly, S. *Can. J. Chem.* **1972**, *50*, 1944.

(7) Suryawanshi, S. N.; Fuchs, P. L. *Tetrahedron Lett.* **1981**, 4201.

(8) In ref 7 it was reported that dienyl ether **10** (=**4a**[8]) was hydrolyzed to the tricyclic α,β-unsaturated ketone **15**, which in turn was converted to conjugated dienyl acetate **4b**[8a] and silyl dienyl ether **4c**,[8a] respectively. The oxone oxidations of these substrates to δ-hydroxy enone **11** (=**6**[8a]) was compared to that of dienyl ether **10** (=**4a**[8a]). (a) This compound number refers to the numbering scheme used in ref 7, not this paper.

(9) Full experimental procedures for these transformations can be found in the supplementary material to this paper.

(10) (a) Nagata, W.; Yoshioka, M.; Terasawa, T. *J. Am. Chem. Soc.* **1972**, *94*, 4635, (b) 4654, (c) 4672.

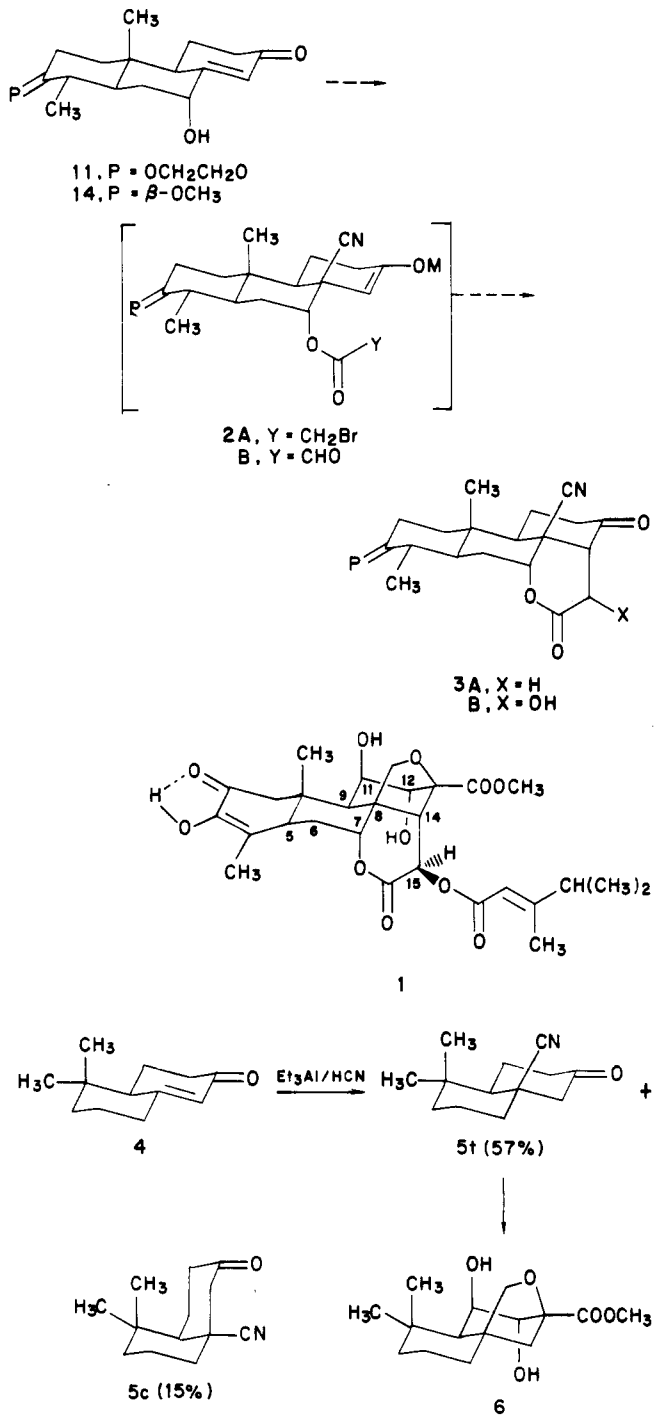
(11) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, 3389.

(12) (a) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914. (b) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.

(13) (a) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452. (b) Clark, J. H. *Chem. Rev.* **80**, **1980**, 429. (c) Yakobson, G. G.; Akhmetova, N. E. *Synthesis* **1983**, 169.

0022-3263/86/1951-0902$01.50/0

Scheme I



fluoride quantitatively afforded **30** in the same diastereomeric ratio. Similar treatment of α-sulfonyl activated ester **32** (92% from **11**, DCC, and (phenylsulfonyl)acetic acid) with cesium fluoride in acetonitrile afforded a single diasteromeric α-sulfonyl lactone **33** in 77% yield after recrystallization (presumably of the exo configuration) (Scheme IV).

Presented with this serendipitous stereocontrolled cyclization, in combination with our inability to satisfactorily control the hydrocyanation reaction, we were prompted to reformulate our synthetic plan along lines inspired by the synthesis of phyllocladene.[14] Namely, it can be seen that conversion of ketone **33** to lactone **34** followed by intramolecular transacylation would establish keto lactone **35** bearing the proper ring stereochemistry. With a view toward the eventual reductive cleavage of the Michael activating group, only α-sulfonyl lactone **33** was examined in the Baeyer–Villiger reaction and the nitrile series (**28**) was terminated at this point.

Treatment of α-sulfonyl lactone **33** with *m*-chloroperoxybenzoic acid (MCPBA)[15a] or more reactive 3,5-dinitroperoxybenzoic acid (3,5-DNPBA)[15b] in methylene chloride at reflux for extended times only serves to return starting material. Use of trifluoroperacetic acid[15d,e,f] or MCPBA in combination with boron trifluoride etherate produces a plethora of products. Buffered trifluoroperacetic acid is unreactive. In none of these reactions is there any indication of the formation of bis lactone **34** or its regioisomer **38**.

In order to assess the nature of the difficulty with the Baeyer–Villiger reaction of **33**, the α-sulfonyl group was reductively cleaved by using aluminum amalgam in THF[16] to afford the keto lactone **36** in 94% yield (after a pyridinium chlorochromate[17] "workup" to reoxidize some secondary alcohol that was produced as a coproduct during aluminum amalgam reduction). Baeyer–Villiger oxidation of keto lactone **36** proceeds very smoothly under mild conditions to afford bis lactone **39** *bearing the incorrect regiochemistry* for the subsequently desired transformations. That the regiochemistry assigned to **39** was correctly assigned was especially apparent from observation of a pair of high-field AB patterns in the 470-MHz proton NMR. Thus it seems likely that the unreactivity of the sulfonyl-substituted keto lactone **33** relative to desulfonylated keto lactone **36** was largely a function of steric congestion of the α-face. (β-Face approach of the peracid would be expected to be severely retarded by the axial A-ring methyl group.)

Inherent in this argument is the assumption that the sulfone moiety of **33** occupies the thermodynamically preferred exo orientation as tentatively depicted. Consistent with this postulate is the observation that the less

(14) (a) Turner, R. B.; Ganshirt, K. H.; Shaw, P. E.; Tauber, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1776. (b) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526.

(15) (a) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64. (b) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *16*, 3163.

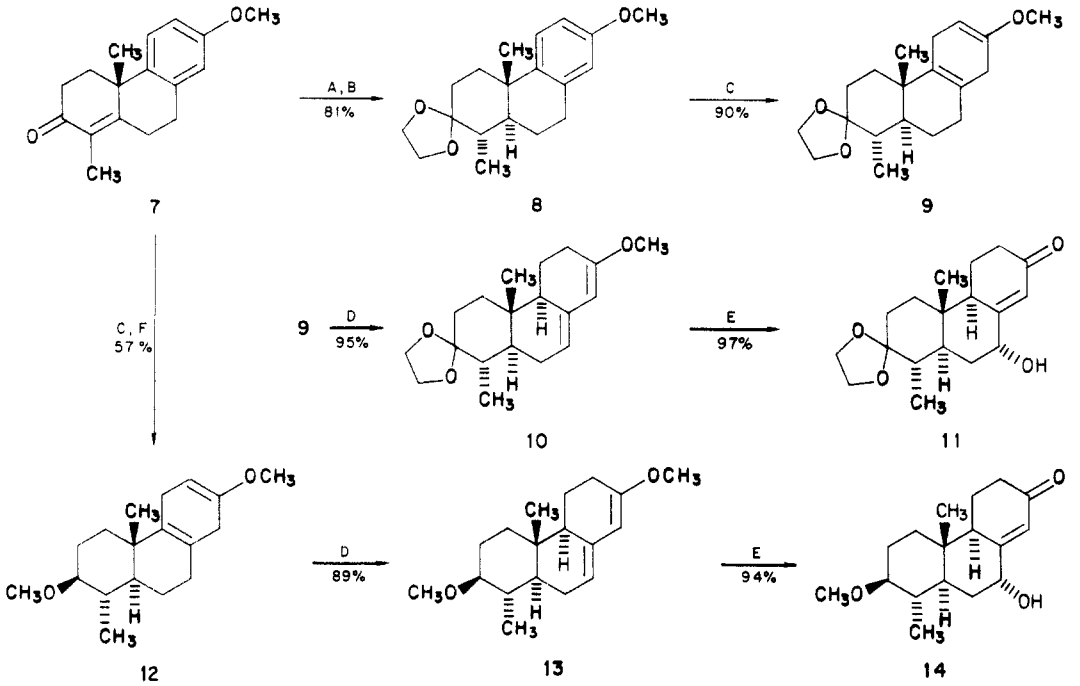
(16) House, H. O.; Larson, J. K. *J. Org. Chem.* **1968**, *33*, 61 and references therein.

(17) For a review on pyridinium chlorochromate oxidations, see: Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.

(18) (a) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, 2569; (b) 2573.

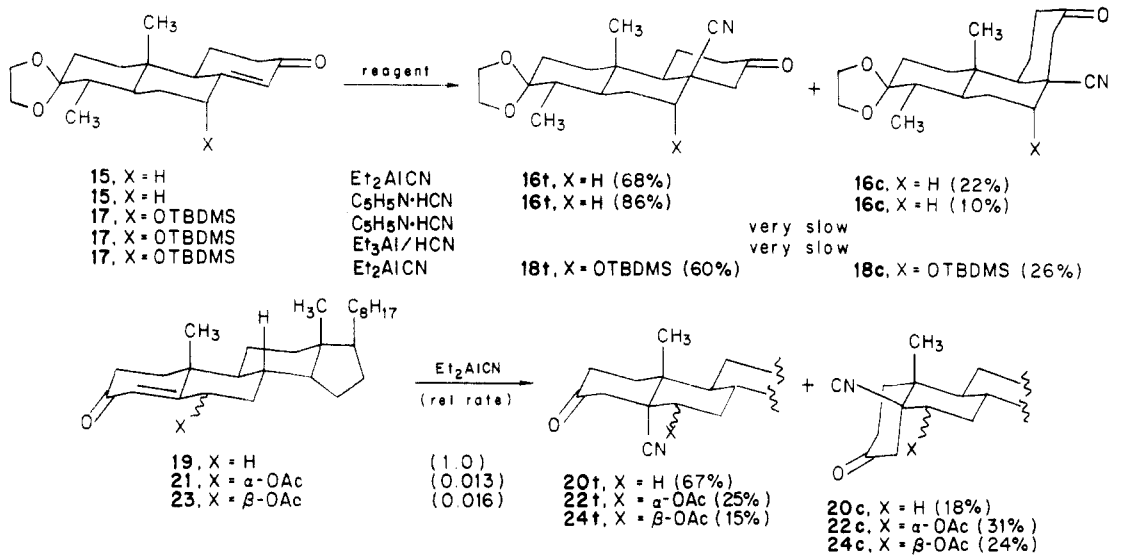
(19) An often cited method[19a,b] for the identification of the low energy conformation of a complex molecule is geometry optimization from models whose components imitate the geometry of known low-energy conformations of similar but simpler systems. In this case, the model chosen to represent both lactones in question consisted of a dimethylcyclohexane (i.e., ring B with enforced axial methyl group at C-10) to which a five-membered cyclic ether and seven-membered lactone had been fused. Investigation of the low-energy forms of the tricyclic model proceeded with MM2 geometry optimization of the combined chair form of the six-membered ring, the near planar conformation of the five-membered ring and several low energy conformations of the lactone described below. Allinger reports three equilibrium conformations for the seven-membered lactone with the chair form 2.72 kcal/mol lower in energy than the boat form which, in turn, is 2.59 kcal/mol lower in energy than the trans form.[19c] He contends that the equilibrium concentrations of the boat and trans conformations are negligible. After reproducing Allinger's results for the chair and boat geometries of the seven-membered lactone three forms along with a modification of the chair were used to find the minima for the tricyclic model. In each case the energy of the optimized structure was equal to or greater than that previously obtained from MM2 optimization using a program featuring direct graphic input.[20] The calculated steric energy of the lowest energy forms of the models for **40C** and **42C** are within 0.06 kcal/mol. (a) Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 757. (b) DeClerq, P. J. *J. Org. Chem.* **1981**, *46*, 667. (c) Allinger, N. L.; Burkert, U. "Molecular Mechanics"; American Chemical Society: Washington, DC, 1982; p 226.

Scheme II[a]



[a] (A) Li/NH_3THF, isoprene quench; (B) $HOCH_2CH_2OH$, C_6H_6, TsOH, 24 h, 80 °C; (C) Li/NH_3/*t*-BuOH; (D) CH_3CO_2H, 25 °C, 3h; (E) $2KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$, H_2O, THF, 25 °C, 3 h; (F) NaH, CH_3I/THF, 60 °C, 2 h.

Scheme III

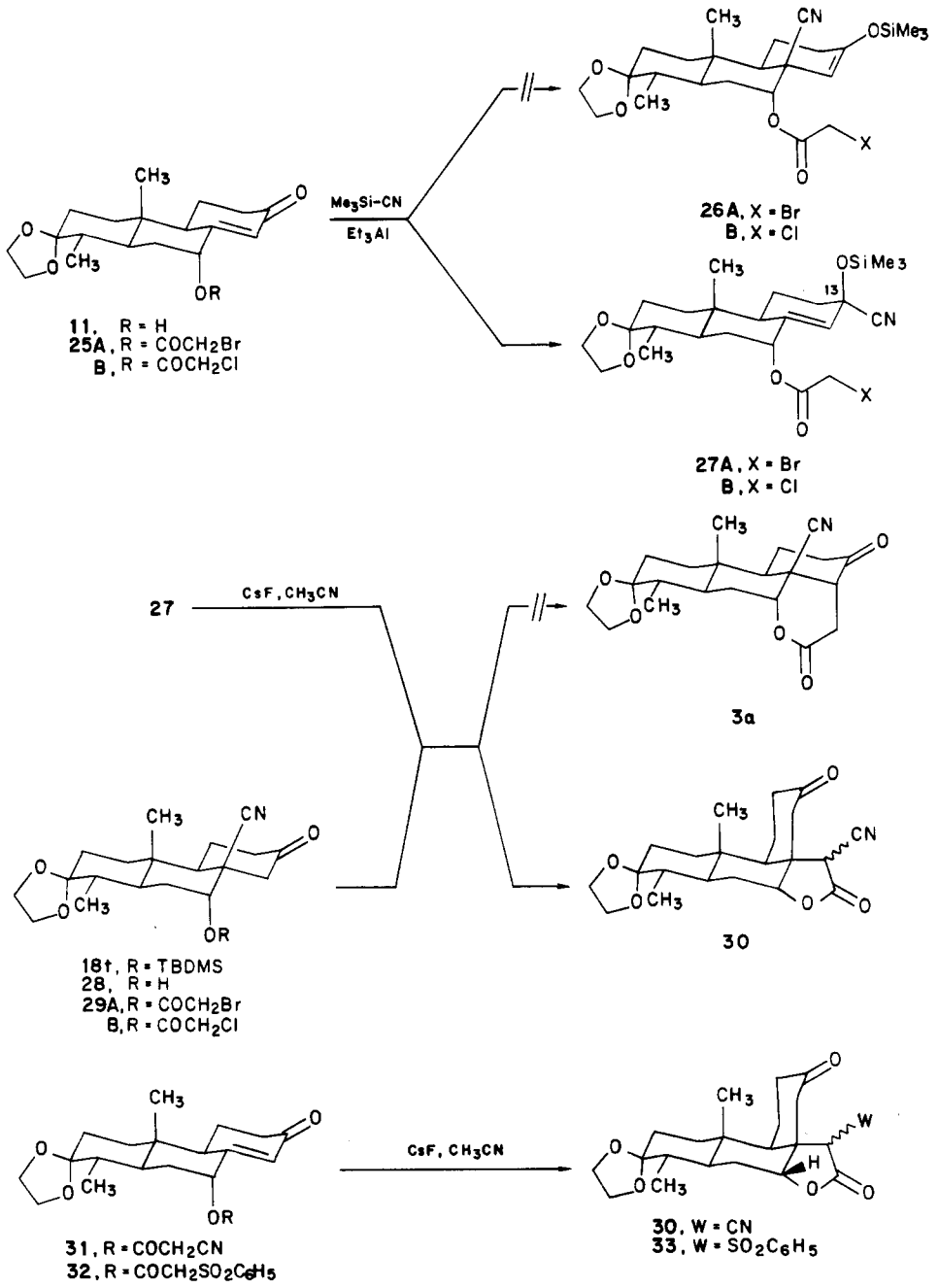


sterically demanding lactone nitriles **30** exist as a ca. 1:1 mixture of diastereomers whereas **33** adopts a single C-15 configuration in the base-catalyzed cesium fluoride cyclization reaction of **32**.

Armed with the hypothesis that ketal instability was responsible for generation of the host of products observed in the reactions of α-sulfonyl lactone **33** with peracid,[15] we returned to the C-3 protected methyl ether **14**. Esterification of **14** with (phenylsulfonyl)acetic acid provided a crystalline α-sulfonyl ester (90%) which was subjected to the cesium fluoride cyclization reaction to afford α-sulfonyl lactone **37A** in 84% yield as a single diastereomer. Treatment of keto lactone **37A** in methylene chloride with MCPBA in the presence of boron trifluoride etherate for 18 h at room temperature again affords a single regioisomeric bis lactone **40A** (Scheme V).

Although the bis lactones **39** and **40A** are useless intermediates vis-à-vis the transacylation plan (cf. **34** to **35**), the regiocontrol in this reaction is worthy of further comment.[1b] The desired lactone **42A** was expected to have been formed by selective migration of bond B since it can be readily seen from models that a substantial steric interaction is present between the "W" group and the acyl peroxy moiety in the transition state appropriate for migration of bond A, leading to the undesired lactone **40A**. Implicit in this argument is the assumption that the peracid will attack from the axial direction because of the highly congested nature of the β-face of **37A–C** (the C-10 axial methyl group is, in effect, an axial C-4 *tert*-butyl group in this cyclohexanone derivative). Evidence passively in support of this postulate is provided by the borohydride reduction of **37B** followed by acetylation to yield the corresponding equatorial acetate in 80% purified yield.[9] Furthermore, molecular mechanics calculations affirm the contention that **37C** exists in all-chair conformation.[20]

Scheme IV



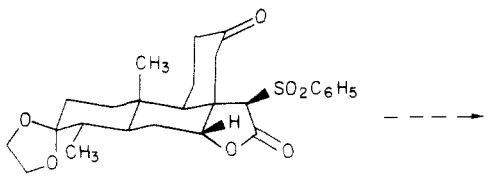
Treatment of **37A** with *m*-chloroperoxybenzoic acid in methylene chloride at 25 °C for 18 h *in the presence of boron trifluoride etherate* (0.75 equiv) affords **40A** in 88% yield after recrystallization. Since Lewis acid catalysis was *required* for this reaction, we were concerned that the regiochemical outcome might have resulted from boron-mediated coordination between the sulfone and the acyl peroxide moiety thereby favoring alignment of bond A in a *trans*-antiparallel fashion with the peroxy group.

In order to more fully understand the factors controlling this reaction, the desulfonylated lactone **37B** was also subjected to Baeyer–Villiger oxidation (Lewis acid not required) with MCPBA in methylene chloride at 25 °C for 18 h to again generate the product of exclusive bond A migration, **40B** (76%). The absence of both the sulfone moiety and the Lewis acid catalyst seems to preclude the possibility of this rearrangement being favored by a specific acyl peroxy rotomer. The next possibility considered was an electronic effect based upon the γ-oxygen substituent at C-7.

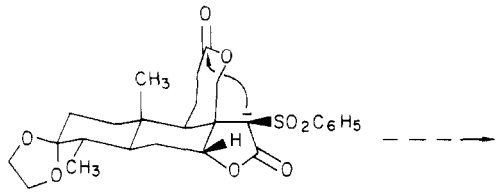
Noyori has recently very convincingly demonstrated in a series of closely related γ-oxygenated ketones **43A–D** that increasing the electron-withdrawing ability of the substituent at the γ position led to a decrease in the migratory aptitude of the α-methylene group.[18] While the Noyori experiments (**43A–D** to **44A–D**/**45A–D**)[18] suggest that this effect is only worth ca. 1 kcal/mol for systems where the oxygen substituent is able to freely rotate, it seemed possible that in the present instance (where a fixed stereoelectronic oxygen relationship exists (**37A–C**)) that this effect might be enhanced to a sufficient extent such as to completely preclude the migration of bond B. Since the Noyori data demonstrate that a simple ether (**45B**) is not sufficient to elicit this effect, we next examined the Baeyer–Villiger oxidation of tetrahydrofuran **37C**. Once again, a single bis lactone **40C** was isolated (66%) (Scheme VI).

(20) Spellmeyer, D. C.; Swenson, C. J.; Jorgensen, W. L., unpublished results.

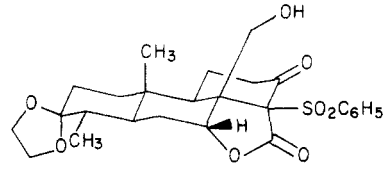
Scheme V



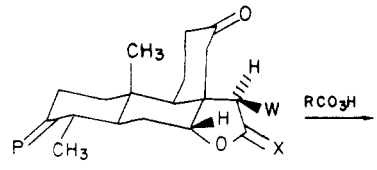
33



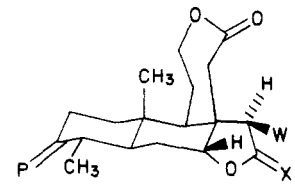
34



35



33, P = OCH_2CH_2O; W = $SO_2C_6H_5$; X = O
36, P = OCH_2CH_2O; W = H; X = O
37A, P = β-OCH_3; W = $SO_2C_6H_5$; X = O
B, P = β-OCH_3; W = H; X = O
C, P = β-OCH_3; W = H; X = H_2



38, P = OCH_2CH_2O; W = $SO_2C_6H_5$; X = O
39, P = OCH_2CH_2O; W = H; X = O
40A, P = β-OCH_3; W = $SO_2C_6H_5$; X = O
B, P = β-OCH_3; W = H; X = O
C, P = β-OCH_3; W = H; X = H_2

A satisfactory explanation for the specificity of these reactions would seem to lie in the area of torsional effects. As the reaction proceeds from intermediate **41** it seems clear that migration of bond A (to intermediate **46**) serves to remove an unfavorable 1,3-diaxial interaction between the C-12 methylene and the axial C-10 methyl group, which is maintained by migration of bond B (to intermediate **47**). Besides accommodating the data, this proposal is further supported by two additional points concerning the reaction profiles. (1) Concern could be expressed that the resonance energy of the protonated lactone carbonyls might differ significantly in the transition states leading to **40** and **42**; however, inspection of models reveals that for both intermediates **46** and **47** the incipient lactone carbonyl is substantially twisted out of conjugation with the electron lone pairs of the ether oxygen. (2) An additional concern is for the overall thermodynamics of the reactions; however, molecular mechanics calculations reveal that lactones **40** and **42** are essentially isoenergetic in the lowest energy extended conformation where the lactone C=O moiety enjoys full resonance delocalization.[1,19,20] Thus, it seems quite likely that the preference for migration of bond A is determined early in the transition state where the selection between dioxolenium ions **46A–C** and **47A–C** strongly favors intermediates **46A–C**. Rehybridization[21] and conformational isomerization[19] of **46A–C** to **40A–C** occur subsequently but do not affect the initial locus of migration (Scheme VII).

Concurrently with our efforts to effect Baeyer–Villiger oxidations of **33** and **37A–C** we also investigated the preparation and oxidation of α-chloro ketones **48** and **49** since it had been nicely demonstrated that steroidal α-halo ketones undergo regiospecific Baeyer–Villiger oxidations in the sense desired, presumably because of electronic destabilization of the migratory aptitude of the haloalkyl group.[22] Furthermore, the resultant α-halo lactones **50** and **51** would possess a leaving group appropriate for dehydrohalogenation to the C-11, C-12 olefin required for eventual introduction of the trans-diol moiety in bruceantin.

Treatment of γ-hydroxy enone **11** with trimethylchlorosilane and triethylamine affords γ-silyloxy enone **52** in 98% yield. Reaction of **52** with LDA followed by quenching with trimethylchlorosilane affords the kinetic silyl dienyl ether[23,24] **53**, which is not purified but is dissolved in THF and directly treated with *N*-chlorosuccinimide[25] in the presence of solid sodium bicarbonate at −78 °C followed by warming to room temperature to yield a 9:1 mixture of axial and equatorial chloroenones from which the major (axial) α-chlorinated γ-silyloxy enone **54** was isolated but not fully characterized. Deprotection of **54** by treatment with boron trifluoride etherate in aqueous acetone[26] afforded the crystalline α-chloro γ-hydroxy enone **55** in 63% overall yield. DCC-mediated esterification of **55** with (phenylsulfonyl)acetic acid smoothly provides crystalline α-chloro enone **56** in 95% yield. Cyclization of **56** with cesium fluoride in acetonitrile provides a mixture of α-chloro keto lactones **48A** (89%) and **48B** (6%). The genesis of "inverted" chloride **48B** apparently lies in cesium fluoride catalyzed precyclization epimerization of **56** since **56** is a single epimer and control experiments show that pure **48A** does not yield **48B** under the reaction conditions. Unfortunately by the time **48A** had been prepared, the ketal instability of the deschloro compound **33** had become readily apparent; therefore it came as no surprise that treatment of **48A** under a variety of forcing Baeyer–Villiger conditions served only to consume starting material without the apparent production of any **50A**.

(21) Ab initio calculations suggest that for cis esters it requires ca. 6 kcal/mol to attain a fully orthogonal relationship between the oxygen and carbonyl moiety (i.e., no resonance delocalization): (a) Radom, L.; Lathan, W. A.; Hehre, W. J.; Pople, J. A. *Aust. J. Chem.* **1972**, *25*, 1601. (b) Perricaudet, M.; Pullman, A. *J. Peptide Protein Res.* **1973**, *5*, 99.

(22) (a) Dave, V.; Stothers, J. B.; Warnhoff, E. W. *Can. J. Chem.* **1980**, *58*, 2666. (b) Bollinger, J. E.; Courtney, J. L. *Aust. J. Chem.* **1964**, *17*, 440.

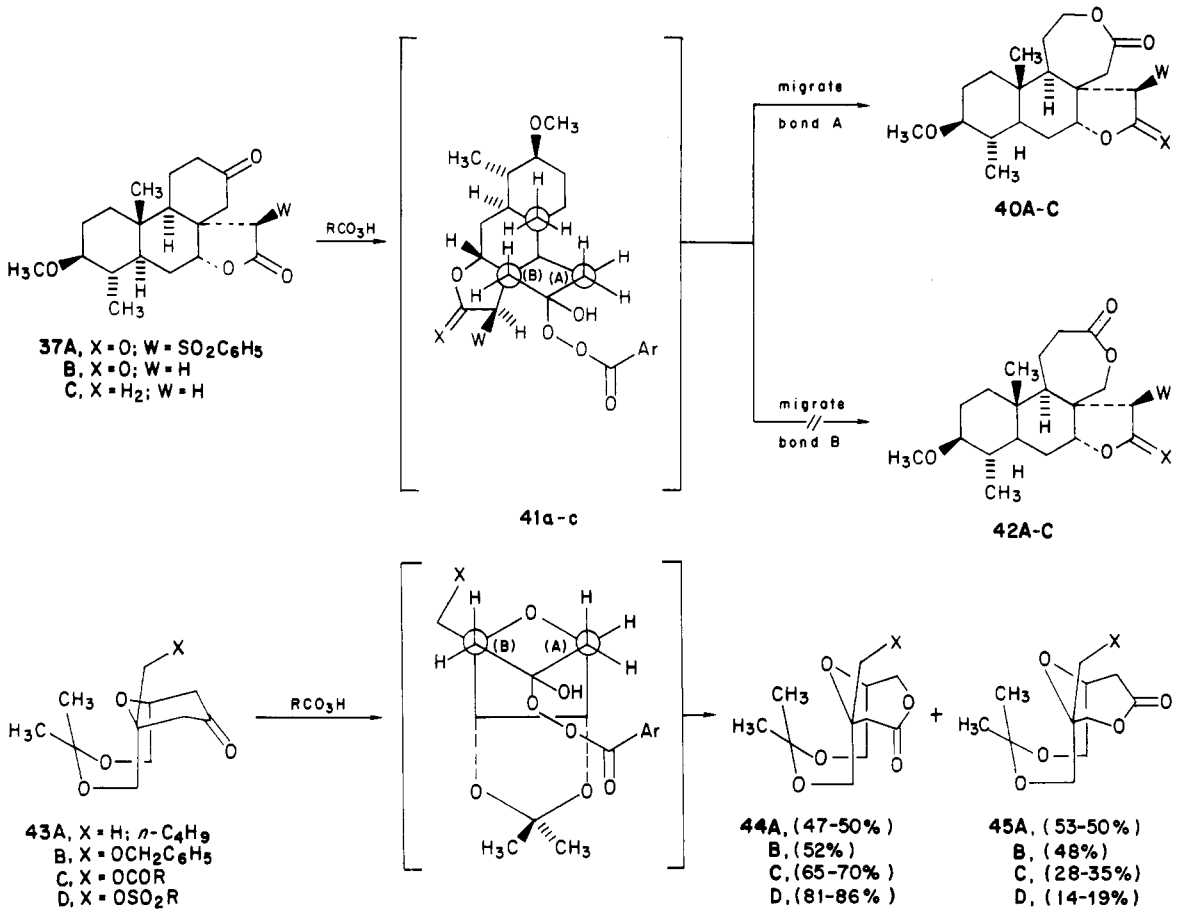
(23) For a review of silyl enol ether chemistry, see: Brownbridge, P. *Synthesis* **1983**, 1, 85.

(24) Treatment of **11** with 2 equiv of LDA followed by quenching with excess trimethylchlorosilane produces **53** in poorer overall yield than the two-step procedure.

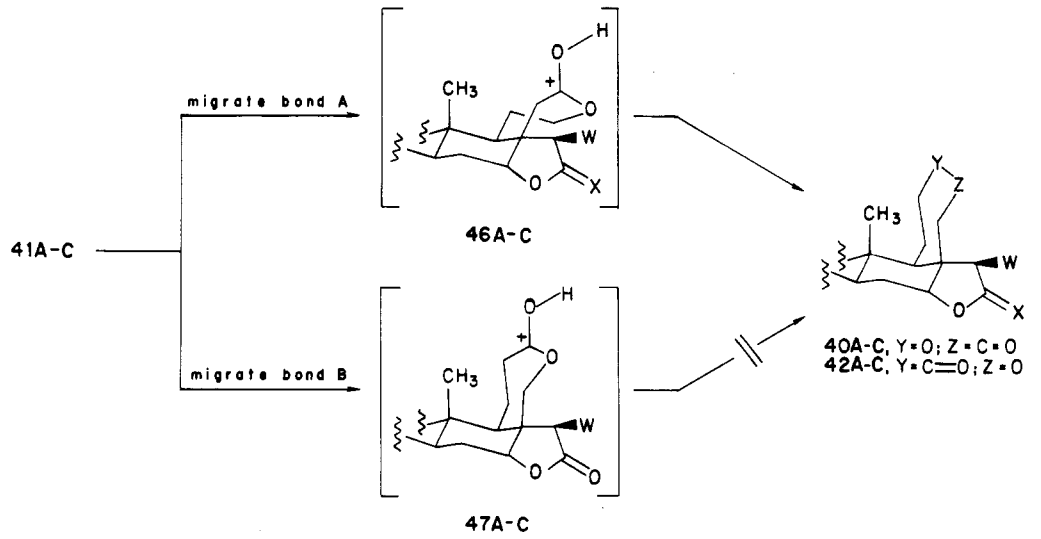
(25) For similar halogenations of silyl enol ethers, see: Rasmussen, J. K. *Synthesis* **1977**, 91 and references therein.

(26) For the **54** to **55** transformation it is not presently known whether the active reagent in the silyloxy cleavage is the boron trifluoride (Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295) or aqueous hydrofluoric acid produced under the reaction conditions (Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

Scheme VI



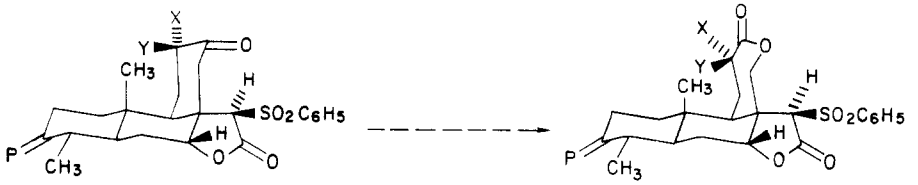
Scheme VII



Anticipating that it would be a straightforward matter to simply apply the experience gained from the C-3 methyl ether protected series (cf. **37**) we again returned to γ-hydroxy enone **14**. With a view toward improving upon the four-step sequence previously employed for synthesis of α-chloro-γ-hydroxy enone **55**, γ-hydroxy enone **14** was sequentially treated with 2 equiv of LDA (presumably to generate intermediate **57** followed by excess *N*-chlorosuccinimide at −78 °C to afford a 1:1 mixture of α-chloro enones **58A**/**58B** in 97% isolated yield.[27a] Chromatographic separation of **58A** and **58B** affords the individual isomers in yields of 44% and 33%, respectively. As will be seen later, both of these isomers ultimately yield the same product so that except for the subsequently described characterization and mechanistic purposes it is no longer necessary to separately convert them to α-sulfonyl esters **59A** and **59B**.

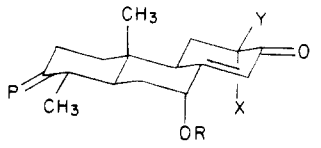
Individual treatment of each enone **58A** and **58B** with DCC and (phenylsulfonyl)acetic acid provides **59A** (94%) and **59B** (95%), respectively. Because the solubility characteristics of **59A** and **59B** would not accommodate the use of acetonitrile as solvent (cf. **56** to **48A**) the cesium fluoride mediated reactions of **59A** and **59B** were conducted in methylene chloride (Scheme VIII). Treatment of *either* **59A** (12 h, 25 °C) or **59B** (24 h, 25 °C) with cesium fluoride[27b] in methylene chloride affords a single

Scheme VIII

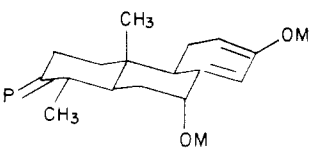


48A, X = Cl; Y = H; P = OCH_2CH_2O
B, X = H; Y = Cl; P = OCH_2CH_2O
49A, X = Cl; Y = H; P = β-OCH_3
B, X = H; Y = Cl; P = β-OCH_3

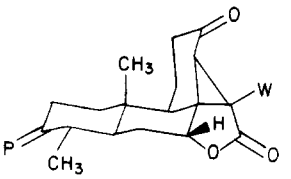
50A,B, P = OCH_2CH_2O
51A,B, P = β-OCH_3



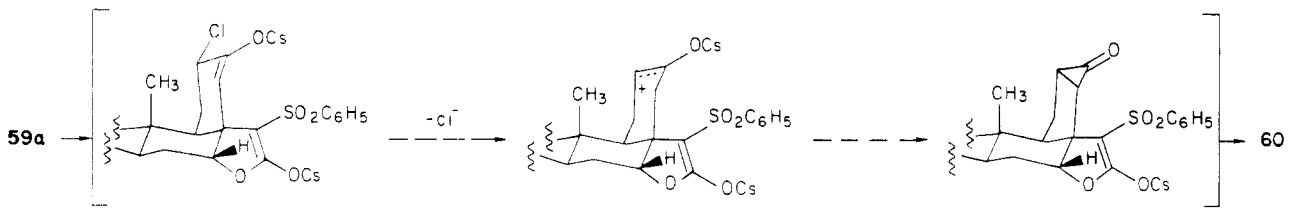
11, X = Y = R = H; P = OCH_2CH_2O
14, X = Y = R = H; P = β-OCH_3
52, X = Y = H; R = Me_3Si; P = OCH_2CH_2O
54, X = Cl; Y = H; P = Me_3Si; P = OCH_2CH_2O
55, X = Cl; Y = H; R = H; P = OCH_2CH_2O
56, X = Cl; Y = H; R = $COCH_2SO_2C_6H_5$; P = OCH_2CH_2O
58A, X = Cl; Y = H; R = H; P = β-OCH_3
B, X = H; Y = Cl, R = H; P = β-OCH_3
59A, X = Cl; Y = H; P = $COCH_2SO_2C_6H_5$; P = β-OCH_3
B, X = H; Y = Cl; R = $COCH_2SO_2C_6H_5$; P = β-OCH_3



53, M = Me_3Si; P = OCH_2CH_2O
57, M = Li; P = β-OCH_3



60, W = $SO_2C_6H_5$; P = β-OCH_3
61, W = $SO_2C_6H_5$; P = OCH_2CH_2O



62A **62B** **62C**

product (83% and 90%, respectively, which contained neither chlorine nor the isolated proton characteristic of a methine adjacent to an α-sulfonyl lactone. After some consideration it became apparent that the structure of this product was the pentacyclic cyclopropane **60**.[27b] That this remarkable difference between the cyclizations of **56** and **59A,B** was in fact attributable to a solvent effect was demonstrated by treating *either* **56** or **48A** under the cesium fluoride–methylene chloride conditions to obtain the corresponding pentacyclic cyclopropane **61**. Apparently it is the insolubility of **48A** (which crystallized out during the *acetonitrile* reaction) that kinetically retards its further conversion to **61**.[30]

Careful HPLC analysis of the conversion of **59A** to **60** reveals that **59A** produces a mixture of intermediates (presumably **49A** as well as its C-12 and C-15 epimers) along with minor amounts of isomer **59B**. Similar examination of the cyclization of **59B** reveals isomerization to **59A** along with production of the same group of intermediates prior to conversion to pentacyclic cyclopropane **60**.

While it seems highly likely that both isomers **59A** and **59B** cyclize to **60** through the intermediacy of chloride **49A**, the further mechanistic details of this transformation are less obvious. The manifold of potential intermediates[27b] would seem to include enolate **62A**, oxallyl cation **62B**, and/or cyclopropanone **68C**.[28] Cyclopropanone **62C** would seem to be a less likely candidate than **62A** and/or **62B** since it requires front-side attack by the lactone enolate; a choice between **62A** and **62B** cannot be made with the current information in hand.[29]

In view of the impractability of the Baeyer–Villiger approaches, we elected to pursue an alternative mode of functionalization of the C-ring ketone. It is well known that silyl enol ethers are susceptible to ozonolytic cleavage and that reduction/hydrolysis of the resulting ester aldehydes afford seco acids which are equivalent to those produced in the Baeyer–Villiger reaction.[31] The silyl enol ether required for application of this strategy to our needs is **64**. Although silylation[32] of the readily available ketone

(27) (a) For comparison purposes **14** was taken through an analogous four-step procedure to that employed with **11** (cf. **11** to **52** to **53** to **54** to **55**). The selectivity for halogenation of the silyl dienyl ether in this case favored the axial chloride by a ratio of 93:7 over the equatorial isomer. The experimental details for these reactions can be found in the supplementary material: (b) Suryawanshi, S. N.; Fuchs, P. L. *Tetrahedron Lett.* **1984**, *25*, 27.

(28) These intermediates are all written as their C-15 enolates, although it seems apparent that reversible deprotonation is also occurring at C-12, C-14, and C-15.

(29) Examples of the S_N2' reaction of an α-sulfonyl ester with β'-enol ether derivatives (palladium (0)–π-allyl intermediate) have been recorded by Trost and Gowland: Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **44**, **1979**, 3448. A failure of the intramolecular variant of this stragegy which would have lead to a cis-fused bicyclo[4.3.0] system has also been recorded by Trost, Bernstein, and Funfshilling; see ref 13 in: Trost, B. M.; Berstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. "Harder" nucleophiles such as organometallic reagents are also known to undergo S_N2' addition to the enolates (and enol ether derivatives) of α-substituted ketones; see: Marino, J. P.; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165. Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114 and references therein.

(30) Cyclization of **59A** or **59B** to **60** in acetonitrile is less efficient (6% and 43%, respectively).

(31) (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1975**, *41*, 1396. (b) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, 2027.

33 produces a single silyl enol ether (63), it is clear from its spectral properties that it is regioisomeric to the one desired. Fortunately, an efficacious solution to this problem was available from the pentacyclic α-sulfonyl lactone 60. Treatment of 60 with lithium dimethyl cuprate at 0 °C effects reductive cleavage of the activated cyclopropane to generate a regiospecific enolate which is subsequently silylated to afford the requisite silyl enol ether 64 in 94% isolated yield (Scheme IX). Ozonolysis of 64 does not afford the expected silyl ester aldehyde 65 but rather yields α-hydroxy ketone 66. α-Ketols have been previously obtained in the ozonolysis of silyl enol ethers.[31] Borohydride reduction of 66 produces a mixture of 1,2-diols 67, which were not further purified but were immediately subjected to periodate cleavage, yielding bis aldehyde 68 (60%). Brief exposure of 68 to triethylamine quantitatively produces the desired aldol product 69 as a white crystalline solid. Treatment of 69 with aluminum amalgam in THF[16] accomplishes 1,2-reduction of the aldehyde moiety concurrently with reductive cleavage of the phenyl sulfone group, generating diol 70 in 71% yield.

Treatment of diol 70 with TBDMS triflate[33] smoothly affords the bis silyl ether 71 in 98% isolated yield. Reaction of lactone 71 with DIBAL or LAH produces lactol 72. Lactol 72 is completely inert to reaction with methylenetriphenylphosphorane under conditions that are typical for the Wittig olefination of lactols through their ω-hydroxy aldehyde tautomers.[34] A further indication of the kinetic stability of lactol 72 is evidenced by reaction of 71 with LAH under forcing conditions; under these circumstances the lactol does not yield the expected diol via overreduction through the ω-hydroxy aldehyde but rather undergoes a (presumably intramolecular) transsilylation reaction[35] to produce hydroxy ketal 73 in high yield.

The stability of lactol 72 toward ring-opening suggested an alternative strategy for the requisite one carbon homologation of γ-lactone moiety; therefore treatment of 71 with a solution of methyl lithium at room temperature afforded the tertiary hemiketal 74 in 93% yield after purification. Reaction of lactol 74 with the Swern reagent[36] provided β-methylthio enol ether 75 in 92% isolated yield (as a single diastereomer of unknown stereochemistry). Similar reaction of 74 with trifluoroacetic anhydride and *phenyl* methyl sulfoxide in place of the dimethyl sulfoxide affords the analogous *phenyl* sulfide 76 in 88% yield.

A working hypothesis for this useful transformation involves dehydration of the tertiary alcohol moiety of 74 via the agency of oxosulfonium ion intermediate 77 to enol ether 78. Nucleophilic attack of enol ether 78 on a second equivalent of the oxosulfonium ion reagent generates oxonium ion 79 which, in turn, undergoes deprotonation and ionization of the trifluoroacetate anion to produce vinyl sulfonium salt intermediate 80. Nucleophilic demethylation of 80 then accounts for production of the observed sulfides 75 and 76.

Application of this strategy to a more advanced bruceantin intermediate was also realized. Selective deprotection of the secondary silyl ether was accomplished by treatment of bis silyl ether 71 with trityl fluoroborate to afford hydroxy lactone 81 in 97% yield. Swern oxidation of 81 produced keto lactone 82, which was smoothly converted to silyl enol ether 83 by reaction with TBDMS triflate and triethylamine[32] (95% × 92%) (Scheme X). Reaction of 83 with methyl lithium at −78 °C affords hemiketal 84 as a 1:1 mixture of diastereomers, which were not separated but directly treated with the Me_2SO/TFAA reagent to produce vinyl sulfide 85 (89% × 79%). It is worth noting that synthesis of 85 requires the oxosulfonium salt reagent to selectively functionalize an exocyclic enol ether in the presence of an endocyclic silylenol ether.

Treatment of β-methylthio enol ethers 75 and 85 with osmium tetraoxide yields the ring-expanded α-keto lactols 86 and 87 (80% and 72%, respectively). The mechanism of this reaction has not been investigated, but a reasonable rationale would seem to involve incipient formation of the 1,2-diol followed by loss of methanethiol and rearrangement of the resultant δ-lactol aldehyde to the observed δ-lactol ketone. Selectivity in the oxidation of the more electron-rich enol ether moiety of 85 again appears noteworthy.

Experimental Section

The solvents hexane, chloroform, and ethyl acetate were distilled prior to use; ether, methanol, and DMF (*N,N*-dimethylformamide) were Mallinkrodt AR or Fisher reagent grade; the DMF was stored over Linde 4-Å molecular sieves. Solvents were evaporated from the reaction mixtures on a Buchi Rotovapor R at water aspirator pressure (ca. 20 mm), with ice-cold condenser water and a bath at 20–30 °C. All other chemicals used were of the best commercial grade, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) on precoated (0.25 mm) silica gel 60F-254 plates from EM Reagents; the plates were observed with a 254 light to detect quenching of the fluorescent binder: UV+ indicates such absorption of the light. The TLC plates were developed with acidified alcoholic *p*-anisaldehyde spray [p-AA spray: 1350 mL of absolute ethanol, 50 mL of concentrated H_2SO_4, 15 mL of glacial acetic acid, and 37 mL of *p*-anisaldehyde (Aldrich) mixed together], and heated to 175 °C until the colors were clearly visible. CAB refers to a TLC solvent system developed by Dr. Charles A. Bunnell and consists of the following (parts by volume): 3:1:2:2 hexane–ether–chloroform–methanol. It was made less polar by mixing with ether where noted.

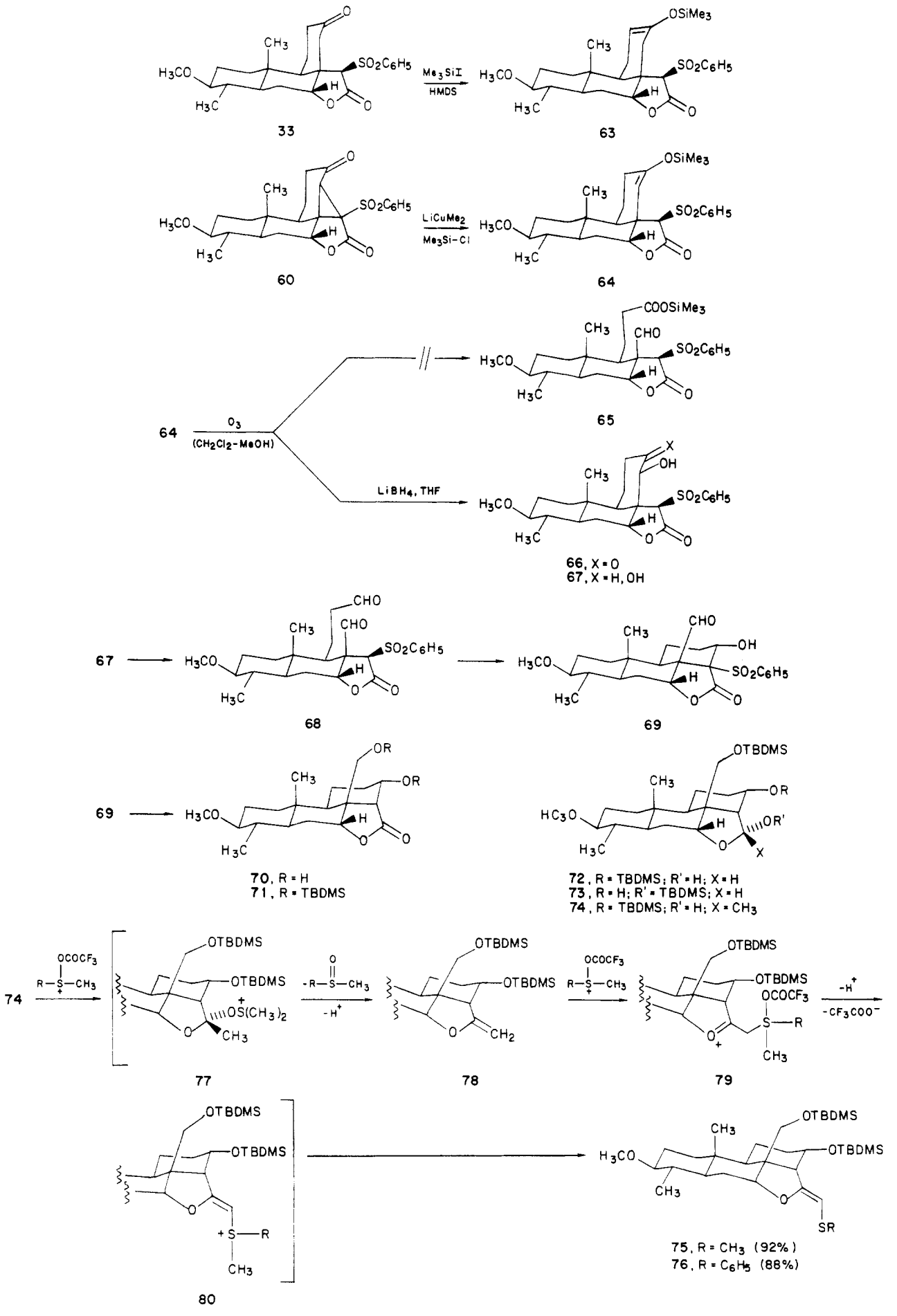
Melting points were measured on a Fisher-Johns melting point apparatus, were uncorrected, and are reported in °C. Infrared spectra were recorded in $CHCl_3$ or neat between NaCl plates, on a Perkin-Elmer Model 267 grating infrared spectrometer, and are reported in μm. NMR spectra were obtained in $CDCl_3$ (with Me_4Si internal standard; Aldrich) and are reported in parts per million downfield from Me_4Si; proton NMR on Perkin-Elmer R-32 (90 MHz) and Nicolet NT-470 instruments; carbon NMR on a Varian CFT-20 (20 MHz) or an XL-200 (50 MHz) instrument. Mass spectra exact mass determinations were obtained by N. Haarbe on a CEC-21-110-B high-resolution mass spectrometer and by Arlene Rothwell on a Finnigan 4121 GC–mass spectrometer (EI, 70-eV electron impact; CI, chemical ionization with isobutane). The combustion analyses were run by Dr. H. D. Lee of the Purdue Microanalytical Laboratory.

2,3,4,4a,9,10-Hexahydro-7-methoxy-1,4aβ-dimethyl-2-phenanthrone (7). *p*-Methoxyphenylacetic acid (1000.00 g, 6.02 mol) was treated with thionyl chloride (500 mL) at 0 °C within 1 h. The mixture was then stirred at 25 °C for 18 h. Four portions of dry benzene (400 mL each) were added and removed in vacuo at 40 °C. The last traces of benzene were removed under vacuum with the receiver cooled to −78 °C. The residual liquid was distilled in two portions to yield *p*-methoxyphenylacetyl chloride as a colorless liquid: 1080 g, 97%; bp 88–90 °C – (0.50 mm), oil bath 120 °C [lit.[37] bp, 80–88 °C (0.5 mm)]; IR 5.6 μM (C=O stretch).

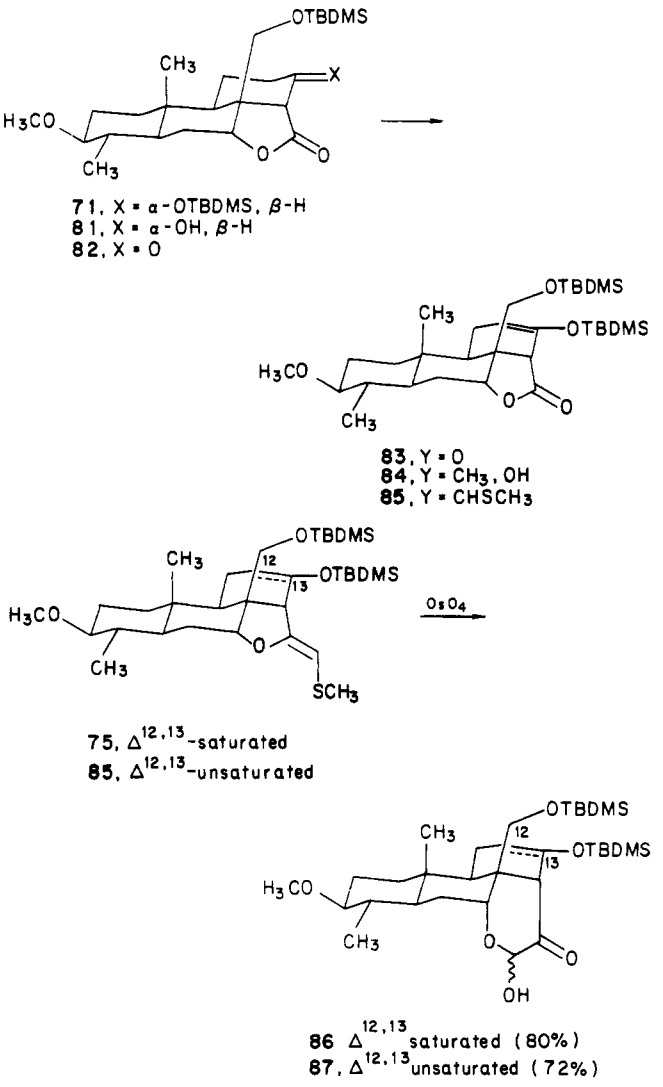
To a 10-L three-neck flask, fitted with a reflux condenser,

(32) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
(33) Emde, H.; et al. *Synthesis* **1982**, 1.
(34) (a) Whitesell, J. K.; Fisher, M.; Jardine, P. D. S. *J. Org. Chem.* **1983**, *48*, 1556. (b) Boland, W.; Ney, P.; Jaenicke, L. *Synthesis* **1980**, 1015. (c) Show, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.
(35) (a) Dodd, G. H.; Golding, B. T.; Ioannou, P. V. *J. Chem. Soc., Chem. Commun.* **1975**, 249. (b) Torisawa, Y.; Shibsaki, M.; Ikegami, S. *Tetrahedron Lett.* **1979**, *21*, 1865.
(36) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
(37) Sims, J. J.; Selman, L. H.; Cadogan, M. *Org. Synth.* **1971**, *51*, 109.

Scheme IX


33
63
60
64
65
66, X = O
67, X = H, OH
68
69
70, R = H
71, R = TBDMS
72, R = TBDMS; R' = H; X = H
73, R = H; R' = TBDMS; X = H
74, R = TBDMS; R' = H; X = CH3
77
78
79
75, R = CH3 (92%)
76, R = C6H5 (88%)
80

Scheme X



dropping funnel, and mechanical stirrer, were added 500 g (3.759 mol) of aluminum chloride and 8000 mL of methylene chloride. The aluminum chloride suspension was then cooled to −78 °C (dry ice/isopropyl alcohol). *p*-Methoxyphenylacetyl chloride (370 g, 2 mol) was added dropwise over a period of 0.5 h to the cold, stirred suspension. After the addition was complete, ethylene gas was continuously bubbled into the reaction mixture for 40 min. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C, and treated with cold water (1000 mL) over a period of 1 h. The aqueous phase was removed, and the organic portion was washed successively with 5% hydrochloric acid (1000 mL × 2), saturated aqueous $NaHCO_3$ (1000 mL × 2), distilled water (1000 mL × 2), and saturated sodium chloride (1000 mL × 2). The organic phase was dried over sodium sulfate, and the solvent was removed to yield a reddish brown viscous liquid (415.00 g). This crude product was then distilled from 5 wt % anhydrous $NaHCO_3$ in four batches to afford 6-methoxy-2-tetralone as a colorless liquid (306.00 g, 87%): bp 108–110 °C (0.05 mm), bath 160–170 °C [lit.[37] bp 114–116 °C (0.2 mm)]; ^1H NMR ($CDCl_3$) δ 2.48 (t, 2 H), 3.00 (t, 2 H), 3.78 (s, 3 H).

A mixture of 6-methoxy-2-tetralone (300.00 g, 1.7 mol), toluene (3000 mL), pyrrolidine (600 mL, 7.00 mol), and *p*-toluenesulfonic acid (6.00 g) was heated at reflux with magnetic stirring for 18 h (water separated = 46 mL). The reaction mixture was cooled to room temperature, and the toluene was removed under reduced pressure. After complete removal of the toluene, dry methanol (3000 mL) was added, and mixture was treated with methyl iodide (250 mL, dropwise addition, 0.5 h) and stirred for 1 h. A second portion of methyl iodide (200 mL) was added, and the reaction mixture was stirred under gentle reflux for 18 h. Excess methyl iodide was removed under vacuum, and the residue was heated at reflux for 45 min in a buffer solution comprised of 200 mL acetic acid, 200 g sodium acetate, and 400 mL water. The reaction mixture was cooled to room temperature and extracted with ether (500 mL × 3). The combined ether extract was washed with 10% aqueous NaOH (250 mL × 2), 10% HCl (250 mL × 2), water, and saturated NaCl solution. After drying (Na_2SO_4), the solvent was removed in vacuo. The crude viscous brown liquid was distilled to yield 1-methyl-6-methoxy-2-tetralone as a colorless viscous liquid (214.0 g 66%), bp 121–125 °C (0.5 mm) [lit.[38] bp 110–112 °C (0.05 mm)]. It solidified upon storing at low temperature: ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 6.00 Hz, 3 H), 2.55 (m, 2 H), 3.05 (m, 2 H), 3.45 (q, 1 H), 3.80 (s, 3 H), 6.75–7.25 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.09 (q), 28.02 (t), 36.90 (t), 46.36 (d), 54.97 (q), 112.00 (d), 113.01 (d), 126.82 (d), 129.76 (s), 137.81 (s), 158.72 (s), 210.38 (s).

To an ice-cooled heterogeneous mixture of 1-methyl-6-methoxy-2-tetralone (1000.00 g, 5.26 mol), anhydrous potassium carbonate (1462.8 g, 10.60 mol), and methanol (4000 mL) was slowly added 1-chloro-3-pentanone[39] (691.00 g, 5.76 mol) over a period of 1 h. The resulting reaction mixture was slowly warmed to the room temperature and stirred mechanically for 48 h. Solid material was removed by filtration and was washed with methanol (500 mL). The resulting filtrate was evaporated to dryness in vacuo. The viscous liquid was taken up in methylene chloride (3000 mL), washed successively with water (1000 mL × 3) and saturated NaCl solution (3000 mL), washed successively with water (1000 mL × 3) and saturated NaCl solution (1000 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo. The viscous yellow liquid was crystallized from ether/acetone in four crops to yield a pale yellow crystalline solid [1008.00 g, 75% (when the experiment was carried out on a 10-mmol scale the yield was 82%)]: mp 86–87 °C. (lit.[6a] mp 86–88 °C; ^1H NMR ($CDCl_3$) δ 1.50 (s, 3 H), 1.85 (s, 3 H), 3.80 (s, 3 H) 6.65–7.30 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 10.85 (q), 27.12 (q), 27.31 (t), 30.22 (t), 34.25 (t), 36.39 (t), 39.19 (s), 55.08 (q), 112.96 (d), 126.66 (d), 128.49 (s), 136.89 (s), 137.04 (s), 157.60 (s), 162.08 (s), 197.76 (s).

1β,2,3,4,4a,9,10,10aα-Octahydro-7-methoxy-1α,4aβ-dimethyl-2-phenanthrone Ethylene Acetal (8). A 5000-mL three-neck flask equipped with a dropping funnel, dry ice condenser, and mechanical stirrer was cooled to −78 °C. Lithium (14.00 g, 2 mol) and ammonia (2000 mL) were added. The deep blue solution was allowed to warm to −40 °C and tricyclic enone **7** (51.20 g, 0.2 mol) in dry THF (1000 mL) was added slowly over a period of 30 min. After 4 h the reaction was quenched by slow addition of isoprene (70.00 mL, 1.5 h). The ammonia was allowed to evaporate overnight at room temperature. The residue was treated slowly with water and extracted with ether. The ether extract was washed with water and saturated NaCl solution and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude ketone (50.0 g) was used in the next step without further purification.

The crude ketone (50.0 g, 0.195 mol) was mixed with benzene (1800 mL), *p*-toluenesulfonic acid (2.4 g), and ethylene glycol (400 mL) and was heated at reflux for 24 h. The mixture was cooled to room temperature, the benzene layer was washed with saturated $NaHCO_3$ (400 mL), water (400 mL × 2), and a saturated NaCl solution (400 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude white solid was recrystallized from methylene chloride/hexane to afford **8** as a crystalline solid (40.80 g, 81%): mp 105–107 °C; ^1H NMR ($CDCl_3$) δ 0.925 (d, J = 6 Hz, 3 H), 1.1 (s, 3 H), 3.75 (s, 3 H), 3.95 (s, 4 H), 6.5–7.3 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 10.67 (q), 22.14 (q), 21.53 (t), 29.86 (t), 31.38 (t), 35.22 (t), 36.13 (s), 39.39 (d), 45.23 (d), 54.92 (q), 64.87 (m), 110.66 (s), 111.72 (d), 113.39 (d), 125.64 (d), 136.47 (s), 139.95 (s), 157.28 (s); mass spectrum for $C_{19}H_{26}O_3$, m/e 302 (M^+).

1β,2,3,4,4a,5,8,9,10,10aα-Decahydro-7-methoxy-1α,4aβ-dimethyl-2-phenanthrone Ethylene Acetal (9). To a solution of lithium (0.70 g, 0.1 mol) in dry ammonia (60 mL) at −78 °C was added the ketal **8** (1.00 g, 3.3 mmol) in THF (30 mL) over a period of 0.5 h. After the mixture was stirred for 0.5 hr, a

(38) Turner, R. B.; Buchardt, O.; Herzog, E.; Morin, R. B.; Rieble, A.; Sanders, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 1766.
(39) Woodward, R. B.; Sandheimer, F.; Taub, D.; Keusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1982**, *74*, 4223.

solution of potassium *tert*-butoxide (0.50 g, 4.4 mmol) in *tert*-butyl alcohol[40] (30 mL) was added over a period of 0.5 h. The reaction mixture was then slowly brought to reflux, and the reflux was continued for 3 h. The reaction was quenched with methanol and then left overnight to allow the ammonia to evaporate. Cold water (25 mL) was added slowly, and the resulting mixture was extracted with ether (75 mL). The combined ether extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to produce a white solid which on recrystallization from ether/hexane furnished **9** as a white crystalline solid (0.90 g, 90%): mp 126–128 °C; ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 6.00 Hz, 3 H), 1.00 (s, 3 H), 3.55 (s, 3 H), 3.95 (s, 4 H), 4.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.36 (q), 17.01 (q), 20.88 (t), 25.46 (t), 30.57 (t), 30.96 (t), 33.25 (t), 33.93 (t), 35.81 (s), 38.89 (d), 45.62 (d), 53.40 (q), 64.69 (2 t, ketal), 90.38 (d), 110.71 (s), 123.59 (s), 133.90 (s), 152.32 (s); mass spectrum for $C_{19}H_{28}O_3$, m/e 304 (M^+).

1β,2,3,4,4a,4βα,5,6,10,10a-Decahydro-7-methoxy-1α,4aβ-dimethyl-2-phenanthrone Ethylene Acetal (10). Finely powdered dienyl ether **9** (18.50 g, 0.06 mol, vaccum-dried overnight) was treated with glacial acetic acid (40.00 mL, freshly distilled from P_2O_5) over a period of 15 min, and the resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then poured into ice-cooled 25% sodium hydroxide (250 mL) and extracted with methylene chloride (150 mL × 3). The combined extract was washed with water (100 mL × 3) and a saturated NaCl solution (100 mL) and dried over sodium sulfate, and the solvent was removed in vacuo. The crude product afforded **10** as a pale yellow viscous liquid after plug filtration (17.00 g, 92%): ^1H NMR ($CDCl_3$, partial) δ 0.68 (s, 3 H), 0.83 (d, 3 H) 3.58 (s, 3 H), 3.95 (s, 4 H), 5.28 (m, 2 H); exact mass calculated for $C_{19}H_{28}O_3$ 304.202, found 304.202.

1β,2,3,4,4a,4bα,5,6,7,9β,10,10aα-Dodecahydro-9α-hydroxy-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (11). To an ice-cooled solution of dienyl ether **10** (0.030 g, 0.1 mmol) and sodium bicarbonate (0.025 g, 0.3 mmol) in THF (1 mL) was added oxone[41] (0.092 g, 0.15 mmol) in H_2O (0.5 mL) over a period of 15 min. After addition the solution was slowly warmed to room temperature and stirred for 1 h. The mixture was poured on 10% sodium bicarbonate (50 mL) and extracted with methylene chloride (25 mL × 2). The combined extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried over sodium sulfate, and the solvent was removed in vacuo to afford **11** as a white solid [0.029 g, 97% (when the experiment was carried out on a 60-mmol scale the yield was 83%)]. An analytical sample was obtained by recrystallization from ether/hexane: mp 192–193 °C; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 3.95 (m, 4 H), 4.35 (s, C_7H), 5.99 (s, $C_{14}H$); ^{13}C NMR ($CDCl_3$) δ 10.70 (q), 13.43 (q), 20.83 (t), 30.83 (t), 32.26 (t), 35.10 (t), 36.71 (t), 38.57 (s), 38.99 (d), 41.80 (d), 44.71 (d), 65.07 (t), 64.90 (t), 70.99 (d), 110.53 (s), 127.48 (d), 164.17 (s), 200.74 (s); exact mass calculated for $C_{18}H_{26}O_4$ 306.182, found 306.180.

1β,2α,3,4,4a,5,8,9,10,10aα-Decahydro-7-methoxy-1α,4aβ-dimethyl-2β-phenanthrol Methyl Ether (12). A 5000-mL three-neck round-bottom flask equipped with dropping funnel, dry ice condenser, and mechanical stirrer was cooled to −78 °C. The reactor was charged with condensed dry ammonia (2000 mL), and lithium metal (28.00 g, 4.00 mol) was then added slowly (2–3 g at a tim) at −78 °C over 0.5 h. After all the lithium had been dissolved, tricyclic enone **7** (102.4 g, 0.4 mol) in dry THF (1000 mL) was added slowly at the same temperature over a period of 1 h, followed by slow addition of *tert*-butyl alcohol (376.5 mL, 4.00 mol) over a period of 1 h. The deep blue reaction was then allowed to warm to −40 °C, refluxed for 2 h, and slowly treated with ethanol (500 mL) over a period of 1 h. Lithium metal (28.00 g, 4.00 mol) was then added in seven portions) over a period of 2 h. After the reduction was complete the ammonia was allowed to evaporate (overnight, room temperature). The ammonia-free reaction mixture was cooled to 0 °C and slowly treated with water (2000 mL) over a period of 1 h. The THF layer was separated, and the aqueous portion was extracted with ether (200 mL). The combined organic layer was concentrated in vacuo, and the residue was extracted with ether (500 mL × 3). Triethylamine (20 mL) was added to the organic layer to prevent dienyl ether isomerization, and the resulting mixture was washed with water (300 mL × 3) and a saturated NaCl solution (300 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous liquid was then crystallized from ether/hexane in three crops to afford the 2β-hydroxy dienyl ether as white crystals (62.00 g, 59%): mp 115–117 °C; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3 H), 1.01 (d, J = 6.4 Hz, 3 H), 3.13 (six-line pattern, J = 10.10, 4.98 Hz, 1 H), 3.55 (s, 3 H), 4.64 (t, J = 3.00 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.71 (q), 18.22 (q), 20.38 (t), 25.19 (t), 30.39 (t), 30.68 (t), 33.70 (t), 34.06 (t), 35.95 (s), 38.58 (d), 47.05 (d), 53.28 (q), 75.85 (d), 90.27 (d), 123.28 (s), 133.84 (s), 152.08 (s); mass spectrum for $C_{17}H_{26}O_2$, m/e 262 (M^+), 247 ($M - CH_3$).

To a slurry of sodium hydride (4.80 g, 0.20 mol) in dry THF (400 mL) was added a solution of hydroxy dienyl ether (27.60 g, 0.105 mol) in dry THF (100 mL) over a period of 0.5 h. After the addition was complete, the reaction was heated at reflux for 1 h. The reaction was cooled to room temperature, slowly treated with methyl iodide (85.5 g, 37.5 mL, 0.6 mol) over a period of 0.5 h, and gently heated at reflux for 1 h. Methyl iodide and THF were removed in vacuo, and the residue was dissolved in H_2O and extracted with ether (250 mL × 3). The combined ether extract was washed with water (200 mL × 3) and saturated NaCl solution (200 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude pale yellow viscous liquid afforded **12** as a white crystalline solid after crystallization from hexane (28.00 g, 97%): mp 74–75 °C; ^1H NMR (C_6D_6) δ 0.90 (s, 3 H), 1.05 (d, J = 6.00 Hz, 3 H), 2.50 (m, 1 H), 3.20 (s, 3 H), 3.30 (s, 3 H), 4.55 (br s, 1 H); mass spectrum for $C_{18}H_{28}O_2$, m/e 276 (M^+), 261 ($M - CH_3$).

1β,2α,3,4,4a,4bα,5,6,10,10aα-Decahydro-7-methoxy-1α,4aβ-dimethyl-2β-phenanthrol Methyl Ether (13). A solution of dienyl ether **12** (4.25 g, 1.5 mmol) in dry methylene chloride (10 mL) was treated with pyridine–*p*-toluenesulfonic acid (0.100 g, 0.37 mmol) at room temperature and stirred for 1 h. The reaction mixture was poured into aqueous $NaHCO_3$ (150 mL) and extracted with methylene chloride (50 mL × 3). The combined extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (SiO_2, 200 mesh) of the crude product afforded **13** as a viscous oil (4.00 g, 89%): ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.95 (d, J = 7 Hz, 3 H), 2.65 (m, 1 H), 3.35 (s, 3 H), 3.55 (s, 3 H), 5.20–5.35 (m, 2 H); mass spectrum for $C_{18}H_{28}O_2$, m/e 276 (M^+).

1β,2α,3,4,4a,4bα,5,6,7,9β,10,10aα-Dodecahydro-9α-hydroxy-1α,4aβ-dimethyl-7-oxo-2β-phenanthrol 2-Methyl Ether (14). An ice-cooled heterogeneous solution of dienyl ether **13** (0.276 g, 1 mmol), THF (5 mL), dioxane (5 mL), and $NaHCO_3$ (0.150 g, 1.8 mmol) was treated with oxone[41] (0.750 g, 1.2 mmol) in water (10 mL) over a period of 0.5 h. After the addition was complete the reaction was warmed to room temperature and stirred for 1 h. The reaction was poured into water (100 mL) and extracted with ether (25 mL × 3). The combined extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid was recrystallized from ether/hexane mixture to afford **14** as a white crystalline solid [0.260 g, 94% (when the experiment was carried out on a 60-mmol scale the yield was 75%)]: mp 129–130 °C; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 1.09 (d, J = 6.2 Hz, 3 H), 2.05 (m, 1 H), 2.11 (m, 1 H), 2.27 (m, 1 H), 2.43 (m, 1 H), 2.52 (m, 1 H), 2.71 (m, 1 H), 3.37 (s, 3 H), 4.34 (br s, 1 H), 5.98 (d, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.04 (q), 15.20 (q) 20.75 (t), 25.69 (t), 32.05 (t), 35.94 (d), 36.62 (d), 37.29 (d), 38.81 (s), 43.41 (d), 44.75 (d), 56.46 (q), 70.83 (d), 84.88 (d), 127.26 (d), 164.44 (s), 200.86 (s); mass spectrum for $C_{17}H_{26}O_3$, m/e 278 (M^+), 260 ($M - H_2O$), 246 $M - CH_3OH$). Anal. Calcd: C, 7.34; H, 9.35. Found: C, 72.12; H, 9.50.

1β,2,3,4,4a,4bα,5,6,7,9,10,10aα-Dodecahydro-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (15). To a solution of dienyl ether **10** (9.50 g, 0.031 mol) in methanol (600 mL) was added a solution of oxalic acid dihydrate (3.375 g, 0.0267 mol) in water (25 mL) and methanol (75 mL) in one portion, and

(40) Dryden, H. L., Jr.; Webber, G. M.; Burtner, R. R.; Cella, J. A. *J. Org. Chem.* **1961**, *26*, 3237.

(41) Potassium hydrogen persulfate, available under the trade name Oxone, is a safe, air-stable, free-flowing mixture containing 2 mol of $KHSO_5$, 1 mol of K_2SO_4, and 1 mol of $KHSO_4$. Oxone is sold by the Alfa division of Ventron Corp.

the reaction was stirred at room temperature for 45 min. Solid sodium bicarbonate (3.15 g, 0.0375 mol) was added, and the reaction was stirred for 0.5 h. Methanol (500 mL) was removed in vacuo and the residue poured into water and extracted with ether (250 mL × 3). The combined ether extract was washed with water (200 mL × 2) and a saturated NaCl solution (200 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford a viscous colorless liquid (10.50 g), which was carried forward to the next reaction without further purification.

To a solution of 10% ethanolic KOH (300 mL) was added above crude β,γ-unsaturated ketone (10.50 g) in ethanol (100 mL) at room temperature. The reaction was slowly brought to reflux, and heating was continued for 1 h. The reaction was cooled to room temperature, ethanol (300 mL) was removed in vacuo, and the residue was poured into water and extracted with ether (250 mL × 3). The combined ether extract was washed with water (200 mL × 2) and saturated NaCl solution (200 mL) and dried over Na_2SO_4. The solvent was removed in vacuo, and the resulting viscous yellow liquid was crystallized from ether/hexane in three crops to afford **15** as yellow crystalline needles (4.90 g, 60%): mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H), 4.00 (br s, 4 H), 4.93 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.74 (q), 13.92 (q), 21.09 (t), 24.69 (t), 30.80 (t), 35.05 (t), 35.34 (t), 36.83 (t), 38.21 (s), 39.35 (d), 48.41 (d), 49.32 (d), 65.10 (t), 64.89 (t), 110.47 (s), 126.10 (d), 164.98 (s), 199.58 (s); mass spectrum for $C_{18}H_{26}O_3$, m/e 290 (M^+).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9,10,10a-Tetradecahydro-8aβ-cyano-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (16t) and 1β,2,3,4,4a,4bα,5,6,7,8,8a,9,10,10a-Tetradecahydro-8aα-cyano-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (16c). (a) Method A (Et_2AlCN).[10] To an ice-cooled solution of enone **15** (0.145 g, 0.5 mmol) in dry toluene (5 mL) was added a solution of diethylaluminum cyanide (2 mol solution in toluene, 0.333 g, 3 mmol, 1.5 mL) slowly over a period of 5 min, and the reaction was stirred for 0.5 h, slowly warmed to room temperature and stirred for 6 h. The reaction mixture was then poured into an ice-cooled aqueous solution of ammonium chloride, stirred for 0.5 h., and then extracted with methylene chloride (50 mL × 3). The combined methylene chloride extract was successively washed with aqueous sodium bicarbonate (50 mL × 2) and water (50 mL × 2) and dried (Na_2SO_4), and solvent was removed in vacuo. The pale yellow viscous liquid was then flash chromatographed over silica gel (230–400 mesh). Elution with 1:1 ether/hexane gave **16c**, which on recrystallization from ether/hexane gave **16c** as a crystalline solid (0.035 g, 22%). Continued elution with same solvent gave unreacted enone **15** (0.015 g). Continued elution with the same solvent gave **16t**, which on recrystallization from ether/hexane afforded **16t**, as a crystalline solid (0.108 g, 68%).

Analytical data for **16t** was as follows: mp 207–208 °C; ^1H NMR ($CDCl_3$) δ 0.83 (d, J = 5.70 Hz, 3 H), 1.07 (s, 3 H), 1.3 (m, 2 H), 1.90 (m, 1 H), 2.15 (m, 2 H) 2.25 (m, 2 H), 2.60 (m, 2 H), 3.90 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 10.62 (q), 11.87 (q), 21.79 (t), 23.38 (t), 30.49 (t), 36.06 (t), 36.88 (s), 38.40, 38.90, 40.27 (s), 40.97 (t), 49.15 (d), 53.05 (d), 53.61 (d), 64.99 (m, ketal), 110.41 (s), 122.19 (s), 205.32 (s); mass spectrum for $C_{19}H_{27}NO_3$, m/e 317 (M^+).

Analytical data for **16c** was as follows: mp 194–195 °C; ^1H NMR ($CDCl_3$) δ 0.80 (d, J = 6.5 Hz, 3 H), 1.05 (s, 3 H), 3.95 (s, 4 H); mass spectrum for $C_{19}H_{27}NO_3$, m/e 317 (M^+).

(b) Method B (Pyridine–HCN). To an ice-cooled solution of pyridine (0.0391 g, 0.04 mL, 0.48 mmol) and HCN (0.33 mL, 0.33 mmol) in THF (0.5 mL) was added triethylaluminum in hexane (0.038 g, 0.15 mL, 0.33 mmol) over a period of 5 min, and the mixture was stirred for 0.5 h. To this cold reagent solution was added enone **15** (0.048 g, 0.165 mmol) in dry THF (1 mL) in one portion, the mixture was stirred for 0.5 h and warmed to room temperature, and stirring was continued for 24 h. The reaction mixture was poured into an ice-cooled solution of aqueous ammonium chloride, stirred for 0.5 h, and extracted with methylene chloride (30 mL × 3). The methylene chloride extract was washed with water (20 mL × 2) and saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude viscous liquid yielded **16c** (5 mg, 10%) and **16t** (45 mg, 86%) after chromatography.

1β,2,3,4,4a,4bα,5,6,7,9β,10,10a-Dodecahydro-9α-[(*tert*-butyldimethylsilyl)oxy]-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (17). The mixture of γ-hydroxy enone **11** (1.00 g, 3.26 mmol), *tert*-butyldimethylsilyl chloride[42] (0.75 g, 4.97 mmol), imidazole (0.70 g, 10 mmol), and dimethyl formamide (3.3 mL) was stirred at room temperature overnight. After the reaction was complete it was poured into water and extracted with ether (50 mL × 3). The combined ether extract was washed with water (30 mL × 2) and a saturated NaCl solution (30 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (silica gel, 1:1 ether/hexane) the crude pale yellow viscous liquid followed by recrystallization from ether/hexane (in three crops) yielded **17** as a white crystalline solid (1.35 g, 98.5%): mp 93–94 °C; ^1H NMR ($CDCl_3$ partial) δ 3.90 (br s, 4 H), 4.20 (s, 1 H), 5.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.61 (q), 13.40 (q), 20.55 (q), 25.59 (m), 30.70 (t), 33.82 (t), 35.09 (t), 36.39 (t), 38.70 (d), 38.70 (s), 41.81 (d), 44.30 (d), 64.68 (t), 64.94 (t), 71.96 (d), 110.23 (s), 126.23 (d), 163.53 (s), 199.87 (s); mass spectrum for $C_{24}H_{40}O_4Si$, m/e 420 (M^+).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10a-Tetradecahydro-8aβ-cyano-9α-[(*tert*-butyldimethylsilyl)oxy]-2,7-phenanthrenedione 2-Ethylene Acetal (18t) and 1β,2,3,4,4a,4bα,-5,6,7,8,8a,9β,10,10a-Tetradecahydro-8aα-cyano-9α-[(*tert*-butyldimethylsilyl)oxy]-2,7-phenanthrenedione 2-Ethylene Acetal (18c). To an ice-cooled solution of γ-silyloxy enone **17** (1.35 g, 3.2 mmol) in dry toluene (1 mL) was added diethyl aluminum cyanide[10] (6.3 mL of 2 M solution in toluene, 13.33 mmol) slowly over a period of 15 min, and the reaction was stirred for an additional 0.5 h. The reaction mixture was slowly warmed to room temperature and stirred for another 6 h. The reaction mixture was poured into an ice-cooled 5% aqueous solution of sodium hydroxide, stirred for 0.5 h, and extracted with methylene chloride (75 mL × 3). The combined extract was successively washed with cold 5% aqueous HCl (50 mL × 2), saturated aqueous $NaHCO_3$ (50 mL × 2), water (50 mL × 2), and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous liquid yielded **18t** (0.500 g, 33.5%) on crystallization from ether/hexane. The mother liquor was flash chromatographed on silica gel (230–400 mesh). Elution with ether/hexane afforded a faster moving mixture of starting material and **18t** (0.740 g), which on crystallization from ether/hexane afforded an additional amount of **18t** (0.140 g, 26%). Continued elution with the same solvent system afforded another nitrile, which in recrystallization from ether/hexane yielded crystalline **18c** (0.140 g, 26%).

Analytical data for **18t** was as follows: mp 242–243 °C; ^1H NMR ($CDCl_3$) δ 0.08 (s, 3 H), 0.14 (s, 3 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.95 (s, 9 H), 1.11 (s, 3 H), 2.32 (dd, J = 14.56, 2.17 Hz, 1 H), 2.83 (d, J = 14.47 Hz, 1 H), 3.96–4.02 (m, ketal); ^{13}C NMR ($CDCl_3$) δ 10.57, 11.48, 18.12, 23.27, 25.87, 29.75, 30.68, 36.08, 36.86, 38.09, 40.14, 40.90, 45.36, 46.93, 49.57, 65.10, 65.03, 71.24, 110.42, 121.60, 207.10; exact mass calculated for $C_{25}H_{41}O_4SiN$ 447.279, found 447.280.

Analytical data for **18c** was as follows: mp 186–187 °C; ^1H NMR ($CDCl_3$) δ 0.13 (s, 3 H), 0.16 (s, 3 H), 0.85 (d, J = 6.38, 3 H), 0.97 (s, 9 H), 1.00 (s, 3 H), 2.63 (q, J = 16.13 Hz, 2 H), 3.95–4.05 (m, ketal); ^{13}C NMR ($CDCl_3$) δ 15.19 (q), 20.56 (q), 26.06 (t), 30.69 (m), 35.22 (t), 35.44 (t), 41.68 (s), 42.39 (t), 43.27 (s), 44.74 (d), 45.34 (d), 50.29, 50.84, 51.44, 69.93 (t), 76.10 (d), 114.86 (s), 127.79 (s), 212.27 (s); exact mass calculated for $C_{25}H_{41}O_4SiN$ 447.279, found 447.282.

1β,2,3,4,4a,4bα,5,6,7,9β,10,10a-Dodecahydro-9α-(2-bromoacetoxy)-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (25A). To a cold (−78 °C) solution of γ-hydroxy enone **11** (0.102 g, 0.33 mmol) and pyridine (0.078 g, 0.08 mL, 0.978 mmol) in dry methylene chloride (2 mL) was added slowly a solution of bromoacetyl bromide (0.202 g, 0.087 mL, 1 mmol) in dry methylene chloride (2 mL) over a period of 10 min, and the reaction mixture was stirred for 1 h. The reaction mixture was poured into crushed ice and extracted with methylene chloride (25 mL × 3). The combined organic portion was washed with water (20 mL × 2) and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid after plug filtration (silica gel) followed by recrystallization

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(43) Kirk, D. N.; Wiles, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1015.

from ether/hexane yielded **25A** as a white crystalline solid (0.140 g, 98.5%): mp 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.35 (d, J = 5.00 Hz, 3 H), 3.80 (s, 2 H), 4.00 (s, 4 H), 5.55 (s, 1 H), 6.50 (d, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.68 (q), 13.52 (q), 20.97 (t), 26.08 (t), 30.11 (t), 30.77 (t), 35.08 (t), 36.69 (t), 38.20 (s), 38.93 (d), 42.87 (d), 45.60 (d), 65.96 (t), 64.19 (t), 74.83 (d), 110.24 (s), 130.56 (d), 156.37 (s), 165.98 (s), 199.54 (s); exact mass calculated for $C_{20}H_{27}O_5Br$ 426.103, found 426.102.

1β,2,3,4,4a,4bα,5,6,7,9β,10,10a-Dodecahydro-9α-(2-chloroacetoxy)-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (25B). To an ice-cooled solution of γ-hydroxy enone **11** (0.306 g, 1 mmol) and pyridine (0.234 g, 0.240 mL, 3 mmol) in dry methylene chloride (5 mL) was added a solution of chloroacetyl chloride (0.339 g, 0.239 mL, 3 mmol) in methylene chloride (3 mL) over a period of 10 min, and the reaction was stirred at 0 °C for 2 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with methylene chloride (50 mL × 3). The combined methylene chloride extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid after plug filtration followed by recrystallization from ether/hexane yielded **25B** as a colorless crystalline solid (0.315 g, 82%): mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 0.85 (d, J = 6 Hz, 3 H), 3.95 (s, 4 H), 4.01 (s, 2 H), 5.52 (m, 1 H), 6.10 (d, J = 3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.65 (q), 11.50 (q), 20.91 (t), 30.19 (t), 30.71 (t), 35.03 (t), 36.59 (t), 38.17 (s), 38.84 (d), 41.11 (t), 42.83 (t), 45.50 (d), 65.90 (t), 65.14 (t), 74.85 (d), 110.12 (s), 130.51 (d), 156.32 (s), 166.03 (s), 199.42 (s); exact mass calculated for $C_{20}H_{27}O_5Cl$ 382.154, found 382.158.

1β,2,3,4,4a,4bα,5,6,7,9β,10,10a-Dodecahydro-9α-(2-chloroacetoxy)-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal, 7-Cyanohydrin Trimethylsilyl Ether (27B). To a solution of chloroacetate **25B** (0.382 g, 1 mmol) and trimethylsilyl cyanide (0.208 g, 0.28 mL, 2.2 mmol) in THF (4 mL) was added triethyl aluminum[11] in hexane (0.912 mL, 2.2 mmol) at room temperature over a period of 15 min. After the addition was complete the reaction mixture was slowly brought to reflux and continued for 24 h under an argon atmosphere. The reaction was cooled to room temperature, quenched with aqueous ammonium chloride, and extracted with methylene chloride (50 mL × 3). The combined methylene chloride extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude reaction product was then chromatographed on silica gel (230–400 mesh). Elution with ether/hexane (1:1) gave **27B** as a viscous liquid (0.012 g, 25%): ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.80 (d, J = 6.00 Hz, 3 H), 3.95 (s, 4 H), 4.00 (s, 2 H), 5.42 (m, 1 H), 5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.67 (q), 12.64 (q), 19.32 (t), 30.34 (t), 30.76 (t), 34.64 (t), 36.49 (t), 37.26 (s), 38.94 (d), 41.20 (t), 43.12 (d), 44.37 (d), 64.92 (t), 65.15 (t), 67.75 (s), 75.08 (d), 110.40 (s), 120.67 (s), 131.31 (d), 139.34 (s), 166.20 (s).

Alternate Preparation of 27B (ZnI_2/Me_3Si–CN). To an ice-cooled solution of chloroacetate **25B** (0.0382 g, 0.1 mmol) and trimethylsilyl cyanide (0.023 g, 0.032 mL, 0.024 mmol) in methylene chloride (3 mL) was added zinc iodide (0.003 g, 0.01 mmol), and the reaction was stirred at 0 °C for 1 h. The reaction mixture was poured into cold aqueous $NaHCO_3$ and extracted with methylene chloride (25 mL × 3). The combined extract was washed with water (20 mL × 2) and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product afforded **27B** as a viscous colorless liquid after plug filtration on SiO_2 (0.030 g, 62%).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10a-Tetradecahydro-8aβ-cyano-9α-hydroxy-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (28). A solution of nitrile **18t** (0.090 g, 0.2 mmol) in THF (2 mL) was treated with tetrabutylammonium fluoride (Aldrich, 0.4 mL of 1 M solution in THF, 0.36 mmol) at 25 °C over 10 min, and stirring was continued at that temperature for 1 h. The reaction mixture was poured into water and extracted with methylene chloride (25 mL × 3). The combined methylene chloride extract was washed with 5% aqueous HCl (20 mL × 2), water (20 mL × 2), and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid yielded **28** as a white crystalline solid (0.064 g, 96%) after recrystallization from methylene chloride/ether in three crops: mp 254–256 °C. ^{1}H NMR ($CDCl_3$) δ 0.9 (d, J = 6.00 Hz, 3 H), 1.1 (s, 3 H), 4.00 (s, 4 H); mass spectrum for $C_{19}H_{27}NO_4$, m/e 333 (M^+).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10a-Tetradecahydro-8aβ-cyano-9α-(2-bromoacetoxy)-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (29A). To a cold (−78 °C) solution of cyano alcohol **28** (0.064 g, 0.19 mmol) and pyridine (0.19 g, 0.2 mL, 2.3 mmol) in methylene chloride (4 mL) was slowly added bromoacetyl bromide (0.231 g, 1.1 mmol) in methylene chloride (1 mL) over a period of 15 min, and the reaction was stirred at that temperature for an additional 1 h. The reaction mixture was poured into cold saturated aqueous $NaHCO_3$ (75 mL) and extracted with methylene chloride (25 mL × 3). The combined methylene chloride extract was washed with water (20 mL × 2) and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid was recrystallized from ether/hexane to yield the colorless crystalline bromo ester **29A** (0.085 g, 97%): mp 160 °C dec; ^{1}H NMR ($CDCl_3$) δ (0.85, s, 3 H) 0.90 (d, J = 6 Hz, 3 H), 3.80 (s, 2 H), 4.00 (s, 4 H), 5.40 (m, 1 H), 5.75 (m, 1 H).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10a-Tetradecahydro-8aβ-cyano-9α-(2-chloroacetoxy)-1α,4aβ-dimethyl-2,7-phenanthrenedione 2-Ethylene Acetal (29B). To an ice-cooled solution of cyano alcohol **28** (0.260 g, 0.78 mmol) and pyridine (0.19 g, 0.2 mL, 2.3 mmol) in methylene chloride (5 mL) was added a solution of chloroacetyl chloride (0.264 g, 0.186 mL, 2.3 mmol) in methylene chloride (3 mL) over a period of 10 min, and the reaction was stirred at that temperature for an additional 2 h. After the reaction was complete it was poured into ice-cooled aqueous sodium bicarbonate and was extracted with methylene chloride (50 mL × 3). The combined methylene chloride extract was successively washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid after plug filtration followed by recrystallization from ether/hexane in three crops yielded white crystalline chloro ester **29B** (0.280 g, 87%): mp 218–220 °C; ^{1}H NMR ($CDCl_3$) δ 0.75 (d, J = 6 Hz, 3 H), 1.10 (s, 3 H), 3.90 (s, 4 H), 4.075 (s, 2 H), 5.15 (m, 1 H); exact mass calculated for $C_{21}H_{28}O_5NCl$ 409.165, found 409.167.

Tetracyclic Cyano Ester 30. A mixture of cyano ester **31** (0.500 g, 1.3 mmol) and cesium fluoride (0.212 g, 1.4 mmol) in dry acetonitrile (5 mL) was stirred at room temperature overnight. The acetonitrile was removed in vacuo and the residue poured into water and extracted with methylene chloride (50 mL × 3). The combined extract was washed with 10% HCl (50 mL × 2), 10% aqueous $NaHCO_3$ (50 mL × 2), water (50 mL × 2), and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid after recrystallization from methylene chloride/ether mixture afforded **30** as a crystalline solid (0.215 g, 43%): mp 249–250 °C; ^{1}H NMR ($CDCl_3$ partial) δ 0.80 (d, J = 6.5 Hz, 3 H), 1.10 (s, 3 H), 3.65 (s, 0.5 H), 3.90 (s, 4.5 H), 4.30 (m, 0.5 H), 4.50 (m, 0.5 H); ^{13}C NMR ($CDCl_3$) δ 10.44 (q), 14.58 (q), 20.37 (t), 21.18 (t), 24.05 (t), 24.36 (t), 30.40 (t), 64.53 (t), 65.04 (t), 83.50 (d), 83.68 (d), 101.81 (s), 112.06 (s), 114.44 (s), 166.63 (s), 167.41 (s), 206.42 (s), 207.63 (s); exact mass calculated for $C_{21}H_{27}O_5N$ 373.192, found 373.191.

Tricyclic Cyano Ester 31. To an ice-cooled solution of δ-hydroxy enone **11** (0.030 g, 0.1 mmol), DCC (0.0226 g, 0.11 mmol), and pyridine (0.01 mL) in dry methylene chloride (4 mL) was added cyanoacetic acid (0.0093 g, 0.11 mmol) in methylene chloride (1 mL) over a period of 5 min. After the addition was completed the solution was warmed to room temperature, and stirring was continued for 3 h. The solid was removed by filtration, and the filtrate was poured into water and extracted with methylene chloride (25 mL × 3). The combined extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue gave a white foam of cyano ester **31** after vacuum drying (0.035 g, 95%); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.90 (d, J = 6.0 Hz, 3 H), 3.45 (s, 2 H), 3.95 (s, 4 H), 5.55 (br s, 1 H), 6.10 (d, J = 3.00 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.69 (q), 13.53 (q), 20.94 (t), 30.22 (t), 30.74 (t), 64.99 (t), 65.16 (t), 75.82 (d), 110.11 (s), 112.83 (s), 130.85 (d), 155.89 (s), 161.92 (s), 199.52 (s); exact mass calculated for $C_{21}H_{27}O_5N$ 373.192, found 373.189.

Tricyclic Sulfone Ester 32. An ice-cooled solution of γ-hydroxy enone **11** (0.102 g, 0.333 mmol), pyridine (0.06 mL, 0.666 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.0753 g, 0.366 mmol)

in dry THF (5 mL) was treated with (phenylsulfonyl)acetic acid (0.0733 g, 0.366 mmol) in dry THF (2 mL). The reaction was slowly warmed to room temperature, and stirring was continued for 3 h. The resulting white solid was removed by filtration, concentrated in vacuo, poured into water, and extracted with ether (25 mL × 3). The combined ether extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude white solid from methylene chloride/ether gave **32** as a white crystalline material (0.150 g, 92%): mp 196–198 °C; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 0.86 (d, J = 6.3 Hz 3 H), 2.32 (six-line pattern, J = 13.24, 5.27 Hz, 1 H), 2.42 (m, 2 H), 3.96–4.08 (m, 4 H) 4.13 (q, J = 13.70 Hz, 2 H), 5.48 (t, J = 2.6 Hz, 1 H), 6.05 (d, J = 2.1 Hz, 1 H), 7.56–7.91 (m, 5 H); ^{13}C NMR (Me_2SO-d_6) 11.28 (q), 13.76 (q), 60.49 (t), 65.19 (t), 65.36 (t), 65.20 (d), 110.29 (s), 130.61 (d), 157.45 (s), 162.35 (s), 199.71 (s).

Tetracyclic Sulfone Ester 33. A mixture of sulfone ester **32** (1.42 g, 2.90 mmol) and dry cesium fluoride (1.00 g, 6.6 mmol) in dry acetonitrile was stirred overnight at room temperature. After completion of the reaction, the solvent was removed in vacuo, and the residue was poured into water and extracted with methylene chloride (50 mL × 3). The combined extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude white solid from ethyl acetate/ether afforded **33** as white crystalline needles (1.10 g, 77%): mp 231–232 °C; ^1H NMR ($CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3 H), 0.99 (s, 3 H), 2.52 (five-line pattern, J = 7.00 Hz), 2.61 (d, J = 19.31 Hz, 1 H), 2.75 (five-line pattern, J = 8.57 Hz, 1 H), 3.57 (d, J = 19.4 Hz, 1 H), 3.87–3.99 (m, 5 H), 4.93 (t, J = 2.65 Hz, 1 H), 7.59–7.88 (m, 5 H); ^1H NMR (CD_3CN) δ 0.74 (d, J = 6.55 Hz, 3 H), 0.99 (s, 3 H), 2.42 (five-line pattern, J = 8.57, 1 H), 2.63 (q, J = 17.14, 8.66 Hz, 1 H), 2.65 (d, J = 19.4 Hz, 1 H), 3.26 (d, J = 19.5 Hz, 1 H), 3.85–3.92 (m, 4 H), 4.22 (s, 1 H), 4.84 (t, J = 2.75 Hz, 1 H), 7.63–7.89 (m, 5 H); ^{13}C NMR (Me_2SO-d_6) δ 11.15 (q), 13.71 (q), 65.26 (t), 73.79 (d), 83.55 (d), 110.17 (s), 129.88 (d), 135.55 (d), 138.43 (s), 168.27 (s), 208.43 (s); mass spectrum for $C_{26}H_{32}O_7S$, m/e 488 (M^+).

Keto Lactone 36. A solution of sulfone **33** (0.110 g, 0.23 mmol) in 10% aqueous THF was treated with aluminum amalgam[16] [clean aluminum foil (0.200 g, 7.4 mmol) was activated with 10% aqueous NaOH, washed with water, ethanol, and ether, dipped in 5% aqueous mercuric chloride for few seconds, and then directly cut into the reaction mixture at room temperature]. The reaction mixture was slowly heated to 65 °C and stirred at that temperature for 1.5 h. The resulting solid was removed by filtration, and the filtrate was concentrated in vacuo and extracted with ether (25 mL × 3). The combined ether extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue (a mixture of ketone and alcohol) was dissolved in methylene chloride (10 mL) and was treated with pyridinium chlorochromate[17] (0.050 g, 0.23 mmol) in the presence of sodium acetate (0.02 g, 0.24 mmol) at room temperature and was stirred for 1.5 h. Most of the methylene chloride was removed in vacuo, and the residue after plug filteration (SiO_2, 200 mesh) afforded **36** as a white foam (0.075 g, 94%): ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.3 Hz, 3 H), 1.17 (s, 3 H), 2.16 (d, J = 15.04 Hz, 1 H), 2.30 (m, 1 H), 2.38 (d, J = 17.22 Hz, 1 H), 2.53 (m, 1 H), 2.55 (d, J = 17.17 Hz, 1 H), 2.86 (d, J = 14.84, 1 H), 3.91–4.00 (m, ketal), 4.29 (t, J = 2.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.49 (q), 14.76 (q), 27.17 (t), 24.81 (t), 30.51 (t), 48.16 (t), 65.06 (t), 83.89 (d), 110.10 (s), 174.91 (s), 208.96 (s).

Methoxy Sulfonyl Keto Lactone 37A. To an ice-cooled solution of γ-hydroxy enone **14** (0.522 g, 2 mmol) and DCC (0.440 g, 2.1 mmol) in dry methylene chloride (20 mL) was added (phenylsulfonyl)acetic acid (0.440 g, 2.2 mmol) in dry methylene chloride (10 mL) over a period of 5 min, the reaction was warmed to room temperature, and stirring was continued for 2 h. The solid was concentrated in vacuo, and the residue was poured into water and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid gave the C-3 β-methoxy analogue of **32** as a crystalline solid after recrystallization from methylene chloride/ether (0.83, 90%): mp 143–145 °C; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 1.02 (d, J = 6.3 Hz, 3 H), 2.08 (m, 1 H) 2.13 (m, 1 H), 2.35 (m, 1 H), 2.43 (m, 1 H), 2.47 (m, 1 H), 2.75 (m, 1 H), 3.39 (s, 3 H), 4.09 (q, J = 13.5 Hz, 2 H), 5.48 (s, 1 H), 6.07 (d, J = 2.00 Hz, 1 H), 7.56–7.87 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.12 (q), 15.09 (q), 56.59 (q), 61.24 (t), 75.45 (d), 84.53 (d), 128.28 (d), 129.36 (d), 130.53 (d), 134.52 (d), 138.64 (s), 156.40 (s), 161.08 (s), 199.85 (s); mass spectrum for $C_{25}H_{32}O_6S$, m/e 460 (M^+), 428 (M – MeOH).

A mixture of the above sulfone ester (0.830 g, 1.80 mmol) and dry cesium fluoride (0.608 g, 4.00 mmol) in dry acetonitrile (30 mL) was stirred at room temperature overnight. The acetonitrile was removed in vacuo, and the residue was poured into water and extracted with methylene chloride (50 mL × 3). The combined extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude solid was recrystallized from methylene chloride/ether to afford **37A** as a white crystalline solid (0.70 g, 84%): mp 214–215 °C; ^1H NMR ($CDCl_3$) δ 0.92 (six-line pattern, J = 13.71, 3.60 Hz, 1 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.98 (s, 3 H), 1.16 (six-line pattern, J = 13.6, 2.65 Hz, 1 H), 1.25 (t, J = 5.58 Hz, 1 H), 1.33–1.45 (m, 2 H), 1.58 (six-line pattern, J = 15.71, 2.56 Hz, 1 H), 1.83 (six-line pattern, J = 13.31, 3.33 Hz, 1 H), 2.00 (m, 1 H), 2.10 (q, J = 15.20, 6.54 Hz, 2 H), 2.48 (six-line pattern, J = 15.65, 2.50 Hz, 1 H), 2.52 (six-line pattern, J = 16.94, 7.10 Hz, 1 H), 2.60 (d, J = 19.36 Hz, 1 H), 2.63 (m, 1 H), 2.73 (five-line pattern, J = 16.85, 8.50 Hz, 1 H), 3.34 (s, 3 H), 3.56 (d, J = 19.05 Hz, 1 H), 3.86 (s, 1 H), 4.94 (t, J = 2.6 Hz, 1 H), 7.59–7.88 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.42 (q), 14.78 (q), 18.93 (t), 23.55 (t), 25.06 (t), 45.69 (d), 48.90 (s), 56.64 (q), 78.68 (d), 83.08 (d), 84.25 (d), 126.16 (d), 129.40 (d), 134.89 (d), 137.41 (s), 167.52 (s), 207.03 (s); mass spectrum for $C_{25}H_{32}O_6S$, m/e 460 (M^+), 319 (M – $SO_2C_6H_5$).

Methoxy Keto Lactone 37B. A solution of sulfone **37A** (0.448 g, 1 mmol) in 10% aqueous THF (50 mL) was treated with aluminum amalgam[16] from aluminum foil (0.80 g, 30 mmol) at room temperature. The resulting reaction mixture was stirred at 65 °C for 12 h. The solid was separated by filtration and the filtrate concentrated in vacuo, poured into water, and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue (mixture of ketone and alcohol) was taken up in methylene chloride (20 mL) and treated with PCC[17] (0.200 g, 0.93 mmol) and sodium acetate (0.080 g, 0.96 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed in vacuo, and the residue was plug filtered (SiO_2, 400 mesh) with ether as a solvent. The residual white solid on recrystallization from methylene chloride/ether afforded **37B** as a white crystalline solid (0.175 g, 80%): mp 195–196 °C; ^1H NMR ($CDCl_3$) δ 0.99 (d, J = 6.20 Hz, 3 H), 1.10 (m, 1 H), 1.17 (s, 3 H), 1.25 (five-line pattern, J = 12.40, 12.40, 2.50 Hz, 1 H), 1.30 (d, J = 7.38 Hz, 1 H), 1.35–1.45 (m, 2 H), 1.55 (five-line pattern, J = 15.35, 15.35, 3.10 Hz), 1.90–2.10 (m, 2 H), 2.17 (d, J = 14.83 Hz, 1 H), 2.25 (six-line pattern, J = 15.35, 2.55 Hz, 1 H), 2.30 (six-line pattern, J = 12.50, 2.55 Hz, 1 H), 2.38 (d, J = 17.06 Hz, 1 H), 2.53 (five-line pattern, J = 12.50, 12.50, 5.75 Hz, 1 H), 2.54 (d, J = 17.06 Hz, 1 H), 2.66 (six-line pattern, J = 10.69, 10.69, 4.30 Hz, 1 H), 2.86 (d, J = 14.83 Hz, 1 H), 3.38 (s, 3 H), 4.76 (t, J = 1.60 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.95 (q), 15.34 (q), 21.19 (t), 24.38 (t), 25.29 (t), 36.26 (d), 36.77 (s), 37.40 (t), 39.05 (t), 42.70 (d), 45.09 (d), 45.57 (t), 45.76 (s), 47.96 (t), 56.70 (q), 83.85 (d), 84.51 (d), 175.05 (s), 208.93 (s); mass spectrum for $C_{19}H_{28}O_4$, m/e 320 (M^+), 288 (M – MeOH).

Methoxy Keto Tetrahydrofuran 37C. To a cold (–78 °C) solution of keto lactone **37B** (0.80 g, 0.25 mmol) in toluene (5 mL) was added diisobutylaluminum hydride (Aldrich 1 M solution in hexane, 0.078 g, 0.55 mL, 0.55 mmol), and the resulting reaction mixture was stirred at that temperature for 0.5 h. The reaction mixture was poured into a saturated solution of NH_4Cl and extracted with ether (25 mL × 3). The combined ether extract was washed with water (25 mL × 2) and a saturated sodium chloride solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The viscous liquid after vacuum-drying afforded a hydroxy lactol as a white foam (0.07 g, 86%).

To a cold (–78 °C) solution of the above crude hydroxy lactol (0.07 g, 0.2 mmol) in CH_2Cl_2 (10 mL) and THF (5 mL) was added

boron trifluoride etherate (0.028 mL, 0.22 mmol) followed by (triethylsilyl)silane (0.035 mL, 0.22 mmol) and the reaction was stirred for 15 min. The reaction mixture was slowly warmed to room temperature and stirred for an additional 0.5 h. After the reaction was complete it was poured into a saturated solution of $NaHCO_3$ and extracted with ether (25 mL × 3). The combined ether extract was washed with water (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude viscous liquid was taken up in methylene chloride (15 mL), treated with sodium acetate (0.05 g, 0.6 mmol), followed by PCC[17] (0.10 g, 0.46 mmol) at room temperature, and stirred for 0.5 h. The methylene chloride was removed in vacuo, and the residue was plug filtered (SiO_2, 400 mesh) with ether as a solvent to afford **37C** as a viscous liquid (0.02 g, 32%): ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 6.20 Hz, 3 H), 1.11 (s, 3 H), 2.205 (d, J = 15.00 Hz, 1 H), 2.20 (m, 1 H), 2.30 (m, 1 H), 2.50 (m, 1 H), 2.65 (m, 1 H), 2.79 (d, J = 14.58 Hz, 1 H), 3.36 (s, 3 H), 3.52 (t, J = 2.4 Hz, 1 H), 3.84 (m, 1 H) 3.89 (m, 1 H).

Bis Lactone 39. A mixture of lactone **36** (0.015 g, 0.043 mmol), $NaHCO_3$ (0.010 g, 0.12 mmol), *m*-chloroperoxybenzoic acid (0.030 g, 0.173 mmol), and dry methylene chloride (5 mL) was stirred at room temperature for 12 h. A second portion of *m*-chloroperoxybenzoic acid (0.030 g, 0.173 mmol) was added, and the reaction was stirred for an additional 12 h. The reaction mixture was poured into water and was extracted with methylene chloride (50 mL). The combined methylene chloride extract was washed with aqueous Na_2CO_3 (20 mL × 3), water (20 mL × 2), and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue after plug filtration followed by vacuum-drying afforded a solid white foam (0.012 g, 76%): ^1H NMR ($CDCl_3$) δ 0.84 (d, J = 6.4 Hz, 3 H), 1.18 (s, 3 H), 2.04 (m, 1 H), 2.19 (six-line pattern, J = 15.17, 2.34 Hz, 1 H), 2.35 (q, J = 17.23, 5.1 Hz, 1 H), 2.45 (d, J = 14.00 Hz, 1 H), 2.50 (d, J = 17.00 Hz, 1 H), 2.71 (d, J = 17.00 Hz, 1 H), 3.54 (d, J = 15.00 Hz, 1 H), 2.90–3.97 (m, 4 H), 4.23 (m, 1 H), 4.38 (t, J = 2.26 Hz, 1 H), 4.53 (t, J = 12.66 Hz, 1 H).

Methoxy Sulfonyl Bis Lactone 40A. A solution of sulfone lactone **37A** (0.050 g, 0.108 mmol) and *m*-chloroperoxybenzoic acid (0.200 g, 1.15 mmol) in dry methylene chloride (5 mL) was treated with boron trifluoride etherate (0.1 mL, 0.812 mmol) and stirred overnight at room temperature. The reaction mixture was poured into water and extracted with methylene chloride (25 mL × 3). The combined extract was washed with 10% NaOH (25 mL × 2), water (25 mL × 2), and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude white solid from methylene chloride/ether afforded **40A** as a white crystalline solid (0.045 g, 88%): mp >300 °C; ^1H NMR ($CDCl_3$) δ 0.86 (six-line pattern, J = 13.73, 3.66 Hz, 1 H), 0.95 (d, J = 6.2 Hz, 3 H), 0.99 (s, 3 H), 1.13 (m, 1 H), 1.38 (m, 2 H), 1.48 (m, 1 H), 1.63 (seven-line pattern, J = 15.52, 12.03, 2.35 Hz, 1 H), 1.75 (six-line pattern, J = 13.16, 3.30 Hz, 1 H), 2.00 (m, 2 H), 2.20 (six-line pattern, J = 15.68, 2.45 Hz, 1 H), 2.31 (ten-line pattern, 1 H), 2.61 (six-line pattern, J = 10.42, 5.40 Hz, 1 H), 2.95 (d, J = 19.37, 1 H), 3.33 (s, 3 H), 3.87 (s, 1 H), 4.29 (six-line pattern, J = 13.65, 3.7 Hz, 1 H), 4.36 (d, J = 19.29 Hz, 1 H), 4.78 (t, J = 12.87, 1 H), 4.85 (t, J = 2.4 Hz, 1 H), 7.61–7.90 (m, 5 H); mass spectrum for $C_{25}H_{32}O_7S$, m/e 476 (M^+) 458 (M – H_2O); ^{13}C NMR ($CDCl_3$) δ 12.76 (q), 14.76 (q), 22.80 (t), 25.00 (t), 25.00 (t), 36.24 (d), 36.24 (t), 37.63 (t), 37.83 (s), 42.20 (d), 47.25 (s), 47.60 (d), 56.65 (q), 63.78 (t), 75.15 (d), 77.20 (d), 84.08 (d), 129.26 × 2 (d), 129.40 × 2 (d), 135.20 (d), 137.02 (s), 167.25 (s), 170.90 (s). Anal. Calcd: C, 63.0; H, 6.72; S, 6.72. Found: C, 63.14; H, 6.64; S, 6.33.

Methoxy Bis Lactone 40B. A mixture of keto lactone **37B** (0.064 g, 0.20 mmol), *m*-chloroperoxybenzoic acid (0.172 g, 1 mmol), and sodium bicarbonate (0.50 g, 0.6 mmol) in methylene chloride (5 mL) was stirred at room temperature for 18 h. The reaction mixture was poured into water (75 mL) and extracted with methylene chloride (25 mL × 3). The combined organic extract was washed with 10% NaOH solution (25 mL × 3), water (25 mL × 2), and a saturated NaCl solution (25 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The residue after plug filtration (SiO_2) and crystallization from methylene chloride/hexane yielded bis lactone **40B** as a white crystalline solid (0.05 g, 77%): mp 239–240 °C; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 6.40 Hz, 3 H), 1.00 (m, 1 H), 1.13 (s, 3 H), 1.20 (m, 1 H), 1.30–1.40 (m, 2 H), 1.45 (seven-line pattern, J = 15.18, 12.68, 2.50 Hz, 1 H), 1.87 (six-line pattern, J = 13.19, 3.00 Hz, 1 H), 2.05 (m, 2 H), 2.21 (six-line pattern, J = 15.18, 2.50 Hz, 1 H), 2.30 (dd, J = 16.97, 4.78 Hz, 1 H), 2.42 (d, J = 13.83 Hz, 1 H), 2.47 (d, J = 17.07 Hz, 1 H), 2.60 (six-line pattern, J = 10.80, 10.80, 4.68 Hz, 1 H), 2.69 (d, J = 17.07 Hz, 1 H), 3.34 (s, 3 H), 3.49 (d, J = 13.83 Hz, 1 H), 14.20 (dd, J = 12.60, 1.75 Hz, 1 H), 4.35 (t, J = 2.50 Hz, 1 H), 4.49 (t, J = 12.60 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.81 (q), 14.81 (q), 24.45 (t), 24.89 (t), 25.06 (t), 35.95 (s), 37.26 (s), 37.34 (t), 40.69 (t), 41.25 (t), 42.43 (d), 42.76 (s), 46.40 (d), 56.69 (q), 66.26 (t), 84.19 (d), 85.99 (d), 172.43 (s), 174.50 (s); mass spectrum for $C_{19}H_{28}O_5$, m/e 336 (M^+), 304 (M – CH_3OH).

Methoxy Tetrahydrofuran Lactone 40C. A mixture of ketone **37C** (0.015 g, 0.049 mmol), *m*-chloroperoxybenzoic acid (0.50 g, 0.29 mmol), $NaHCO_3$ (0.020 g, 0.24 mmol), and methylene chloride was stirred at room temperature for 48 h. The reaction mixture was poured into water and extracted with methylene chloride (20 mL × 3). The combined methylene chloride extract was washed with aqueous $NaHCO_3$ (20 mL × 3), water (20 mL × 2), and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue afforded **40C** as a white foam after plug filtration (SiO_2, 400 mesh) and vacuum-drying (0.01 g, 66%): ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.00 Hz, 3 H), 1.12 (s, 3 H), 2.27 (m, 1 H), 2.28 (d, J = 13.58 Hz, 1 H), 2.63 (m, 1 H), 3.35 (s, 1 H), 3.42 (d, J = 13.90 Hz, 1 H), 3.62 (s, 1 H), 3.89 (dd, J = 9.15, 5.60 Hz, 2 H), 4.18 (m, 1 H), 4.53 (t, J = 12.30 Hz, 1 H); mass spectrum for $C_{19}H_{30}O_4$, m/e 322 (M^+), 290 (M – CH_3OH), 262 (M – CH_3COOH).

Tetracyclic α-Chloro Ketones 48A/48B. A mixture of chlorosulfone ester **56** (1.35 g, 2.58 mmol), cesium fluoride (0.75 g, 4.96 mmol), and dry acetonitrile (50 mL) was stirred at room temperature for 3 h. After the reaction was complete most of the acetonitrile was removed in vacuo. The residue was poured into water and extracted with ethyl acetate (75 mL × 3). The combined ethyl acetate extract was washed with 10% aqueous HCl (50 mL × 2), water (50 mL × 2), and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and solvent was removed in vacuo. Recrystallization of the crude white solid from methylene chloride/ether afforded **48A** as a white crystalline solid (1.03 g, 76%): mp 234–235 °C; ^1H NMR ($CDCl_3$) δ 0.80 (d, J = 6.5 Hz, 3 H), 1.25 (s, 3 H), 2.32 (six-line pattern, J = 14.12, 6.13 Hz, 1 H), 2.75 (eight-line pattern, J = 15.35, 6.70, 1.44 Hz, 1 H) 2.97 (d, J = 17.51 Hz, 1 H), 3.44 (q, J = 17.59, 1.83 Hz, 1 H), 3.85–3.95 (ketal), 4.08 (s, 1 H), 4.87 (t, J = 2.70 Hz, 1 H), 4.94 (q, J = 13.92, 6.91 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 11.26 (q), 16.58 (q), 61.59 (d), 65.28 (t), 73.73 (d), 83.33 (d), 110.11 (s), 129.84 (d), 135.5 (d), 138.49 (s), 167.90 (s), 197.88 (s); mass spectrum for $C_{26}H_{31}O_7SCl$, m/e 522 (M^+), 486 (M – HCl), 345 (M – HCl – $SO_2C_6H_5$).

The mother liquor (0.550 g) was chromatographed on SiO_2 (400 mesh). Ether elution gave a second chlorosulfone, which on recrystallization from CH_2Cl_2/Et_2O afforded **48B** as a white crystalline compound (0.075 g, 6%): mp 244–245 °C; ^1H NMR (CD_3CN) δ 0.77 (d, J = 6.5 Hz, 3 H), 0.86 (s, 3 H) 2.81 (m, 1 H), 2.88 (d, J = 20.3 Hz, 1 H), 3.42 (m, 1 H) 3.53 (d, J = 20.00 Hz, 1 H), 3.83–3.93 (m, ketal), 4.46 (s, 1 H), 4.87 (s, 1 H), 5.25 (q, J = 13.03, 9.17 Hz, 1 H), 7.61–7.95 (m, 5 H).

Continued elution with ether produced a second portion of the major chlorosulfone **48A** (0.175 g, total yield of **48A** 89%). Anal. Calcd: C, 59.8; H, 5.94. Found: C, 59.34; H, 6.23.

γ-Silyloxy Enone 52. To an ice-cooled solution of δ-hydroxy enone **11** (3.06 g, 10 mmol) and triethylamine (2.02 g, 2.76 mL, 20 mmol) in dry methylene chloride (30 mL) was added chlorotrimethylsilane (1.188 g, 1.38 mL, 11 mmol) over 5 min. The reaction was slowly warmed to room temperature and was stirred overnight. The resultant mixture was poured into aqueous $NaCHO_3$ (150 mL) and extracted with methylene chloride (50 mL × 3). The combined extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (SiO_2) followed by crystallization of the crude pale brown solid from ether/hexane afforded δ-silyloxy enone **52** as a white crystalline solid (3.70 g, 98%): mp 125–126 °C; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 1.99 (m, 1 H) 2.07 (m, 1 H), 2.28 (m, 1 H), 2.40 (m, 1 H), 2.57 (t, J = 7.00 Hz, 1 H), 3.98 (m, ketal), 4.26 (t, J = 2.5 Hz, 1 H), 5.93 (d, J = 1.8 Hz, 1 H); exact mass calculated for $C_{21}H_{34}O_4Si$ 378.222, found 378.22.

α-Chloro γ-Hydroxy Enone 55. To a cold (−78 °C) solution of LDA (11 mmol) in THF (25 mL) was added γ-silyloxy enone **52** (3.78 g, 10 mmol) in THF (10 mL) over 0.5 h. After the mixture was stirred at −78 °C for 0.5 h chlorotrimethylsilane (1.188 g, 1.38 mL, 11 mmol) was added slowly over 15 min, and the reaction was stirred for 0.5 h. The reaction mixture was slowly warmed to room temperature, triethylamine (5 mL) was added, and the mixture was poured into aqueous $NaHCO_3$ (150 mL) and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous liquid was dried under vacuum to produce silyl dienyl ether **53** (4.50 g), which was used as a crude foam for the next step without further purification: ^1H NMR ($CDCl_3$) δ 0.75 (d, J = 7.5 Hz, 3 H), 0.85 (s, 3 H), 3.93 (br s, 4 H, ketal), 4.2 (t, 1 H), 4.63 (m, 1 H), 5.50 (s, 1 H).

The mixture of silyl dienyl ether **53** (4.50 g, 10 mmol), $NaHCO_3$ (0.92 g, 11 mmol), and dry THF (75 mL) was cooled to −78 °C and slowly treated with *N*-chlorosuccinimide[25] (1.46 g, 11 mmol) in dry THF (25 mL) over a period of 15 min. After the addition was complete the reaction was stirred at the same temperature for an additional 0.5 h. The reaction mixture was slowly warmed to room temperature, poured into aqueous $NaHCO_3$, and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 2) and saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude viscous liquid was chromatographed (SiO_2, 200 mesh); elution with ether/hexane (1:1) gave **54** as the major chloride (3.50 g): ^1H NMR ($CDCl_3$) δ 0.75 (d, J = 7.0 Hz, 3 H), 0.80 (s, 3 H), 4.00 (s, 4 H, ketal), 4.25–4.45 (m, 2 H), 5.50 (d, 1 H). Continued elution with same solvent gave the equatorial chloride (as a very unstable oil) (0.400 g).

To an ice-cooled solution of γ-silyloxy α-chloro enone **54** (3.50 g) in 10% aqueous acetone (100 mL) was added boron trifluoride etherate (1.56 g, 1.36 mL, 11 mmol) over a period of 5 min. After the addition was complete the reaction was warmed to room temperature, and stirring was continued for 1 h. The reaction mixture was poured into aqueous $NaHCO_3$ (200 mL) and extracted with ethyl acetate (100 mL × 3). The combined extract was washed with water (100 mL × 2) and a saturated NaCl solution (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude solid from ether/hexane afforded **55** as a white crystalline solid (2.15 g, 63%): mp 160–170 °C dec; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 2.18 (m, 1 H), 2.39 (m, 1 H), 2.89 (t, J = 2.3 Hz, 1 H), 3.97 (m, 4 H, ketal), 4.32 (t, J = 4.00 Hz, 1 H), 4.35 (t, J = 2.00 Hz, 1 H), 6.01 (s, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 11.41 (q), 14.04 (q), 38.59 (q), 58.57 (d), 65.36 (t), 65.19 (t), 69.83 (d), 110.47 (s), 123.98 (d), 166.46 (s), 192.69 (s); mass spectrum for $C_{18}H_{25}O_4Cl$, m/e 340 (M^+).

α-Chloro γ-Sulfonyl Acetate 56. An ice-cooled solution of γ-hydroxy, α-chloro enone **55** (0.340 g, 1 mmol), DCC (0.22 g, 1.1 mmol), and pyridine (0.2 mL, 2.2 mmol) in dry THF (10 mL) was treated with (phenylsulfonyl)acetic acid (0.22 g, 1.1 mmol) in THF (5 mL) over 5 min. After the addition was complete the solution was warmed to room temperature and stirred for 3 h. The resultant white solid was separated by filtration, the filtrate was concentrated to dryness, and the residue was poured into water and was extracted with methylene chloride (25 mL × 3). The combined extract was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude solid from methylene chloride/ether mixture afforded **56** as a white crystalline solid (0.500 g, 95%): mp 178–180 °C; ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.00 Hz, 3 H), 0.78 (s, 3 H), 2.18 (m, 1 H), 2.36 (m, 1 H), 2.60 (t, 1 H, 1 H), 3.97–4.04 (m, 4 H, ketal), 4.15 (q, J = 14.20 Hz, 2 H) 4.32 (t, J = 4.35 Hz, 1 H), 5.46 (t, J = 2.5 Hz, 1 H), 6.04 (d, J = 2.8 Hz, 1 H), 7.57–7.95 (m, 5 H); ^{13}C NMR (Me_2SO-d_6) δ 11.29 (q), 13.98 (q), 58.09 (d), 60.36 (t), 65.25 (t), 65.37 (t), 74.96 (d), 110.23 (s), 127.79 (d), 158.21 (s), 162.44 (s), 192.31 (s); mass spectrum for $C_{26}H_{31}O_7SCl$, m/e 522 (M^+).

1β,2,3,4,4a,4bα,5,6α,7,9β,10,10aα-Dodecahydro-1α,4β-dimethyl-2β-methoxy-6β-chloro-9α-hydroxy-7-phenanthrone (58B) and 1β,2,3,4,4a,4bα,5,6β,7,9β,10,10aα-Dodecahydro-1α,4aβ-dimethyl-2β-methoxy-6α-chloro-9α-hydroxy-7-phenanthrone (58A). To a cold (−78 °C) solution of LDA (11 mmol) in THF (100 mL) was added slowly a solution of δ-hydroxy enone **14** (1.38 g, 5 mmol) in THF (50 mL) over a period of 20 min under argon atmosphere. The reaction mixture was stirred for an additional 0.5 h and then slowly treated with *N*-chlorosuccinimide (1.45 g, 11 mmol) in THF (100 mL) over a period of 1 h, and stirring was continued for an additional 0.5 h. The reaction mixture was slowly warmed to room temperature, the THF was removed in vacuo at room temperature, and the residue was poured into water (500 mL) and was extracted with ether (60 mL × 3). The combined ether extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude white solid was flash chromatographed on silica gel (230–400 mesh). Elution with ether/hexane (25:75) gave a faster moving compound (0.750 g), which on recrystallization from methylene chloride/ether in two crops yielded chloro enone **58B** as a white crystalline solid (0.685 g, 44%). Continued elution with ether furnished a second compound (0.650 g) as a white solid, which on recrystallization from ether yielded chloro enone **58A** as a crystalline solid (0.500 g, 32%). Anal. Calcd: C, 65.4; H, 8.01; Cl, 11.4. Found: C, 65.04; H, 8.20, Cl, 11.81.

Spectra data for **58A** was as follows: mp 150–155 °C; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H), 1.00 (d, J = 6.20 Hz, 3 H), 2.55 (m, 1 H), 2.70 (m, 1 H), 3.37 (s, 3 H), 4.36 (t, J = 2.36 Hz, 1 H), 4.51 (q, J = 14.53, 5.45 Hz, 1 H), 6.07 (d, J = 2.2 Hz, 1 H); mass spectrum for $C_{17}H_{25}ClO_3$, m/e 312 (M^+, base peak), 280 (M − MeOH), 276 (M − HCl).

Spectral data for **58B** was as follows: mp 106–110 °C dec; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 1.02 (d, J = 6.3 Hz, 3 H), 1.25–1.33 (m, 2 H), 1.35–1.40 (m, 1 H), 1.52 (seven-line pattern, J = 15.24, 12.24, 3.00 Hz, 1 H), 1.65 (seven-line pattern, J = 12.80, 11.20, 1.62 Hz, 1 H), 1.76 (six-line pattern, J = 9.05, 3.30 Hz, 1 H), 2.05–2.10 (m, 2 H), 2.19 (six-line pattern J = 14.84, 8.63, 3.55 Hz, 1 H), 2.41 (six-line pattern J = 14.87, 5.00 Hz, 1 H), 2.72 (m, 1 H), 2.82 (seven-line pattern J = 7.76, 5.76, 2.00 Hz, 1 H), 3.38 (s, 3 H), 4.34 (t, J = 4.10, 1 H), 4.37 (t, J = 2.40 Hz, 1 H), 6.09 (d, J = 2.00 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.32 (q), 15.20 (q), 25.26 (t), 29.34 (t), 31.37 (t), 35.39 (t), 37.05 (d), 38.50 (s), 41.27 (d), 43.01 (d), 56.72 (q), 57.01 (d), 70.31 (d), 84.34 (d), 123.66 (d), 165.64 (s), 193.37 (s); mass spectrum for $C_{17}H_{25}ClO_3$, m/e 312 (M^+), 280 (M − MeOH), 276 (M − HCl, base peak).

1β,2α,3,4,4a,4bα,5,6β,7,9β,10,10aα-Dodecahydro-1α,4aβ-dimethyl-2β-methoxy-6α-chloro-9α-[(2-phenylsulfonyl)acetoxy]-7-phenanthrone (59A). To an ice-cooled solution of γ-hydroxy α-chloro enone **58A** (0.169 g, 0.54 mmol) and DCC (0.119 g, 0.6 mmol) in dry methylene chloride (5 mL) was added a solution of (phenylsulfonyl)acetic acid (0.119 g, 0.6 mmol) over 5 min. After the addition was complete the reaction was slowly warmed to room temperature and was stirred for an additional 2 h. The solid was removed by filtration, and the residue was washed with more methylene chloride (10 mL × 2). The combined filtrate was diluted with methylene chloride (70 mL) and successively washed with 10% aqueous HCl (20 mL × 2), water (20 mL × 2), and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude white solid from ether/hexane yielded the white crystalline ester **59A** in two crops (0.248 g, 94%): mp 169–170 °C; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 1.01 (d, J = 6.2 Hz, 3 H), 2.24 (m, 1 H), 2.40 (m, 1 H), 2.65 (m, 1 H), 2.75 (m, 1 H), 3.38 (s, 3 H), 4.11 (q, 2 H), 4.35 (t, J = 4.42 Hz, 1 H), 5.46 (br s, 1 H), 6.06 (d, J = 1.7 Hz, 1 H), 7.56–7.92 (m, 5 H); mass spectrum for $C_{25}H_{31}ClO_6S$, m/e 494 (M^+).

1β,2α,3,4,4a,4bα,5,6α,7,9β,10,10aα-Dodecahydro-1α,4aβ-dimethyl-2β-methoxy-6β-chloro-9α-[(2-phenylsulfonyl)acetoxy]-7-phenanthrone (59B). To an ice-cooled solution of γ-hydroxy α-chloro enone **58B** (0.169 g, 0.54 mmol) and DCC (0.119 g, 0.6 mmol) in dry methylene chloride (5 mL) was added a solution of (phenylsulfonyl)acetic acid (0.119 g, 0.6 mmol) over 5 min. After the addition was complete the reaction was slowly warmed to room temperature and stirred for an additional 2 h. The solid was removed by filtration, and the residue was washed with more methylene chloride (10 mL × 2). The combined filtrate was diluted with methylene chloride (70 mL) and successively washed with 10% aqueous HCl (20 mL × 2), water (20 mL × 2), and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the white

solid from methylene chloride/hexane yielded the white crystalline ester **59B** in two crops (0.250 g, 95%): mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 0.76 (s, 3 H) 1.01 (d, J = 6.20 Hz, 3 H), 2.59 (m, 1 H), 2.65 (m, 2 H), 2.38 (s, 3 H), 4.12 (q, J = 13.51 Hz, 2 H) 4.61 (q, J = 14.47, 5.34 Hz, 1 H), 5.52 (s, 1 H), 6.19 (d, J = 2.26 Hz, 1 H), 7.56–7.82 (m, 5 H); mass spectrum for $C_{25}H_{31}ClO_6S$, m/e 494 (M^+, weak).

Methoxy Pentacyclic Sulfone 60. A cold (−78 °C) solution of diisopropylamine (12.31 mL, 88 mmol) in THF (1000 mL) was treated with n-butyllithium (1.6 M solution in hexane 56 mL, 88 mmol) and was stirred at the same temperature for 0.5 h. γ-Hydroxy enone **14** (11.04 g, 40 mmol) in THF (300 mL) was added slowly over a period of 0.5 h. After the addition was complete, the reaction mixture was treated at −78 °C with N-chlorosuccinimide (11.74 g, 88 mmol, vacuum-dried for 1 h) in THF (500 mL) over a period of 0.5 h. After the addition was complete the reaction was stirred at the same temperature for an additional 0.5 h. The reaction was slowly warmed to room temperature, the THF was removed in vacuo at room temperature, and the residue was poured into water and extracted with ether (150 mL × 3). The combined ether extract was washed with water (100 mL × 3) and a saturated NaCl solution (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (SiO_2, 200 mesh, ether) of the pale yellow viscous liquid afforded α-chloro ketones **58A/58B** as a white foam (TLC 1:1 mixture, 13.20 g, 97%). The mixture of α-chloro ketones was used for the next step without separation.

To an ice-cooled solution of crude α-chloro ketones **58A/58B** (12.00 g, 38.6 mmol) and DCC (8.80 g, 42.7 mmol) in dry methylene chloride (250 mL) was added a solution of (phenylsulfonyl)acetic acid (8.80 g, 44 mmol) in methylene chloride (300 mL) slowly over a period of 0.5 h. After the addition was complete the reaction was warmed to room temperature and treated with a second portion of (phenylsulfonyl)acetic acid (1.00 g, 5 mmol) and DCC (1.00 g, 4.86 mmol), and stirring was continued at ambient temperature for 1 h. The resulting solid was removed by filtration, and the residue was washed with methylene chloride (25 mL × 3). The combined filtrate was successively washed with 10% aqueous $NaHCO_3$ (150 mL × 2), 10% aqueous HCl (150 mL × 2), water (150 mL × 2), and a saturated NaCl solution (150 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Vacuum-drying of the crude viscous liquid afforded a white foam of sulfone esters **59A/59B** (19.20 g, crude). Sulfone esters **59A/59B** were used in the next step without further purification.

A solution of **59A/59B** (19.20 g) in dry methylene chloride (1000 mL) was treated with dry cesium fluoride powder (10.00 g, 65.78 mmol) in one portion, and the reaction was stirred at ambient temperature for 48 h and then heated at reflux for 12 h. The reaction mixture was then successively washed with 10% aqueous HCl (100 mL × 2), 10% aqueous $NaHCO_3$ (100 mL × 2), water (100 mL × 2), and a saturated NaCl solution (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude viscous liquid was crystallized in three crops from methylene chloride/ether mixture to yield **60** as a white crystalline solid (11.00 g, 60%): mp 220–221 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 1.00 (d, J = 6.20 Hz, 3 H), 2.09 (s, 1 H), 2.62 (m, J = 18.76, 2.00, 1.44 Hz, 1 H), 2.72 (dd, J = 13.09, 2.70 Hz, 1 H), 2.77 (m, 1 H), 2.90 (seven-line pattern, J = 18.76, 14.13, 5.15 Hz, 1 H), 3.40 (s, 3 H), 4.76 (dd, J = 9.30, 4.17, Hz, 1 H), 7.58–7.96 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.02 (q), 16.11 (q), 25.16 (t), 25.59 (t), 32.46 (t), 43.66 (d), 44.26 (s), 53.71 (s), 56.68 (q), 75.47 (d), 83.98 (d), 128.90 (d), 129.29 (d), 134.62 (d), 138.81 (s), 166.84 (s), 201.29 (s); mass spectrum for $C_{25}H_{30}O_6S$, m/e 458 (M^+), 426 (M − MeOH). Anal. Calcd: C, 65.5; H, 6.55; S, 6.99. Found: C, 65.53; H, 6.85; S, 6.84.

Reaction of 59A with Cesium Fluoride in Methylene Chloride. Isolation of 60. To a solution of chloro enone **59A** (0.025 g, 0.05 mmol in methylene chloride (5 mL) was added cesium fluoride (0.030 g, 2.00 mmol) in one portion, and the reaction was stirred at room temperature for 8 h (TLC and HPLC shows 25–30% completion of reaction). The reaction was stirred for another 18 h, poured into 10% aqueous HCl, and extracted with methylene chloride (25 mL × 3). The combined methylene chloride extract was successively washed with water (20 mL × 2) and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to afford a crude pale yellow solid. Plug filtration followed by recrystallization from methylene chloride/ether yielded two crops of **60** as a white crystalline solid (0.019 g, 83%).

Reaction of 59B with Cesium Fluoride in Methylene Chloride. Isolation of 60. To a solution of chloro enone **59B** (0.025 g, 0.05 mmol) in methylene chloride (5 mL) was added cesium fluoride (0.030 g, 2.00 mmol) in one portion, and the reaction was stirred at room temperature for 8 h (TLC and HPLC shows ca. 30% completion of reaction). The reaction was stirred for an additional 18 h, poured into 10% aqueous HCl, and extracted with methylene chloride (25 mL × 3). The combined methylene chloride extract was successively washed with water (20 mL × 2) and a saturated NaCl solution (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration followed by recrystallization of the crude pale yellow solid from methylene chloride/ether yielded **60** as a white crystalline solid (0.021 g, 91%).

Pentacyclic Sulfone 61. A solution of γ-hydroxy α-chloro enone **55** (0.170 g, 0.5 mmol) and DCC (0.110, 0.53 mmol) in methylene chloride (5 mL) was treated with (phenylsulfonyl)acetic acid (0.110 g, 0.55 mmol) in methylene chloride (5 mL) at 0 °C. After the addition was complete (15 min) the reaction mixture was warmed to room temperature and stirred for 3 h. The white solid was removed by filtration and washed with more methylene chloride (5 mL), and the total filtrate was treated with cesium fluoride (0.170 g, 1.1 mmol) and was stirred at room temperature for 24 h. The crude reaction mixture was poured into water and extracted with methylene chloride (50 mL × 3). The combined organic extract was washed with 10% HCl (50 mL × 2), aqueous $NaHCO_3$ (50 mL × 2), water (50 mL × 1), and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude solid from methylene chloride/ether afforded **61** as a white crystalline solid (0.185 g, 76%): mp 264–265 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 6.5 Hz, 3 H), 0.94 (s, 3 H), 2.08 (m, 1 H), 2.12 (s, 1 H), 2.62 (six-line pattern, J = 19.00, 2.50, 1.20 Hz, 1 H) 2.75 (dd, J = 12.96, 2.80 Hz, 1 H), 2.92 (seven-line pattern, J = 18.72, 14.55, 5.00 Hz, 1 H), 3.93–4.02 (m, ketal), 4.74 (t, J = 6.56 Hz, 1 H), 7.58–7.98 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.38 (q), 15.69 (q), 25.27 (t), 30.64 (t), 32.54 (t), 35.16 (d), 35.29 (s), 37.02 (t), 38.99 (t), 40.58 (d), 41.07 (d), 42.29 (d), 44.36 (s), 53.91 (s), 64.96 (t), 65.23 (t), 75.50 (d), 109.62 (s), 129.06 (d), 129.32 (d), 134.52 (d), 138.73 (s), 166.87 (s), 201.10 (s); mass spectrum for $C_{26}H_{30}O_7S$, m/e 486 (M^+), 345 ($M - SO_2C_6H_5$).

Synthesis of 61 from 48A. A solution of chloro ketone **48A** (0.052 g, 0.1 mmol) in dry methylene chloride (10 mL) was treated with dry cesium fluoride powder (0.0302 g, 0.2 mmol) at room temperature and stirred for 24 h at ambient temperature. Removal of the solvent in vacuo followed by plug filtration (SiO_2, 200 mesh) and recrystallization from methylene chloride/ether afforded **61** as a white crystalline solid (0.045 g, 93%).

Silyl Enol Ether 64. A well-stirred slurry of cuprous iodide (0.060 g, 0.315 mmol) in dry ethyl ether (5 mL) was treated with methyllithium (ether solution, 0.4 mL, 0.630 mmol) at 0 °C over a period of 15 min and stirred at the same temperature for 0.5 h (colorless solution). Sulfone **60** (0.0458 g, 0.1 mmol) in THF (3 mL) was then added slowly over a period of 10 min, and stirring was continued for 0.5 h. HMPA (0.5 mL) was added (until the reaction mixture became homogeneous) followed by triethyl amine (0.03 mL, 0.215 mmol) and chlorotrimethylsilane (0.03 mL, 0.230 mmol). After the addition was complete the reaction mixture was slowly warmed to room temperature and stirred for another 0.5 h. The reaction mixture was poured into aqueous NH_4Cl (pH 9) and was extracted with ether (25 mL × 3). The combined ether extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude viscous liquid was vacuum-dried for 18 h to afford a white foam of trimethylsilyl enol ether **64** (0.050 g, 94%), which was used for the next step without further purification: ^{1}H NMR ($CDCl_3$ partial) δ 0.90 (d, J = 6.00 Hz, 3 H), 1.05 (s, 3 H), 3.30 (s, 3 H), 3.70 (s, 1 H), 5.10 (br s, 2 H), 7.60–8.00 (m, 5 H).

α-Ketol 66. Ozone was passed for 0.5 h into a cold (−78 °C) solution of trimethylsilyl enol ether **64** (0.200 g, 0.375 mmol) dissolved in a 1:1 mixture of methylene chloride/methanol (40 mL). Nitrogen was then passed through the solution for 0.5 h to remove excess ozone. The reaction mixture was slowly warmed to room temperature, and the solvents were removed in vacuo.

The viscous liquid was vacuum-dried to afford a white foam of α-keto alcohol **66** (0.175 g, 98%). **66** was used for the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.90 (d, J = 6.00 Hz, 3 H), 3.30 (s, 3 H), 4.00 (s, 1 H), 5.15 (t, 1 H), 5.50 (s, 1 H), 7.60 -8.00 (m, 5 H).

Bis Aldehyde 68. A cold (-78 °C) solution of α-keto alcohol **66** (0.420 g, 0.88 mmol) in dry THF (50 mL) was treated with lithium borohydride (0.150 g, 6.8 mmol) in three portions over a period of 1.5 h. The reaction mixture was warmed to room temperature and stirred for an additional 1 h. Most of the THF was removed in vacuo, and the residue was poured into water and was extracted with methylene chloride (50 mL × 3). The combined extract was washed with 10% aqueous HCl (50 mL × 2), water (50 mL × 2), and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude α-diol was taken up in methanol (50 mL) and treated with sodium periodate (1.00 g, 4.67 mmol) in water (10 mL) in one portion. The resulting reaction mixture was then stirred at room temperature for 18 h. The methanol was removed in vacuo at room temperature, and the residue was poured into water and extracted with methylene chloride (50 mL × 3). The combined extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (SiO_2 200 mesh, ether) of the crude product followed by vacuum-drying afforded **68** as a white foam (0.250 g, 60%): ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.90 (d, J = 6.00 Hz, 3 H), 3.30 (s, 3 H), 5.50 (t, 1 H), 7.6–8.05 (5 H).

β-Hydroxy Sulfone 69. Triethylamine (0.1 mL) was added to a solution of bis aldehyde **68** (0.250 g, 0.52 mmol) in methylene chloride (10 mL), and the reaction was stirred at 25 °C for 1 h. Removal of the solvent in vacuo gave the crude aldol product **69** (0.250 g, 100%). Recrystallization from ether/hexane furnished a white crystalline analytical sample of **69**: mp 214–215 °C; ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.92 (d, J = 6.20 Hz, 3 H), 2.61 (m, 1 H), 3.33 (s, 3 H), 4.60 (dd, J = 7.06, 4.14 Hz, 1 H), 5.57 (t, J = 2.75 Hz, 1 H), 7.59–7.85 (m, 7 H), 10.15 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.33 (q), 14.53 (q), 25.08 (t), 25.53 (t), 26.39 (t), 56.59 (q), 58.41 (d), 66.12 (d), 78.72 (d), 84.43 (s), 84.82 (d), 129.04 (d), 131.23 (d), 135.25 (d), 135.62 (s), 161.31 (s), 198.50 (d); mass spectrum for $C_{25}H_{32}O_7S$, m/e 476 (M^+), 458 (M - H_2O), 447 (M - CHO), 335 (M - $SO_2C_6H_5$).

Diol 70. A solution of sulfone **69** (0.250 g, 0.52 mmol) in 10% aqueous THF (20 mL) was treated with aluminum amalgam [aluminum foil (0.270 g, 10 mmol) was activated with 10% aqueous NaOH, washed with water, ethanol, and ether, and then dipped in 5% solution of mercuric chloride for a few seconds followed by being directly cut into the reaction mixture] at room temperature for 3 h. The resulting solid was removed by filtration, the residue was washed with more methylene chloride (5 mL × 2), and the filtrate was concentrated in vacuo. The residue was poured into water and extracted with methylene chloride (25 mL × 3). The combined extract was washed with water (25 mL × 2) and a saturated NaCl solution, (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Recrystallization of the crude solid from ether afforded **70** as a white crystalline solid (0.125 g, 71%): mp 119–120 °C; ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.92 (d, J = 6.23 Hz, 3 H), 0.99 (six-line pattern, J = 13.62, 3.95 Hz, 1 H), 1.13 (seven-line pattern, J = 14.01, 10.51, 3.5 Hz, 1 H), 1.69 (six-line pattern, J = 13.06, 3.55 Hz, 1 H), 1.75 (six-line pattern, J = 12.87, 4.50, 1 H), 2.03 (dd dd, J = 12.74, 8.04, 4.10 Hz, 1 H), 2.15 (dd dd, J = 12.30, 8.70, 4.15, 1 H), 2.20 (six-line pattern, J = 15.64, 3.00 Hz, 1 H), 2.62 (six-line pattern, J = 10.58, 5.00 Hz, 1 H), 3.35 (s, 3 H), 3.51 (d, J = 6.47 Hz, 1 H), 3.81 (dd, J = 11.25 Hz, 2 H), 3.94 (five-line pattern, J = 5.67 Hz, 1 H), 4.59 (t, J = 2.61 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.74 (q), 17.76 (t), 75.48 (d), 77.08 (q), 78.67 (d), 84.77 (d), 179.20 (s); mass spectrum for $C_{19}H_{30}O_5$, m/e 338, (M^+), 323 (M - CH_3), 320 (M - H_2O), 302 (M - $2H_2O$).

Disilyl Ether 71. To an ice-cold solution of dialcohol **70** (0.676 g, 2 mmol) in methylene chloride (20 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (Aldrich 1.10 g, 0.965 mL, 4.20 mmol) over a period of 5 min. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. The reaction was poured into aqueous $NaHCO_3$ (150 mL) and extracted with methylene chloride (50 mL × 3). The combined organic extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (SiO_2 gel), using 1:1 ether/hexane as a solvent, of the pale yellow viscous liquid followed by crystallization from ether yielded bis silyl ether **71** as white crystals (1.12 g, 98%): mp 166–167 °C; ^{1}H NMR (470 MHz, $CDCl_3$) δ 4.31 (t, J = 2.38 Hz, 1 H), 3.96 (five-line pattern, J = 10.43, 6.08, 4.39 Hz, 1 H), 3.63 (AB q, J_{AB} = 10.85 Hz, 2 H), 3.34 (s, 3 H), 3.30 (d, J = 6.08, 1 H), 2.62 (six-line pattern, J = 10.42, 10.42, 4.86 Hz, 1 H), 2.14 (dt, J = 15.43, 2.75 Hz, 1 H), 2.02 (m, 1 H), 1.84 (m, 1 H), 0.91 (d, J = 6.27 Hz, 3 H), 0.69 (s, 3 H), ^{13}C NMR ($CDCl_3$) δ 13.40 (q), 14.54 (q), 17.06 (t), 24.32 (t), 25.94, 31.78 (t), 35.10 (s), 36.16, 36.66, 44.95 (d), 46.03 (d), 47.72 (s), 49.44 (d), 56.57 (q), 59.94 (q), 66.04 (d), 76.83 (d), 84.84 (d), 174.85 (s); mass spectrum for $C_{31}H_{58}O_5Si_2$, m/e 566 (M^+), 534 (M - CH_3OH).

Tetracyclic Lactol 72. To a cold (-78 °C) solution of bis silyl ether **71** (0.097 g, 0.2 mmol) in THF (5 mL) was added diisobutylaluminum hydride (0.46 mL of 1 M solution in hexane 0.24 mmol), and the resulting reaction mixture was stirred for 0.5 h. The reaction mixture was slowly warmed to 0 °C and stirred for another hour. The reaction mixture was poured into a saturated solution of NH_4Cl (75 mL) and extracted with methylene chloride (25 mL × 3). The combined organic extract was washed with water (25 mL × 3) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product after flash chromatography afforded the lactol as a viscous liquid (0.06 g, 62%): 470-MHz ^{1}H NMR δ 0.65 (s, 3 H), 0.85 (d, J = 6.5 Hz, 3 H), 2.55–2.70 (m, 2 H), 3.30 (s, 3 H), 3.55 (AB q, 2 H), 3.95 (m, 1 H), 4.20 (br s, 1 H), 5.60 (m, 2 H).

Tetracyclic Lactol TBDMS Ether 73. To a well stirred slurry of LAH (0.074 g, 1.96 mmol) in ether (10 mL) was added bis(*tert*-butyldimethylsilyl) ether **71** (0.111 g, 0.196 mmol) at 0 °C over a period of 10 min. The resulting reaction mixture was slowly warmed to room temperature and stirred for 6 h. The excess LAH was destroyed by careful addition of water (0.1 mL), 10% sodium hydroxide (0.1 mL), and water (0.3 mL) and stirred for another 0.5 h. The solid was separated by filtration and the residue washed with more ether (20 mL × 3). The combined filtrate was washed with water (25 mL × 2) and a saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product after flash chromatography afforded isomerized alcohol (0.09 g, 81%): 470-MHz ^{1}H NMR ($CDCl_3$) δ 0.73 (s, 3 H), 0.93 (s, 12 H), 2.78 (m, 1 H), 3.40 (s, 3 H), 3.70 (br s, 2 H), 4.05 (br s, 2 H), 4.30 (br s, 1 H), 5.63 (d, J = 5.00 Hz, 1 H).

Tetracyclic Lactol 74. To a solution of bis(*tert*-butyldimethylsilyl) ether **71** (0.56 g, 1 mmol) in ether (20 mL) was added methyllithium (Alfa 0.73 mL of 1.5 M solution in ether, 1.1 mmol) at room temperature over a period of 15 min. The resulting reaction mixture was stirred for another 0.5 h, poured into saturated solution of NH_4Cl (150 mL), and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Plug filtration (SiO_2 gel) using 1:1 ether/hexane and crystallization from ether afforded **74** as white crystals (0.545 g, 93%): mp 146–148 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.68 (s, 3 H), 0.80 (s, 21 H), 1.50 (s, 3 H), 2.75 (d, J = 9.00 Hz, 1 H), 3.33 (s, 3 H), 3.60 (AB q, J_{AB} = 11.00 Hz, 2 H), 3.83 (br s, 1 H), 4.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ -5.50 (q), -4.71 (q), 13.92 (q), 14.52 (q), 18.13, 25.04 (t), 25.97, 32.31 (q), 34.78, 35.64 (s), 36.52, 36.59, 44.35, 44.98, 48.57 (s), 52.73 (d), 56.62 (q), 60.94 (t), 69.45 (d), 77.27 (d), 85.15 (d), 105.17 (s); mass spectrum for $C_{32}H_{62}O_5Si_2$, m/e (582, very weak) 564 (M - H_{20}), 549 (M - CH_3). Anal. Calcd C, 66.0; H, 10.7; Si, 9.62. Found: C, 66.00; H, 10.85; Si, 9.38.

Vinyl Methyl Sulfide 75. To a cold (-78 °C) solution of trifluoroacetic anhydride (0.567 g, 0.383 mL, 2.70 mmol) in methylene chloride (10 mL) was added dimethyl sulfoxide (0.429 g, 0.39 mL, 5.5 mmol), and the reaction was stirred for 10 min. Hemiketal **74** (0.422 g, 0.73 mmol) in methylene chloride (10 mL) was added, and the resulting reaction mixture was stirred for 0.5 h. Triethyl amine (3.00 mL) was then added to this reaction mixture, and the reaction was slowly warmed to room temperature and stirred for 24 h. The reaction mixture was poured into water and extracted with methylene chloride (50 mL × 3). The combined organic extracts were then washed with water (50 mL × 3) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4),

and the solvent was removed in vacuo. The pale yellow viscous liquid was plug filtered (SiO_2 gel, 25:75 ether/hexane) to yield vinyl sulfide **75** as a colorless viscous liquid (0.411 g, 92%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.63 (s, 3 H), 0.88 (s, 21 H), 2.20 (s, 3 H), 3.30 (s, 3 H), 3.68 (br s, 2 H), 4.00 (m, 1 H), 4.18 (br s, 1 H), 5.30 (2 s, 1 H); ^{13}C NMR ($CDCl_3$) δ -5.52 (q), -4.78 (q), 13.62 (q), 14.64 (q), 17.83, 17.98, 18.78, 24.78 (t), 25.83, 32.80 (t), 35.22 (s), 36.34, 36.57, 45.04 (d), 46.81 (d), 48.83 (s), 49.79 (d), 56.58 (q), 60.05 (t), 68.50 (d), 79.83 (d), 84.97 (d), 91.71 (d), 155.88 (s); mass spectrum for $C_{33}H_{62}O_4SSi_2$, *m/e* 610 (M^+), 578 (M - CH_3OH). Anal. Calcd C, 64.9; H, 10.2. Found: C, 64.7; H, 10.18.

Phenyl Vinyl Sulfide 76. To a cold (-78 °C) solution of sulfuryl chloride[44] (10.90 g, 80 mmol) in methylene chloride (100 mL) was added a solution of thioanisole (10.00 g, 9.25 mL, 81 mmol) in methylene chloride (10 mL) over a period of 0.5 h. The reaction mixture was stirred for another 2 h and slowly treated with 95% ethanol (100 mL) over a period of 0.5 h. The reaction mixture was slowly warmed to room temperature, most of the solvent was removed in vacuo, and the mixture was poured into saturated Na_2CO_3 solution (300 mL) and was extracted with methylene chloride (100 mL × 3). The combined organic extract was washed with water (100 mL × 2) and a saturated NaCl solution (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Distillation of the crude liquid yielded colorless phenyl methyl sulfoxide [11.00 g, 97%; bp 85–90 °C (0.5 mm)].

To a cold (-78 °C) solution of phenyl methyl sulfoxide (0.042 g, 0.3 mmol) in methylene chloride (3 mL) was added trifluoroacetic anhydride (0.063 g, 0.042 mL, 0.15 mmol), and the reaction was stirred for 15 min. Hemiketal **74** (0.029 g, 0.05 mmol) in methylene chloride (2 mL) was added, and the reaction was stirred for an additional 15 min. To this reaction mixture was then slowly added triethylamine (0.25 mL); the reaction was warmed to room temperature and stirred for 24 h. The reaction mixture was then poured into water and extracted with methylene chloride (25 mL × 3). The combined organic extract was washed with water (25 mL × 2) and NaCl (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous liquid was flash chromatographed (SiO_2, 1:1 ether/hexane) to yield vinyl sulfide **76** as a colorless viscous liquid (0.030 g, 88%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.90 (s, 21 H), 3.32 (s, 3 H), 3.50 (d, J = 9 Hz, 1 H), 3.70 (br s, 2 H), 4.00 (m, 1 H), 4.25 (br s, 1 H), 5.70 (2 s, 1 H), 7.30 (m, 5 H).

Alternate Preparation of Phenyl Vinyl Sulfide 76. To a cold (-78 °C) CH_2Cl_2 solution of hemiketal **74** (0.029 g, 0.05 mmol) and triethyl amine (0.065 mL, 0.5 mL) was added methanesulfonyl chloride (0.019 mL, 0.25 mmol) and stirred for 0.5 h. The reaction mixture was slowly warmed to room temperature and treated with phenylsulfinyl chloride [from thiophenol (0.011 g, 0.10 mmol) and NCS (0.014 g, 0.11 mmol)] in 2 mL of methylene chloride and stirred for 0.5 h. The reaction mixture was poured into water (50 mL) and extracted with methylene chloride (20 mL × 3). The combined organic extract was washed with water (25 mL × 3) and saturated NaCl solution (25 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product after flash chromatography afforded **76** as a white foam (0.02 g, 72%).

Hydroxy Lactone 81. To a solution of bis(*tert*-butyldimethylsilyl) ether **71** (0.284 g, 0.50 mmol) in methylene chloride (25 mL) was added triphenylcarbenium tetrafluoroborate (0.181 g, 0.55 mmol) in one lot, and the resulting reaction mixture was stirred at room temperature for 0.5 h. The reaction was poured into aqueous $NaHCO_3$ (150 mL) and extracted with methylene chloride (50 mL × 3). The combined organic extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude pale yellow viscous liquid was flash chromatographed (SiO_2, 400 mesh, 1:1 ether/hexane) to give alcohol **81** as a white foam (0.220 g, 97%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.72 (s, 3 H), 0.92 (s, 21 H), 2.60 (m, 1 H), 3.35 (s, 3 H), 3.45 (d, J = 9.00 Hz, 1 H), 3.50–4.00 (m, 4 H), 4.50 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.67 (q), 14.48 (q), 17.64 (t), 18.16 (t), 24.06 (t), 25.63, 25.81, 34.43 (t), 35.18 (s), 36.00 (t), 36.42 (d), 45.04 (d), 48.43 (d), 48.67 (d), 48.67 (s), 56.65 (q), 58.99 (t), 65.90 (d), 78.88 (d), 84.62 (d), 178.15 (s). **81** was carried to the next step without further purification.

Keto Lactone 82. To a cold (-78 °C) solution of dimethyl sulfoxide (0.115 g, 0.10 mL, 1.47 mmol) in methylene chloride (15 mL) was added trifluoroacetic anhydride (0.210 g, 0.14 mL, 1 mmol), and the mixture was stirred for 15 min. Alcohol **81** (0.220 g, 0.49 mmol) in methylene chloride (5 mL) was slowly added to the resultant solution over a period of 5 min, and the reaction mixture was stirred for an additional 0.5 h. To this reaction mixture was then added triethylamine (0.202 g, 0.278 mL, 2 mmol); the mixture was slowly warmed to room temperature and stirred for an additional 0.5 h. The reaction mixture was poured into water (150 mL) and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 3) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous ligand was plug filtered (SiO_2, 1:1 ether/hexane) to yield ketone **82** as a white foam (0.210 g, 95%): ^1H NMR (470 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 0.95 (d, J = 6.36 Hz, 3 H), 1.05 (six-line pattern, J = 13.33, 13.33, 3.83 Hz, 1 H), 2.05 (m, 2 H), 2.24 (six-line pattern, J = 15.51, 2.81 Hz, 1 H), 2.40 (five-line pattern, J = 17.51, 8.68 Hz, 1 H), 2.55 (ddd, J = 17.49, 6.80, 2.52 Hz, 1 H), 2.65 (six-line pattern, J = 10.50, 10.50, 4.90 Hz, 1 H), 3.37 (s, 3 H), 3.80 (s, 1 H), 3.79 (AB q, J_{AB} = 10.85 Hz, 2 H), 4.48 (t, J = 2.40 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.36 (q), 14.57 (q), 18.13 (t), 18.19 (t), 24.34 (t), 25.55, 25.73, 35.58 (s), 35.96 (t), 36.42 (d), 39.85 (t), 44.33 (d), 47.85 (d), 49.55 (s), 56.71 (q), 59.74 (d), 60.92 (t), 78.61 (d), 84.46 (d), 170.95 (s), 201.61 (s); mass spectrum for $C_{25}H_{42}O_5Si$, *m/e* 450 (M^+), 418 (M - CH_3OH).

Silyl Enol Ether Lactone 83. To an ice-cooled solution of ketone **82** (0.210 g, 0.47 mmol) in methylene chloride (20 mL) was added triethyl amine (0.06 g, 0.083 mL, 0.60 mmol) followed by slow addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.158 g, 0.137 mL, 0.60 mmol) over a period of 5 min and stirring for 0.5 h. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (150 mL) and extracted with methylene chloride (50 mL × 3). The combined organic extract was washed with water (50 mL × 3) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous liquid was plug filtered (SiO_2, 25:75 ether/hexane) to yield *tert*-butyldimethylsilyl enol ether **83** as a colorless foam (0.242 g, 92%). Recrystallization from ether afforded an analytical sample: mp 148–149 °C; ^1H NMR (90 MHz $CDCl_3$) δ 0.80 (s, 3 H), 0.95 (s, 21 H), 2.65 (m, 1 H), 3.35 (s, 3 H), 3.50 (s, 1 H), 3.70 (AB q, J_{AB} = 10.00 Hz, 2 H), 4.65 (t, J = 3.00 Hz, 1 H), 4.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ -5.59 (q), -5.48 (q), -4.55 (q), -4.37 (q), 13.37 (q), 14.64 (q), 19.98 (t), 24.51 (t), 25.70, 34.92 (s), 36.07, 36.61, 44.49 (d), 45.54 (d), 46.82 (s), 50.18 (d), 56.65 (q), 58.16 (t), 76.78 (d), 84.78 (d), 104.23 (d), 144.66 (s), 174.76 (s). Anal. Calcd C, 66.0; H, 9.93; Si, 9.93. Found: C, 66.27; H, 9.79; Si, 9.61.

Lactol Silyl Enol Ether 84. To a cold (-78 °C) solution of *tert*-butyldimethylsilyl enol ether **83** (0.180 g, 0.32 mmol) in ether (20 mL) was slowly added methyllithium (Alfa product, 0.022 g, 0.666 mL, 1 mmol) over a period of 5 min, and the reaction was stirred for an additional 0.5 h. The reaction mixture was slowly warmed to 0 °C over 0.5 h. The reaction mixture was quenched with aqueous NH_4Cl solution, poured into water (100 mL), and extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 3) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The colorless viscous liquid was flash chromatographed (SiO_2, 400 mesh, 1:1 ether/hexane) to yield hemiketal **84** as a colorless foam (0.164 g, 89%): ^1H NMR and ^{13}C NMR show a 1:1 mixture. **84** was used in the next step without further purification.

Vinyl Sulfide Silyl Enol Ether 85. To a cold (-78 °C) solution of dimethyl sulfoxide (0.117 g, 0.1 mL, 1.50 mmol) in methylene chloride (15 mL) was added trifluoroacetic anhydride (0.21 g, 0.14 mL, 1 mmol), and the mixture was stirred for 15 min. Lactol **84** (0.148 g, 0.25 mmol) in methylene chloride (5 mL) was added to the above solution, and the reaction was stirred for an additional 0.5 h. Triethylamine (0.278 g, 3.00 mL, 2.75 mmol)

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was added to the reaction mixture, and the reaction was slowly warmed to room temperature followed by heating at reflux for 24 h. The reaction was poured into water (150 mL) and extracted with methylene chloride (50 mL × 3). The combined organic extract was washed with water (50 mL × 3) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude pale brown viscous liquid was flash chromatographed (SiO_2, 400 mesh, 25:75 ether/hexane) to afford vinyl sulfide **85** as a colorless viscous liquid (0.120 g, 79%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 0.95 (s, 21 H), 2.25 (s, 3 H), 2.70 (m, 1 H), 3.38 (s, 3 H), 3.62 (s, 1 H), 3.70 (AB q, J_{AB} = 10.00 Hz, 2 H), 4.31 (br s, 1 H), 4.85 (m, 1 H), 4.98 (2 s, 1 H); mass spectrum for $C_{33}H_{60}O_4S\,Si_2$, *m/e* 608 (M^+). Anal. Calcd: C, 65.1; H, 9.87. Found: C, 64.73; H, 10.18.

Saturated α-Ketol Lactol 86. To an ice-cooled solution of vinyl sulfide **75** (0.282 g, 0.462 mmol) in THF (20 mL) was added osmium tetraoxide (0.097 g, 0.50 mmol) in one portion, and the reaction was stirred for 15 min. The reaction mixture was slowly warmed to room temperature and stirred for an additional 4 h. To this reaction mixture was then added a saturated aqueous solution of sodium sulfite (5 mL), and the mixture was stirred for 1 h. The black residue was separated by filtration (Celite), the filtrate was poured into water (100 mL), and the mixture was extracted with ether (50 mL × 3). The combined organic extract was washed with water (50 mL × 2) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The pale yellow viscous liquid was flash chromatographed (SiO_2, 400 mesh, 25:75 ether/hexane) to yield keto lactol **86** as a white foam (0.23 g, 80%).

Unsaturated α-Keto Lactol 87. To an ice-cooled solution of vinyl sulfide **85** (0.120 g, 0.20 mmol) in THF (10 mL) was added osmium tetraoxide (0.042 g, 0.22 mml) in one portion. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. To the above reaction mixture was then added a saturated solution of Na_2SO_3 (1 mL), and the mixture was stirred for an additional 3 h. The black solid was separated by filtration (Celite), the filtrate was poured into water (100 mL), and the mixture was extracted with ether (50 mL × 3). The combined ether extract was washed with water (50 mL × 3) and a saturated NaCl solution (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residual viscous liquid was flash chromatographed (SiO_2, 400 mesh, 25:75 ether/hexane) to produce keto lactol **87** (0.085 g, 72%). Anal. Calcd: C, 64.6; H 9.76. Found: C, 64.23; H, 10.11.

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Supplementary Material Available: Procedures for the syntheses of **4b,c**, **11**, and the C-3 methoxy analogues of **15** and **52–55** and for the borohydride reduction/acylation of **37B**, ^{13}C NMR spectral data for synthesized enones, nitriles, enone esters, lactones, and Baeyer–Villiger lactones, and 470-MHz ^1H NMR spectral data for synthesized lactones and enones (12 pages). Ordering information is given on any current masthead page.

Unsymmetrically Substituted 1,8-Diarylanthracenes[1]

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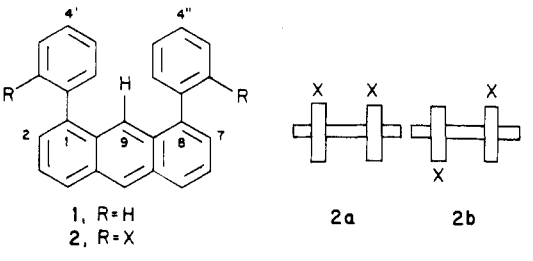
Unsymmetrically substituted 1,8-diarylanthracenes where the aryl rings are *m*-tolyl (**5**), *o*-tolyl (**6**), and 2,3-dimethylphenyl (**7**) have been synthesized; the barriers to aryl ring rotation in these hydrocarbons were found to be 5.3, 10.4, and 16.3 kcal/mol, respectively. Addition of either an acetoxyl (**14**) or a methyl (**15**) substituent at C-9 of the dixylylanthracene gave mixtures of cis and trans isomers that also exhibited rotation of an aryl ring within the temperature range 25–120 °C. X-ray crystal structures for the *cis*- (**14b**) and *trans*- (**14a**) 9-acetoxydixylylanthracenes demonstrated significant distortion in the geometry of the anthracene ring, permitting rotation of the aryl rings with unexpected ease in solutions at temperatures above 100 °C.

Our studies of 1,8-diphenylanthracene (**1**, Scheme I) and its derivatives have provided evidence that these molecules exist largely in conformations with the two phenyl rings approximately parallel and approximately perpendicular to the plane of the anthracene ring.[2,3] Such conformers possess a molecular cavity bounded on the bottom by the anthracene ring and on two sides by phenyl rings. This cavity is of sufficient size to allow reagents to enter and engage in chemical reactions at the bottom of the cavity, namely, at the C-9 position of the anthracene ring.

Scheme I



Consideration of this geometry leads to the conclusion that 1,8-diarylanthracene derivatives **2** with unsymmetrically substituted aryl rings will exist as two geometrical isomers, a cis form (**2a**) and a trans form (**2b**). Furthermore, the trans form **2b** would be composed of two nonsuperimposable mirror images (enantiomers). Resolution of an appropriate set of enantiomers possessing a functional group at C-9 would provide two molecules, each with

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