# Sulfur-Substituted Dienes and the Silylene Protecting Group in Synthesis. Deoxypillaromycinone

Barry M. Trost,* Charles G. Caldwell, Eigoro Murayama, and Denis Heissler

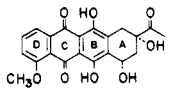
*McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706*

*Received October 22, 1982*

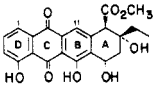
A general approach directed toward the anthracycline antitumor compounds and the tetracycline antibiotics evolves from the sequential use of a 1-oxy- and 2-oxybuta-1,3-diene in regiocontrolled Diels–Alder reactions with juglone. By appropriately choosing the 1-(acyloxy)buta-1,3-diene, the absolute as well as relative stereochemistry of the final products is controlled. 2-Acetoxy-3-*p*-anisylthiobuta-1,3-diene controls the orientation of the second cycloaddition and permits direct introduction of the enone functionality. The success of this second Diels–Alder reaction with a very sensitive cyclohexenone as a dienophile attests to its extraordinary reactivity and therefore utility in synthesis. The elaboration of the A ring functionality of pillaromycinone employs a cis hydroxylation and conversion of the cyclohexanone unit to a 1-acetylcyclohexene system via singlet oxygen oxidation of a homologated enol ether. Aromatization then completes the synthesis of deoxypillaromycinone. The virtues of the di-*tert*-butylsilyl protecting group for 1,2- and 1,3-diols are summarized.

## Introduction

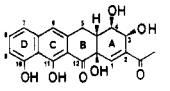
The potent antitumor activity of the anthracyclines, the glycosides of derivatives of 7,8,9,10-tetrahydro-5,12-naphthacenequinones, stimulates the evolution of their chemistry in conjunction with their biological evaluation.[1] The aglycons such as daunomycinone (**1**)[2] and aklavinone (**2**),[3,4] two highly prized targets that possess such a quinone



*1*

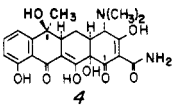


*2*



*3*

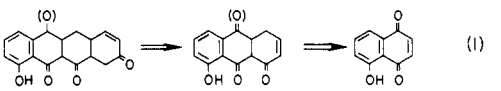
moiety, differ from each other by the substitution of the A ring and the lack of a hydroxyl group at C(11). Pillaromycinone (**3**), the aglycon of pillaromycin, while not formally an anthracycline since it lacks the quinone moiety, bears a structural similarity.[5,6] In addition to possessing yet another substitution pattern in ring A, it lacks the oxygen substituents found at C(11) and C(12) of daunomycinone. Lower cardiotoxicity appears to accompany removing the oxygen substituents at these positions. A clear resemblance to tetracycline (**4**), a broad spectrum antibiotic, is also noteworthy.[7] Dehydration of the C(6)



*4*

alcohol of **4** generates the dihydroxynaphthyl ketone chromophore of pillaromycinone.

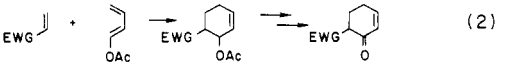
A synthetic strategy that would possess sufficient structural flexibility to permit diversion into more than one family of compounds would be most satisfactory. Inclusion of an oxygen substituent on a tetracyclic intermediate like **5** provides this sought-after flexibility.



*5* (1)

Dehydration at the benzylic position creates the aromatic C ring of **3**. Alternatively, oxidation at the same position creates the quinone unit of **2** and permits addition of a methyl group to form the tetracycline system. The enone present in ring A offers the opportunity to elaborate the A rings of these systems.

In addition to the structural significance attached to this oxygen, it also helps unravel the tetracyclic framework via a succession of Diels–Alder reactions to juglone with the dienes capable of introducing a 2-en-1-one and a 3-en-2-one (numbering with respect to the activating group of the initial dienophile) as shown in eq 1. 1-Acetoxybutadiene embodies the structural features required for the former task as shown in eq 2. However, simply transposing the



(2)

oxygen function to C(2) of the diene fails to allow the annulation required for the latter task. For example, the elegant work of Danishefsky utilizing diene **6** creates a

(1) For recent reviews see: (a) Henry, D. W. In "Cancer Chemotherapy"; Sartorelli, A. C., Ed.; American Chemical Society: Washington, D.C., 1976. (b) Brown, J. R., *Prog. Med. Chem.* **1978**, *15*, 125. (c) Arcamone, F. "Daunomycin and Related Antibiotics" in "Topics in Antibiotic Chemistry. Volume 2"; Sammes, P. G., Ed.; J. Wiley and Sons: New York, 1978. (d) Remers, W. A., "The Chemistry of Antitumor Antibiotics. Volume 1"; J. Wiley and Sons: New York, 1979. (e) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288.

(2) For an excellent leading reference see: Kelly, T. R., Vaya, J.; Ananthasubramanian, L. *J. Am. Chem. Soc.* **1980**, *102*, 5984. Also see: Parker, K. A.; Kallmerten, J. *Ibid.* **1980**, *102*, 5881; Swenton, J. S.; Anderson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825; Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378; Kimball, S. D.; Wall, D. R., Johnson, F. *Ibid.* **1981**, *103*, 1561.

(3) (a) Oki, T.; Matsuzawa, A.; Yoshimoto, K.; Numata, K.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Naganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1975**, *28*, 830. (b) Tresselt, D.; Eckardt, K.; Tax, J. *Tetrahedron* **1975**, *31*, 613.

(4) For recent synthetic work see: Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247; Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *Ibid.* **1981**, *103*, 4248; Confalone, P. N.; Pizzolato, G. *Ibid.* **1981**, *103*, 4251; Li, T. T.; Wu, Y. L. *Ibid.* **1981**, *103*, 7007.

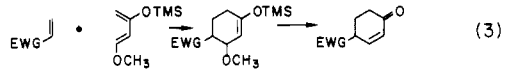
(5) (a) Shibata, M.; Asia, M.; Mizuno, K.; Miyake, A.; Tatsuoka, S. *Proc. Jpn Acad.* **1964**, *40*, 296. (b) Asai, M. *Chem. Pharm. Bull.* **1970**, *18*, 1699. (c) Asai, M. *Ibid.* **1970**, *18*, 1706. (d) Asai, M. *Ibid.* **1970**, *18*, 1713. (e) Asai, M.; Mizuta, E.; Mizuno, K.; Miyake, A.; Tatsuoka, S. *Ibid.* **1970**, *18*, 1720. (f) Kamiya, K.; Asia, M.; Nishikawa, M.; Mizuno, K.; Tomiie, Y.; Nitta, I. *Ibid.* **1970**, *18*, 1724.

(6) (a) Pezzanite, J. O.; Clardy, J.; Law, P.-Y.; Wood, G.; Walker, D. L.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 6250. (b) Walker, D. L.; Fraser-Reid, B. *Ibid.* **175**, *97*, 6251. (c) Fraser-Reid, B.; Walker, D. L. *Can. J. Chem.* **1980**, *58*, 2694.

(7) For recent reviews see: (a) Mitscher, L. A. "The Chemistry of the Tetracycline Antibiotics"; Marcel Dekker: New York, 1978. (b) Durkheimer, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 721. (c) Johnson, F. In "The Total Synthesis of Natural Products, Vol 1"; AsSimon, J., Ed.; Wiley-Interscience: New York, 1973. (d) Muxfeldt, H.; Bangert, R. *Fortschr. Chem. Org. Natust.* **1963**, *21*, 80. (e) Brown, J. R.; Ireland, D. S. *Adv. Pharmacol. Chemother.* **1978**, *15*, 161.

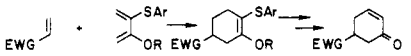
0022-3263/83/1948-3252$01.50/0 

2-en-4-one annulation as shown in eq 3.[8] On the other



(3)

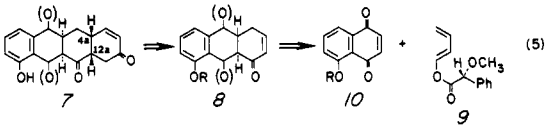
hand, the ability of sulfur to control the orientation of the two reacting partners in Diels–Alder reactions suggested an alternative as embodied in eq 4.[9-11] The fact that this



(4)

annulation will be performed on a sensitive cyclohexenone, a notoriously poor type of dienophile, will truly test the mettle of this diene. Applying the concepts symbolized by eq 2 and 4 to the sequence envisioned in eq 1 then provides a resolution of this synthetic problem.

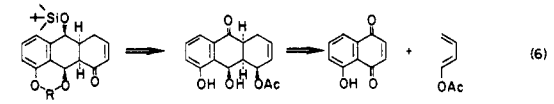
With pillaromycinone as the target, this strategy can resolve yet another facet of the synthetic problem—control of absolute stereochemistry. Cis hydroxylation of **7** would be directed from the $\beta$ face in an intermediate like **7**—the stereochemistry required for **3**. The $\beta$ configuration for C(4a) and C(12a) arises from least hindered attack of the diene on an enone such as **8**. Thus, if the absolute configuration of C(4a) and C(9a) of **8** which evolves from the initial Diels–Alder reaction can be controlled, both the relative and absolute stereochemistry of pillaromycinone will emerge as outlined in eq 5. Indeed use of the



(5)

mandelate ester **9** in a Diels–Alder reaction with juglone **10** (R = H) gives a single adduct whose stereochemistry corresponds to that required for **3**.[12] Thus, realization of this strategy can translate into an enantiomerically controlled synthesis. During the course of this work, we explored the applicability of the di-*tert*-butylsilylene protecting group for diols and report on its utility in synthesis.[13]

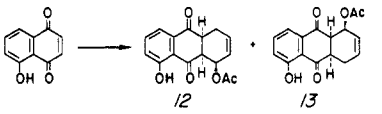
**Synthesis of Tricyclic Dienophile. The Di-*tert*-Butylsilylene Protecting Group.** We chose **11** as our tricyclic dienophile since it permitted differentiation of the two alcohol functions and provided substantial steric differentiation of the two faces of the enone. As outlined in eq 6, its synthesis commenced with the regiocontrolled



(6)

*11a* R = $C(CH_3)_2$
*b* R = $Si(t\text{-}C_4H_9)_2$

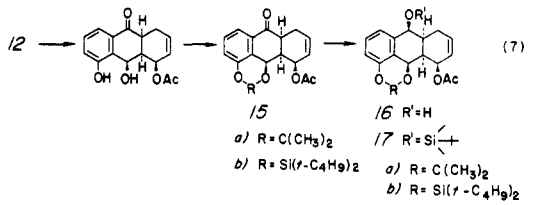
Diels–Alder reaction of 1-acetoxybutadiene and juglone.[14] Repetition of the thermal reaction with juglone gave a 2:1 ratio of **12**:**13** as determined by NMR spectroscopic



*12* *13*

analysis of the crude reaction mixture. This is in reasonable agreement with the 4.8:1 ratio reported after isolation of each pure regioisomer.[14] It is striking to note the exceptionally high-field shift of the acetate group ($\delta$ 1.38) that results from a conformation placing it directly above the aromatic ring. Lewis acid catalysis dramatically improved this reaction. First, the ratio of products increased to >20:1 in favor of **12**.[15] Second, the ratio of starting materials could be made nearly stoichiometric (~1.5:1 diene:dienophile) in contrast to the 5:1 ratio employed in the thermal reaction.

Chemoselective reduction to **14** was conveniently achieved with sodium borohydride. In fact, the product

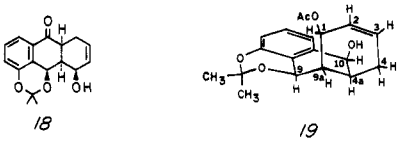


(7)

*15*
*a)* R = $C(CH_3)_2$
*b)* R = $Si(t\text{-}C_4H_9)_2$

*16* R' = H
*17* R' = Si
*a)* R = $C(CH_3)_2$
*b)* R = $Si(t\text{-}C_4H_9)_2$

was inert to further reduction under these conditions. Comparison of the product melting point and UV data to the reported for **14**[14] confirmed the stereo- and chemoselectivity. Initial attention focused on the acetonide **15a**[16] related to **14** which formed smoothly by acid-catalyzed ketal exchange in DMF. Numerous experiments determined that lithium borohydride in THF most efficiently and selectively reduced **15a** to **16a**. Since significant amounts of the diol resulting from acetate cleavage accompanied the product when the reaction was taken to completion, it was normally stopped at 50% conversion and recycled, in which case **16a** was essentially the only product. DIBAL-H (diisobutylaluminum hydride) attacked the ketone and acetate carbonyl groups of **14** with little discrimination; sodium bis(2-methoxyethoxy)aluminum hydride selectively cleaved the allylic acetate to give **18**. The stereochemistry and conformation of **16a**,



*18* *19*

which is deduced from the NMR spectrum, is represented in **19**. The proton geminal to the hydroxyl group ($\delta$ 4.64) shows coupling to both the hydroxyl proton ($\delta$ 2.28 disappears upon addition of $D_2O$) and the C(4a) proton ($J$ = 12 and 4 Hz, respectively). The benzylic proton at C(9) ($\delta$ 4.99) shows coupling of 6 Hz to C(9a). The acetate continues to show the extraordinarily high-field shift for the methyl group ($\delta$ 1.26).

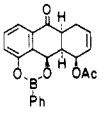
For reasons to be outlined later, the acetonide group proved inadequate for this synthesis. The optimum protecting group should have the following properties: (a) stability to Lewis acids, (b) ability to be removed selectively

(8) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.
(9) (a) Trost, B. M.; Bridges, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 5017. (b) Trost, B. M.; Ippen, J.; Vladuchick, W. C. *Ibid.* **1977**, *99*, 8116. (c) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *Ibid.* **1980**, *102*, 3548. (d) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *Ibid.* **1980**, *102*, 3554.
(10) Also see: Cohen, T.; Kosarych, Z. *Tetrahedron Lett.* **1980**, *21*, 3955; Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbute, R. M.; Alston, P. B. *J. Org. Chem.* **1978**, *43*, 4052.
(11) (a) Trost, B. M.; Godleski, S. A., Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (b) Trost, B. M.; Ippen, J.; Godleski, S. J. *J. Org. Chem.* **1978**, *43*, 4559.
(12) Trost, B. M.; O'Krongly, D.; Belletire, J. *J. Am. Chem. Soc.* **1980**, *102*, 7595.
(13) For a preliminary report of this silylene protecting group see Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999.
(14) Inhoffen, H. H.; Muxfeldt, H.; Schaefer, H.; Krämer, H. *Croat. Chem. Acta* **1957**, *29*, 329.
(15) Stork also noted the marked improvement in regiochemistry by addition of Lewis acids in independent work. See: Stork, G.; Hagedorn, A. A., III *J. Am. Chem. Soc.* **1978**, *100*, 3609.
(16) (a) Kolosov, M. N.; Popravko, S. A.; Gurevich, A. I.; Korobko, V. G.; Vasina, I. V.; Shemyakin, M. M. *Zh. Obshch. Khim.* **1964**, *34*, 2534. (b) Kolosov, M. N.; Popravko, S. A.; Shemyakin, M. M. *Dokl. Akad. Nauk. SSSR*, **1963**, *150*, 1285.

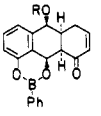
Table I. Conditions for Silylation of 14

| solvent | silyl transfer agent (equiv) | base (equiv) | temp, °C | time, h | yield, % |
|---|---|---|---|---|---|
| DMF | imidazole (2.5) | none | 50 | 48 | 55 |
| DMF | none | $(C_2H_5)_3N$ (4.6) | 45 | 24 | 36 |
| $CH_3CN$ | imidazole (6) | none | 70 | 4 | 31 |
| $CH_3CN$ | DMAP (3) | none | 70 | 2.75 | 45 |
| $CH_3CN$ | none | $(C_2H_5)_3N$ (6.7) | 70 | 3 | 53 |
| $CH_3CN$ | DMAP (2) | $(C_2H_5)_3N$ (4) | 70 | 1 | 65 |
| $CH_3CN$ | 1-hydroxybenzotriazole (0.1) | $(C_2H_5)_3N$ (5) | 65 | 0.5 | 84 |

in the presence of *tert*-butyldimethylsiloxy and acetate groups, and (c) ability to be removed under neutral conditions. For the first alternative, we envisioned the use of the boronate[17] as in **20** since it possessed the possibility of serving as an internal Lewis acid for enhancing the dienophilic properties of **21**. Mixing phenylboronic acid

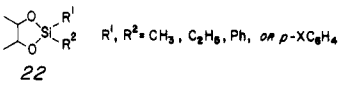


*20*



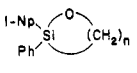
*21*

with diol **14** in acetone at 25 °C led to smooth formation of **20**, which was purified by recrystallization. However, its sensitivity to chromatography did not bode well for subsequent stages of the synthesis. Our search led to the selection of a dialkylsilylene group for two reasons: (1) Bøe found the cyclic derivatives **22** to solvolyze more rapidly

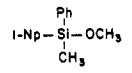


*22*

than similar trialkylsilyl ethers[18] and (2) Corriu noted a ring effect in the rates of solvolysis of **23** compared to its acyclic analogue **24**.[19-22]



*23*



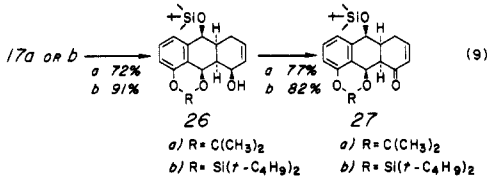
*24*

We settled on the di-*tert*-butylsilylene group, which required the availability of di-*tert*-butyldichlorosilane (**25**).[23,24] The most convenient approach followed the route outlied in eq 8.[25] Table I outlines the conditions examined

$$HSiCl_3 + t\text{-}C_4H_9Li \rightarrow (t\text{-}C_4H_9)_2SiClH \xrightarrow{Cl_2} \underset{\mathbf{25}}{(t\text{-}C_4H_9)_2SiCl_2} \quad (8)$$

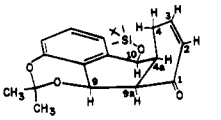
for introducing this group in **14**. As the data show, a silyl transfer agent such as imidazole, DMAP, or 1-hydroxybenzotriazole improves the silylation, with 1-hydroxybenzotriazole being preferred. *N*-Hydroxysuccinimide also suffices and may be superior.

Conversion of **15b** to **17b** used the same reduction (59%) and protection (86%) steps as described previously. Unmasking the enone **27** proceeded straightforwardly in both series by reductive cleavage of the acetate with DIBAL-H and simple Moffatt oxidation[26] with acetic anhydride in $Me_2SO$ as outlined in eq 9. The NMR spectrum of **27a**



(9)

exhibits several interesting features that define the conformation of the molecule as depicted in **28**. The signal



*28*

at $\delta$ 1.76, which must be assigned to one of the protons at C(4), appears as a ddt ($J$ = 20, 12, 3 Hz). The 12-Hz coupling indicates this proton has a diaxial relationship with the proton at C(4a). The signal at $\delta$ 3.17 (dd, $J$ = 9, 4 Hz), assigned to the proton at C(9a), supports the maintenance of the cis ring fusion by 4-Hz coupling for the protons at C(4a) and C(9a). The 3-Hz coupling for the methine proton at C(10) ($\delta$ 4.80) with the proton at C(4a) supports the axial–equatorial relationship and the 9-Hz coupling for the methine proton at C(9) with that at C(9a) demands an almost eclipsed orientation of these protons.

**Diels–Alder Reaction.** The initial step in this sequence involves cycloaddition to the sensitive enone embodied in **27**. In addition to its being a cyclohexenone, a notoriously poor dienophile, it also bears a benzylic oxygen substituent which receives activation as a leaving group from both the aromatic ring and the carbonyl group. The diene **29** was routinely prepared from 1-acetoxy-2-(*p*-anisylthio)cyclobutene on 4-g scales by FVP at 0.02–0.05 torr through a horizontally mounted tube possessing a 100-mL bubble in the hot zone.[9c,27,28] It is anticipated that

(17) Sugihara, J. M.; Bowman, C. M. *J. Am. Chem. Soc.* **1958**, *80*, 2443; Ferrier, R. J.; Prasad, D.; Rudowski, A.; Sangster, I. *J. Chem. Soc.* **1964**, 3330.

(18) Bøe, B. *J. Organomet. Chem.* **1972**, *43*, 275.

(19) Corriu, R. J. P.; Guérin, C.; Guiraud, G. *J. Chem. Soc., Chem. Commun.* **1979**, *8*.

(20) However see Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1981**, *46*, 5348.

(21) For a recent review of displacement at silicon see: Corriu, R. J. P.; Guérin, C. *J. Organomet. Chem.* **1980**, *198*, 231.

(22) After completion of our work, two silicon protecting groups for diols have been reported. For the diphenylsilylene group see: Jenner, M. R.; Khan, R. *Chem. Commun.* **1980**, 50. We found this derivative to be labile towards chromatography. For the tetraisopropyldisiloxane-1,3-diyl group see: Markiewicz, W. T. *J. Chem. Res., Synop.* **1979**, 24; Verdegaal, C. H. M.; Jansse, P. L.; de Rooij, J. F. M.; van Boom, J. H. *Tetrahedron Lett.* **1980**, 1571; Groeli, C.; Kwiatkowski, M.; Oberg, B.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 1741.

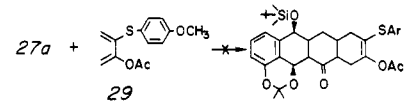
(23) Commercially available from Petrarch Systems Inc., Bristol, Pa.

(24) (a) Tyler, L. J.; Sommer, L. H.; Whitemore, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 2876. (b) Doyle, M. P.; West, C. T. *Ibid.* **1975**, *97*, 3777. (c) Triplett, K.; Curtis, M. D. *J. Organomet. Chem.* **1976**, *107*, 23. (d) Desheimer, E. M.; Spialter, L. *Tetrahedron Lett.* **1975**, 1771. For a most recent preparation by the chlorination of di-*tert*-butylsilane see: Watanabe, H.; Ohkawa, T.; Muraoka, T.; Nagai, Y. *Chem. Lett.* **1981**, 1321.

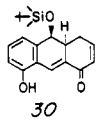
(25) For the preparation of di-*tert*-butylchlorosilane see: Weidenbruch, M.; Pesel, H.; Peter, W.; Steichen, R. *J. Organomet. Chem.* **1977**, *141*, 9. Using our equipment, the introduction of *tert*-butyllithium to the volatile trichlorosilane produced a crust of lithium chloride around the tip of the addition funnel. As this interfered with control of the addition, it was deemed safer to add the trichlorosilane to the *tert*-butyllithium, although the resulting yield (50–54%) was somewhat lower.

(26) For reviews of $Me_2SO$ oxidations see: (a) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247. (b) Butterworth, R. F.; Hanessian, S. *Synthesis* **1971**, 70.

larger scale reactions would be equally efficient. Lewis acid ($MgBr_2$ or $BF_3$·ether) catalyzed Diels–Alder reactions of **27a** with **29** led to the disappearance of the dienophile, but no trace of cycloadduct was found. From the magnesium

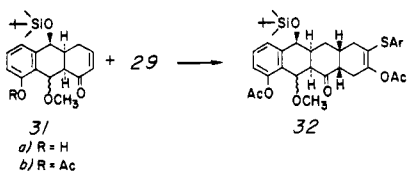


bromide attempt, identification of the major product as the enone **30** demonstrated that the problem was associated with the sensitive acetonide group. Attempts to avoid



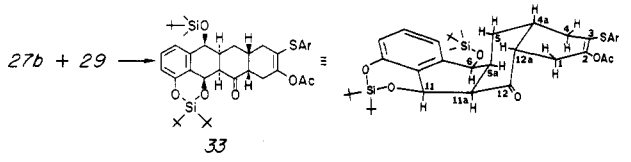
Lewis acids by performing a thermal cycloaddition either with preformed diene or by generating the diene in situ from the precursor cyclobutene also led to decomposition and, in one case, isolation of the elimination product **30**.

Recognizing the lability of the acetonide as the source of the problems, we focused our next attempts on its selective hydrolysis—attempts that were, for the most part, thwarted by the lability of the molecule. At best, methanolysis of **27a** produced **31a**, which was further characterized as its acetate **31b**. While it was not anticipated



that the Diels–Alder adducts of **31** would be of use in the pillaromycinone synthesis, the ability of **31** to participate at all in such a reaction wuld instill confidence in this approach. Grafifyingly, preliminary experiments produced the adduct **32** in nearly quantitative yield at 43–45% conversion using $BF_3$·ether as catalyst.

Armed with the successful Diels–Alder reaction, the alternative dienophile **27b**, whose synthesis was executed at this point as already outlined, was envisioned to resolve the problem by sterically and electronically making the ether oxygen a poorer Lewis base. The survival of the *tert*-butyldimethylsilyl ether in the previous attempts bespeaks to the correctness of this concept. In the presence of 0.05–0.1 equiv of $BF_3$·ether, dienophile **27b** cycloadded with diene **29** at 0 °C in 50–60% yields at 40–50% conversion to give **33**. Stannic chloride gave similar results,

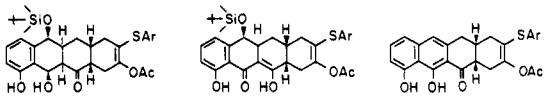


but magnesium bromide failed to catalyze the reaction.

Strikingly, use of 0.06 equiv of boron trichloride at −15 °C to 0 °C produced 83% of the adduct **33** and 4% of starting enone after 3 h.

The regiochemistry of the cycloaddition was assigned by analogy to the reaction of 2-cyclohexen-1-one with **29**.[9] The stereochemistry at C(4a) is based upon the prediction that steric factors will direct the diene to approach the enone from the face syn to the protons at C(4a) and C(9a) of **27b**. The cis fusion of the newly formed ring was suggested by the 6.5-Hz coupling between C(4a) and C(12a). The coupling pattern for C(5a), C(6), C(11), and C(11a) ($J_{5a,6}$ = 4.5 Hz, $J_{5a,11a}$ = 5 Hz, $J_{11,11a}$ = 9.5 Hz) confirms that the stereochemistry around ring C is unaffected.

**Adjustment of the Oxidation Pattern of the Tetracyclic Intermediate.** Rings A and C require modification of their oxidation pattern. Initial attention focused on aromatization of ring C. Attempts to cleave the silylene group with tetra-*n*-butylammonium fluoride were thwarted by dehydration of the product alcohol at C(11). On the other hand, pyridinium hydrofluoride[29] smoothly removed only the silylene group to give **34** in 88% yield after re-



crystallization. This reagent, prepared by adding pyridinium poly(hydrogen fluoride) to pyridine in THF, remained effective after several weeks of storage.

The facile elimination of the C(11) hydroxyl group of **34** also complicated its oxidation. For example, Moffatt-type oxidations led to substantial elimination in addition to varying amounts of the ketone **35**. The optimum reagent proved to be manganese dioxide,[30] whose success depended critically on the choice of solvent. In carbon tetrachloride, ethyl acetate, and acetonitrile the yields were 22–35%, 35%, and 53–57%, respectively. Acetone was optimal, giving **35** in 76% yield. It should be noted that two large an excess of manganese dioxide caused a substantial reduction in yield. The presence of two distinct hydroxyl protons in the NMR spectrum at $\delta$ 11.7 and 15.04 as well as the IR absorption at 1580 and 1610 $cm^{-1}$ suggested the 1,3-diketone existed in the enolic form depicted in **35**. Final aromatization to **36** was effected in nearly quantitative yield by heating a suspension of **35** in 10:1 $HOAc/CF_3CO_2H$ at 95 °C.

The manipulations needed to transform the A ring functionality of **36** into that of pillaromycinone required that the hydroxyl groups and the C(12) carbonyl function be protected. Numerous attempts to do either failed. The stable arrangement of the carbonyl group and the two hydroxyl groups of **36** is the apparent source of this frustration. As a result, we returned our attention to the Diels–Alder adduct **33**.

Since both A and C rings needed to be modified, we initiated the further transformations in ring A. For this purpose, the carbonyl group at C(12) was protected by ketalization with 2,2-dimethyl-1,3-propanediol catalyzed by camphorsulfonic acid to give **37** in 75–80% yield with 20% recovered starting material. Special attention should

(27) While 4-methoxythiophenol is commerically available, it can be conveniently prepared from the more economical 4-methoxybenzenesulfonyl chloride (Morgan, M. S.; Cretcher, L. H. *J. Am. Chem. Soc.* **1948**, *70*, 375) by reduction with zinc and sulfuric acid (Adams, R.; Marvel, C. S. "Org. Syn."; Wiley: New York, 1941; Collect. Vol. 1, p 504). For a list of methods for the preparation of 4-methoxythiophenol, including previous reductions of 4-methoxybenzenesulfonyl chloride see: Szmuskovicz, J. *Org. Prep. Proced. Int.* **1969**, *1*, 43.

(28) Cyclobutanone was obtained by our previously reported method (Trost, B. M.; Vladuchick, W. C. *Synthesis* **1978**, 821) or by oxidation of cyclobutanol (Krumpolc, M.; Rocek, J. *Org. Synth.* **1981**, *60*, 20).

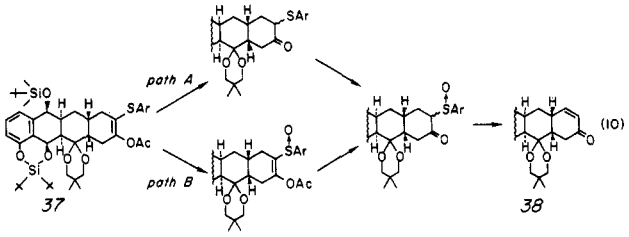
(29) Nicolaou also recently disclosed use of this reagent for cleavage of silyl ethers: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

(30) Fatiadi, A. J. *Synthesis*, **1976**, 67.

(31) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

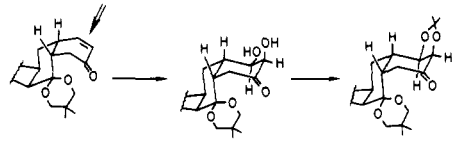
(32) For reviews see: Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453; *Chem. Rev.* **1978**, 363.

be drawn to the stability of the silylene protecting group to these conditions. Releasing the enone moiety in ring A was initially accomplished by unmasking the β-keto sulfide followed by oxidation and elimination to **38**, with dihydropyran as a sulfenic acid trap in the elimination step (eq 10, path A, overall 45–50% yield). Substantial improvement in the yield to 60–74% resulted by inverting the steps, i.e., oxidation to the sulfoxide then cleavage of the enol acetate and elimination (eq 10, path b). The improvement in the yield was attributed to a different ratio of the diasteromeric sulfoxides immediately prior to elimination. Four such diastereomers which vary in the chirality at C(3) and S exist. Previous reports also noted a dependence of the elimination on such stereochemical features.[33] The molecule is now primed for the elaboration of the A ring.

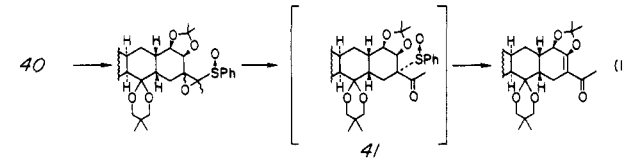


(10)

**Elaboration of Ring A.** The enone functionality of ring A possesses the reactivity for the introduction of the cis vicinal diol and acetyl groups. The stereochemistry of the diol should follow from the cis fusion of the AB rings which directs approach of reagents to the β face. Osmium tetraoxide in pyridine generated a single diol. Consistent yields were obtained only by adding THF as a cosolvent prior to the cleavage of the osmate ester. NMR spectroscopy in $C_6D_6$ with added $D_2O$ to remove the couplings to the hydroxyl protons reveals the protons at C(3) and C(4) at δ 4.11 and 4.32 as a d ($J$ = 4 Hz) and dd ($J$ = 11, 4 Hz). The 11-Hz coupling between C(4) and C(4a) indicates a diaxial relationship between the respective protons. The crude diol was directly converted to the acetonide **40** in an overall yield of 72% from **38**.

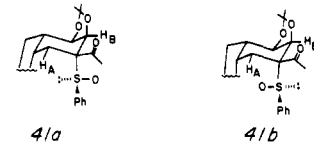



Acylative elimination to convert the ketone of **40** to an α,β-unsaturated acetyl grouping proved more elusive than expected. Methods based upon 1-ethoxyvinyllithium,[34] 1-chloroethyl phenyl sulfoxide,[35] and 2-(diethylphosphono)propionitrile[36] failed. It is interesting to note that the failure of the 1-chloroethyl phenyl sulfoxide approach resides in the chemoselectivity of the elimination as shown in eq 11. This result is most surprising since the sulfoxide elimination normally shows a propensity to generate the olefin distal from an electron-withdrawing group such as an oxygen.[31,32] Conformational distortions

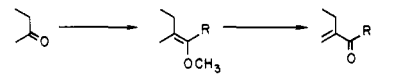


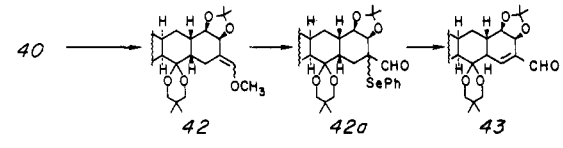
(11)

of ring A due to 1,3-diaxial interactions between the sulfoxide and ring B may make the C–$H_A$ bond overlap more poorly with the cleaving C–S bond in generating the olefin than the C–$H_B$ bond (e.g., structures **41a** and **41**). Alternately, the stereochemistry of the sulfoxide may play a role. The configuration depicted in **41a** would disfavor abstraction of $H_a$ since the phenyl group must be forced under the cyclohexyl ring—a feature that is absent in the epimer depicted in **41b**. To the extent the sulfoxide possessed the stereochemistry depicted in **41a** elimination to the enol ether as depicted in eq 11 would be preferred.



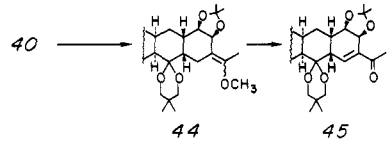

A sequence based upon the oxidation of an enol ether as outlined in eq 12 offers a number of approaches for introduction of the double bond. For example, the enol ether **42** reacts with benzeneselenenyl chloride in $CH_2Cl_2$ containing potassium carbonate[37] to give **42a**, which upon oxidation with MCPBA gave the desired α,β-unsaturated aldehyde **43** (eq 13). It is striking to note the selectivity of the elimination of **42a** in contrast to that of **41** which must be due to a difference in stereochemistry of the sulfur and selenium groups.


(12)



(13)

While it should be possible to convert **43** into the desired methyl ketone, a more direct approach involved the enol ether **44**. Literature reports discouraged the use of the ylide from (1-methoxyethyl)triphenylphosphonium chloride or the anion of (1-methoxyethyl)diphenylphosphine oxide for olefination of ketones. Nevertheless, use of the anion of this phosphine oxide **46** at −100 °C produces the desired enol ether **44** in 66% yield as a 2:1 mixture of olefin isomers which have been separated. However, since this stereochemistry is lost in the next step, the mixture was normally directly carried on. The previous reported failure may be traced to impurities in the phosphine oxide that promote enolization of ketones. In our hands, **46** is a sharp melting crystalline solid (mp 77–78 °C), whereas previously




(33) For leading references see ref 32. Also see: Isobe, M.; Iio, H.; Kitamura, M.; Goto, T. *Chem. Lett.* **1978**, 541; Confalone, P. N.; Kulesha, I. D.; Uskokovic, M. R. *J. Org. Chem.* **1981**, *46*, 1030.

(34) Schöllkopf, U.; Hänssle, P. *Justus Liebigs Ann. Chem.* **1972**, *763*, 208; Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

(35) Taber, D. F.; Bunn, B. P. *J. Org. Chem.* **1979**, *44*, 450; Reutrakul, V.; Kanghae, W. *Tetrahedron Lett.* **1977**, 1377.

(36) Raggio, M. L.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 1873; Wroble, R. R.; Watt, D. S. *Ibid.* **1976**, *41*, 2939.

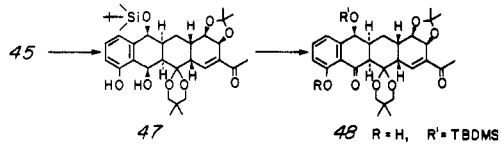
(37) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J. *Synthesis* **1979**, 982; Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404.

(38) Coulson, D. R. *Tetrahedron Lett.* **1964**, 3323.

no mention is made of its being crystalline.[39,40] The general feeling that enolization at the expense of carbonyl addition for many nucleophiles—especially for ylides and their close relatives—resides in the intrinsic reactivity of the reagents may be less valid than supposed. Adventitious alkoxide impurities may be a major culprit. The purity of the phosphine oxide utilized in our reactions then may account for its success.

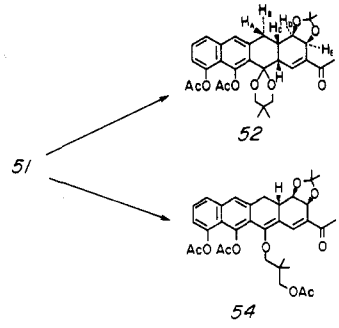
Unfortunately, reaction of **44** with benzeneselenenyl chloride did not produce the α-phenylselenenyl ketone. An alternate/sequence utilized the ene reaction of enol ethers with singlet oxygen.[41] Irradiation of a mixture of **44** and oxygen in the presence of methylene blue as sensitizer followed by in situ reduction of the hydroperoxide by triphenylphosphine gave the requisite enone **45** in 53% yield. The location of the olefinic bond in the A ring is supported by the presence of three doublets at δ 5.25, 4.95, and 4.67 as well as a doublet of doublets at δ 4.61 ($J$ = 11 and 5.5 Hz) for the C(4) proton. The C(1) vinyl proton appears as a doublet ($J$ = 5 Hz) at δ 7.58. At this point, the A ring lacks only the 12a-hydroxyl group.

**Pentaacetate of 12a-Deoxypillaromycinone.** Aromatization of ring C followed the general path previously outlined. Deblocking of the silylene group to diol **47** proceeded selectively—highlighting the utility of the di-*tert*-butylsilylene group. Oxidation of the benzylic alcohol

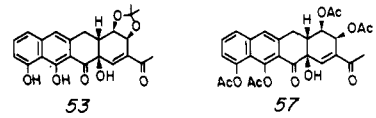



with limited quantities of $MnO_2$ in acetone gave routinely 90–93% yields (based upon recovered starting material) of the ketone **48**. For subsequent elimination of the C(12) alcohol, the phenolic hydroxyl group was best acetylated (98%). The base liability of **49** dictated the use of benzoic acid in conjunction with tetrabutylammonium fluoride to give **50** (97%), which was quantitatively mesylated to give **51**.

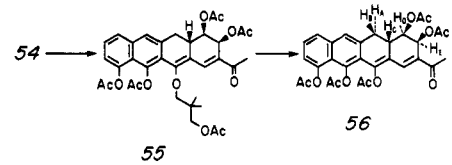
Tetra-*n*-butylammonium oxalate in the presence of lutidine[42] smoothly aromatized ring C without affecting either ketal to give **52** after acetylation. Its NMR spectrum




revealed absorptions for the aromatic and vinyl protons at δ 7.59 (d, $J$ = 6.5 Hz, 1 H), 7.43 (s, 1 H), 7.40 (t, $J$ = 6.5 Hz, 1 H), 7.04 (d, $J$ = 6.5 Hz, 1 H), and 6.71 (s, 1 H), singlets for the methyl groups of the acetates and methyl ketone at δ 2.13, 2.39, and 2.42, singlets for the saturated methyl groups at δ 0.89 (3 H), 1.40 (3 H), and 1.45 (6 H), and the normal absorptions for the $CH_2O$ grouping of the ketal. Most importantly, the spin system for $H_a$–$H_f$ is readily revealed—δ 5.13 (d, $J$ = 6 Hz, $H_e$), 4.46 (dd, $J$ = 6, 3 Hz, $H_d$), 4.00 (bd, $J$ = 3 Hz, $H_f$), 3.16 (t, $J$ = 10 Hz, $H_b$), 2.93 (m, $H_c$), and 2.51 (d, $J$ = 10 Hz, $H_a$). This pattern is in remarkably good agreement for the corresponding absorptions of the acetonide of pillaromycinone, **53**. On




the other hand, employing a stronger base, DBU, in conjunction with tetra-*n*-butylammonium oxalate initiated cleavage of the C(6) ketal concomitant with aromatization. The initial product was best characterized as its triacetate. Final deblocking involved first removal of the acetonide with camphorsulfonic acid and acetylation to give **55**. Hydrolysis of the enol ether with aqueous acetic acid in the presence of NBS followed by acetylation gave the pentaacetate of 12a-deoxypillaromycinone **56**. The sen-




sitivity of the free alcohol corresponding to **56** prevented its isolation. On the other hand, the pentaacetate is a sharp melting, mp 211–212 °C, yellow crystalline solid. It shows an intense molecular ion peak at $m/e$ 564.1633 (calcd 564.1631). Its NMR spectrum in $CDCl_3$ shows the aromatic and vinyl proton absorptions at δ 7.11 (d, $J$ = 8 Hz, 1 H), 7.48 (t, $J$ = 8 Hz, 1 H), 7.60 (s, 1 H), 7.64 (s, 1 H), and 7.67 (d, $J$ = 8 Hz, 1 H) and the singlets for the methyl groups of the acetates and methyl ketone at δ 2.02 (3 H), 2.13 (3 H), 2.38 (6 H), and 2.42 (6 H). Shifting to $C_6D_6$ fully resllved the protons on saturated carbon to a first-order spectrum—δ 2.56 (t, $J$ = 14.5 Hz, $H_a$), 2.87 (dd, $J$ = 14.5 and 5 Hz, $H_b$), 3.11 (ddd, $J$ = 14.5, 12, and M 5 Hz, $H_c$), 5.01 (dd, $J$ = 12 and 3 Hz, $H_d$), and 6.60 (d, $J$ = 3 Hz, $H_e$). Comparison of these data to that for the tetraacetate of pillaromycinone reveals a surprisingly good match.

## Discussion

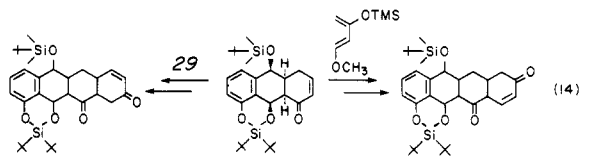
The synthesis of the pentaacetate of pillaromycinone validates the general synthetic strategy adopted herein. Most importantly, the juxtaposition of functionality in **15** and **38** offer great flexibility to divert these compounds into several families of linear tetracyclic natural products. The success of the Diels–Alder reaction between the sulfur-substituted diene **29** and cyclohexenone **27b** unambiguously demonstrates the excellent reactivity profile of this diene and its use in synthesis. This dienophile not only represents one of the least reactive types (i.e., a cyclohexenone) but it bears an oxygen substituent that is both benzylic and β to the carbonyl group—a prime opportunity for elimination to supercede the desired cycloaddition. Nevertheless, cycloaddition proceeds in 83% yield! The oxidation pattern available from **29** complements that which would derive from the Danishefsky diene (see eq 14).[43]

(39) (a) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099. (b) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, 314. (c) For related results see: Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.

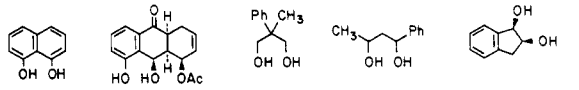
(40) A recent report also records **46** as a solid but mp 60–62 °C. Maleki, M.; Miller, A.; Lever, D. W. *Tetrahedron Lett.* **1981**, *22*, 365.

(41) Rousseau, G.; Le Perchec, P.; Conia, J. M. *Synthesis* **1978**, *67*; Neef, G.; Eder, U.; Seeger, A.; Wiechert, R. *Chem. Ber.* **1980**, *113*, 1184; Asveld, E. W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1980**, ,02, 3644.

(42) Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.




The development of the silylene protecting group also holds promise as a useful alternative to the more common ketals and acetals. A range of diols have been examined, as **58–62** illustrate. It is noteworthy that hydroxylamine



**58** **59** **60** **61** **62**

type group transfer reagents (*N*-hydroxysuccinimide and 1-hydroxybenzotriazole) are more effective than the nitrogen counterparts (imidazole, DMAP)—a feature that may be more general for silylations. The order of reactivity in forming the silyl derivatives roughly decreases from **58** (most reactive) to **62** (least reactive). Six-membered rings form more rapidly than five. Phenolic hydroxyl groups derivatize more rapidly than hydroxyl groups bound to saturated carbon, and primary alcohols participate more efficiently than secondary ones.

The properties exhibited by the di-*tert*-butylsilylene derivatives are attractive. While the isopropylidene derivative **15a** was only sparingly soluble in THF at temperatures below 25 °C, solutions of the silicon protected compound **15b** were much more readily obtained. Although the solubility in most ether and hydrocarbon solvents was very good for the simple derivatives, recrystallization from warm acetonitrile provided an efficient purification for a number of these compounds. Stability toward chromatography and a wide range of reaction conditions proved excellent. The mildness of the reaction for the removal of the di-*tert*-butylsilylene group is also to be noted. Ketals, enones, and even *tert*-butyldimethylsilyl ethers resist the hydrolysis conditions necessary to cleave this cyclic derivative.

The strategy that emanates from this methodology offers great flexibility to proceed into several families—most notably the tetracycline antibiotics and aklavinones in addition to pillaromycin. For example, **15** easily permits selective addition of the methyl group of tetracycline **4** and the A ring functionality of **38** permits ready elaboration of the A ring of **4** by routes analogous to those developed herein. The availability of such synthetic divergence through the use of bifunctional sulfur-substituted dienes represents a great strength of these new conjunctive reagents.

## Experimental Section

**General Procedures.** All reactions were run under a positive pressure of dry nitrogen unless otherwise noted. Infrared (IR) spectra were obtained from 1–5% solutions in the indicated solvent on a Beckman Acculab 7 or a Perkin-Elmer 267 spectrophotometer and are reported in $cm^{-1}$. Spectra bear a calibration mark at 1601 $cm^{-1}$ obtained from polystyrene film. Ultraviolet (UV) spectra were obtained from solutions in the indicated solvent by using a Cary Model 118 spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were determined in the indicated solvent on a JEOLCO MH-100 (100 MHz) or a Bruker WH270 (270 MHz) instrument; chemical shifts are reported in ppm downfield from tetramethylsilane. Splitting patterns are designated as s (single), d (doublet), t (triplet), q (quartet), and m (multiplet); addition of b indicates a broadened pattern. Coupling constants are given in Hz. $^{13}C$ nuclear magnetic resonance ($^{13}C$ NMR) spectra were determined on a JEOLCO FX-60 (15.1 MHz) instrument; chemical shifts are reported in ppm downfield from tetramethylsilane. Mass spectra were recorded on an AEI-MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 mA unless otherwise specified. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. Preparative layer chromatography plates were prepared as a 1.5-mm thick layer of Macherey-Nagel silica gel $P/UV_{254}$ (distributed by Brinkmann Instruments) and activated at 140 °C for 2 h. Thin layer chromatography (TLC) plates were prepared by coating this silica gel on glass slides or were purchased as a coated plastic sheet (E. Merck silica gel 60 F-254). Eluting solvents are indicated in the text. Removal of material from silica gel was accomplished by successive washings with ethyl acetate or ether. Preparative high-pressure liquid chromatography (HPLC) was accomplished by using a Waters Associates Prep LC-System 500 A with the solvent mixture indicated. Column chromatography was performed on Grace silica gel, grade 62, mesh 60–200 (Davison Chemical).

In experiments requiring dry solvents, tetrahydrofuran (THF), ether, dimethoxyethane (DME), benzene, and toluene were distilled from sodium benzophenone ketyl. In the cases of benzene and toluene, 1–5% tetraglyme was added to the ketyl. Methylene chloride, acetonitrile, triethylamine, diisopropylamine, pyridine, *N,N*-dimethylformamide (DMF), hexamethylphosphoramide (HMPA), and dimethyl sulfoxide ($Me_2SO$) were distilled from calcium hydride, with the distillations of DMF, HMPA, and $Me_2SO$ carried out at reduced pressure. Methanol and ethanol were distilled from suspensions of their respective magnesium alkoxides. Acetic anhydride was fractionally distilled through a 2.5 × 45 cm Vigreaux column. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen. The term "in vacuo" refers to removal of solvents on a rotary evaporator (water aspirator pressure) followed by a period of at least 2 h at 0.02–0.5 mm pressure.

**Catalyzed Reaction of Juglone with (*E*)-1-Acetoxy-1,3-butadiene.** To a solution of juglone[44] (50 mg, 0.29 mmol), 1 mg of methylene blue, and 200 μL (190 mg, 1.7 mmol) of (*E*)-1-acetoxy-1,3-butadiene[45] in 2.4 mL of benzene was added 4 mg (3.5 mL, 0.03 mmol) of boron trifluoride etherate. The solution was stirred for 15 min at ambient temperature, quenched by addition of 0.5 mL of methanol, poured into 25 mL of chloroform, and washed with 25 mL of saturated aqueous chloride. The aqueous layer was extracted with 25 mL of chloroform, and the combined organic layers were washed with 25 mL of saturated aqueous sodium bicarbonate and 25 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo to yield 85 mg of a pale yellow oil which crystallized upon standing. The 100-MHz NMR spectrum ($CDCl_3$) of this material with added $Eu(fod)_3$ showed the acetate singlet for 8-hydroxy-1-acetoxy-1(*R**),4,4a(*S**),9a(*S**)-tetrahydroanthraquinone with less than 5% of its regioisomer detectable.

In a preparative experiment, juglone (20.0 g, 115 mmol) and (*E*)-1-acetoxy-1,3-butadiene (19.0 g, 170 mmol) were dissolved in 200 mL of chloroform at 25 °C. Boron trifluoride etherate (0.60 mL, 0.69 g, 4.9 mmol) was added via syringe to the stirred reaction, which became exothermic and warmed to 50 °C. The reaction was stirred an additional 15 min at 50 °C before being cooled to 25 °C by an ice bath. The solution was washed with 2 × 150 mL of 5% aqueous sodium chloride, 2 × 150 mL of saturated aqueous sodium bicarbonate, and 150 mL of 5% aqueous sodium chloride and dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo, the combined crude product from this reaction and two additional runs (starting from a total of 50.0 g (287 mmol) of juglone) was dissolved in 400 mL of warm ethyl acetate and the solution was cooled slowly to 0 °C. This yielded 54.3 g of pale yellow needles, mp 131–132 °C (lit.[14] mp 132–133 °C). The

(43) For an interesting demonstration of this complementarity see: Danishefsky, S.; Kahn, S. *Tetrahedron Lett.* **1981**, *22*, 489.

(44) Willstätter, R.; Wheeler, A. S. *Chem. Ber.* **1914**, *47*, 2798; Fieser, L. F., Dunn, J. T. *J. Am. Chem. Soc.* **1937**, *59*, 1016.

(45) Hagemeyer, H. J.; Hull, D. C. *Ind. Eng. Chem.* **1949**, *41*, 2920.

mother liquor was concentrated in vacuo to a volume of 125 mL, warmed to dissolve the solid, and cooled slowly to 0 °C to deposit 11.2 g of yellow needles, mp 131–132 °C. A third crop, 6.1 g, mp 130–132 °C, was similarly obtained by concentrating the mother liquor to a volume of 80 mL. The total yield of adduct **12** was 71.6 g (87%). IR ($CHCl_3$) 1740, 1705, 1640, 1605, 1575, 1450, 1365, 1325; NMR (100 MHz, $CDCl_3$) δ 7.80–7.52 (2 H, m), 7.26 (1 H, dd, $J$ = 8, 2 Hz), 6.24–5.84 (2 H, m), 5.56–5.24 (1 H, m), 3.56–3.36 (2 H, m), 3.28 (1 H, bdd, $J$ = 19, 4 Hz), 2.24 (1 H, dm, $J$ = 19 Hz), 1.38 (3 H, s); UV (EtOH) 230 (19000), 348 (4800); $^{13}$CMR ($CDCl_3$) δ 202.90, 194.61, 168.95, 161.57, 137.06, 136.72, 131.74, 122.82, 118.43, 117.11, 65.79, 50.70, 50.30, 42.21, 21.89, 19.83; MS, $m/e$ (%) 286 (5), 226 (71), 197 (22), 175 (43), 149 (24), 148 (18), 121 (50), 120 (100), 105 (18); calcd for $C_{16}H_{14}O_5$, 286.0841; found, 286.0847.

**Preparation of 8,9-Dihydroxy-1-acetoxy-10-oxo-1-(*R**),4,4a(*S**),9(*R**),9a(*R**),10-hexahydroanthracene (14).** The adduct **12** (10.0 g, 34.9 mmol) was dissolved in a solution of 168 g (194 mL) of toluene and 85 g (107 mL) of methanol. After the resulting solution had been cooled to 5 °C, sodium borohydride (1.4 g, 37 mmol) was added in portions over 5 min. A salted ice bath was used to keep the reaction temperature below 10 °C. The solution was stirred for 7 min after completion of the addition and was then cautiously poured into a separatory funnel containing 500 mL of aqueous 0.35 N sodium bisulfate and 100 mL of ethyl acetate. The aqueous layer was separated and extracted with 2 × 100 mL of ethyl acetate. The combined organic layers were washed with 2 × 100 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave 9.64 g (95%) of **14** as pale tan crystals, mp 167–172 °C (lit.[14,16a] mp 174–175 °C, 175–173 °C). This material was estimated to be of ~95% purity (as determined by NMR and TLC) and was generally used without purification. Recrystallization from ether or toluene, accompanied by some decomposition, produced colorless crystals of mp 172–173 °C. IR ($CHCl_3$) 3440–3120, 1700, 1600, 1580, 1455, 1420, 1360; NMR (100 MHz, $CDCl_3$) δ 9.06 (1 H, s, exchanges with $D_2O$), 7.60 (1 H, dd, $J$ = 7, 2 Hz), 7.28 (1 H, t, $J$ = 7 Hz), 7.08 (1 H, dd, $J$ = 7, 2 Hz), 6.28–6.06 (1 H, m), 5.86–5.38 (3 H, m), 3.32 (1 H, dd, $J$ = 19, 4 Hz), 3.08–2.82 (2 H, m), 2.24 (1 H, dm, $J$ = 19 Hz), 1.24 (3 H, s); UV (EtOH) 224 (11,000), 257 (6000), 313 (2100); MS, $m/e$ (%) 289 (2), 288 (13), 228 (34), 211 (11), 210 (21), 181 (15), 150 (100), 121 (21); calcd for $C_{16}H_{16}O_5$, 288.0998; found, 288.1020.

**Preparation of 1-Acetoxy-8,9-(isopropylidenedioxy)-10-oxo-1(*R**),4,4a(*S**),9(*R**),9a(*R**),10-hexahydroanthracene (15a).** The crude sodium borohydride reduction product **14** (9.14 g, 31.7 mmol) was dissolved in 250 mL of dry DMF and 30 mL (25 g, 240 mmol) of 2,2-dimethoxypropane was added followed by 200 mg (1.05 mmol) *p*-toluenesulfonic acid monohydrate. After stirring for 24 h at ambient temperature, the reaction was seeded with **15a** from a previous preparation, resulting in precipitation of the product as white crystals. Additional precipitate formed as stirring was continued for another 24 h. The solvent was then removed on a rotary evaporator at reduced pressure (~1 mm) and temperatures below 25 °C. The residue was taken up in 300 mL of methylene chloride and washed with 3 × 50 mL of saturated aqueous sodium bicarbonate and 2 × 75 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Recrystallization from 100 mL of warm THF cooled to −10 °C gave 7.19 g (69%) of **15a** as white needles, mp 212–213 °C (lit.[16b] mp 206–207 °C). Concentration of the mother liquor in vacuo to a volume of 30 mL and cooling to −10 °C gave an additional 740 mg (7%) of **15a** as white needles, mp 212–213 °C, for a total yield of 76%. IR ($CHCl_3$) 2850, 1730, 1685, 1600, 1585, 1465, 1380, 1370; NMR (270 MHz, $CDCl_3$) δ 7.58 (1 H, d, $J$ = 8 Hz), 7.22 (1 H, t, $J$ = 8 Hz), 6.95 (1 H, d, $J$ = 8 Hz), 5.96 (1 H, ddd, $J$ = 11, 6, 3 Hz), 5.65 (1 H, dm, $J$ = 11 Hz), 5.54 (1 H, bt, $J$ = 4 Hz), 5.42 (1 H, d, $J$ = 5 Hz), 3.30 (1 H, dd, $J$ = 19, 5 Hz), 5.42 (1 H, d, $J$ = 5 Hz), 3.30 (1 H, dd, $J$ = 19, 5 Hz), 3.09–2.92 (2 H, m), 2.24 (1 H, dm, $J$ = 19 Hz), 1.61 (3 H, s), 1.58 (3 H, s), 1.18 (3 H, s); UV (EtOH) 227 (12,000), 262 (6400), 315 (2200); MS, $m/e$ (%) 329 (2), 328 (11), 270 (24), 228 (53), 210 (68), 199 (21), 181 (15), 159 (25), 150 (22); calcd for $C_{19}H_{20}O_5$, 328.1311; found, 328.1320.

**Preparation of 10-Hydroxy-1-acetoxy-8,9-(isopropylidenedioxy)-1(*R**),4,4a(*S**),9(*R**),9a(*R**),10(*S**)-hexahydroanthracene (16a).** The ketone **15a** (2.01 g, 6.12 mmol) was dissolved in 100 mL of dry THF and stirred at 25 °C as 12.0 mL of 0.93 M lithium borohydride (11.2 mmol) in THF was added via syringe. The resulting solution was stirred for 36 h and was then poured into 100 mL of 2 N aqueous ammonium chloride and 100 mL of methylene chloride. The aqueous layer was extracted with 100 mL of methylene chloride and the combined organic layers were washed with 50 mL of saturated aqueous sodium bicarbonate followed by 2 × 75 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield the crude product as a colorless oil. Preparative layer chromatography, eluting with 3% acetone in chloroform, gave 0.23 g (11%) of the starting ketone **15a** ($R_f$ 0.5) and 1.46 g (72%) of alcohol **16a** ($R_f$ 0.4) as white crystals, mp 124–125 °C. IR ($CHCl_3$) 3600–3420, 1740, 1590, 1375; NMR (270 MHz, $CDCl_3$) δ 7.16 (1 H, td, $J$ = 8, 1 Hz), 7.08 (1 H, d, $J$ = 8 Hz), 6.69 (1 H, dd, $J$ = 8, 1 Hz), 6.21–6.11 (1 H, m), 5.75–5.66 (2 H, m), 4.99 (1 H, d, $J$ = 6 Hz), 4.64 (1 H, dd, $J$ = 12, 4, collapses to d, $J$ = 4 Hz upon addition of $D_2O$), 2.78 (1 H, d, $J$ = 12 Hz, exchanges with $D_2O$), 2.64–2.45 (4 H, m), 1.57 (3 H, s), 1.55 (3 H, s), 1.26 (3 H, s); $^{13}$CMR ($CDCl_3$) δ 168.38 (s), 149.69 (s), 138.37 (s), 134.09 (d), 127.91 (d), 123.00 (d), 121.06 (d), 118.77 (s), 114.82 (d), 100.53 (s), 69.10 (d), 66.36 (d), 63.44 (d), 36.06 (d), 32.46 (d), 28.41 (q), 27.72 (t), 23.49 (q), 19.83 (q); UV (EtOH) 221 (4200), 277 (1200), 286 (1000); MS, $m/e$ (%) 330 (4), 272 (18), 212 (74), 211 (21), 195 (24), 194 (37), 183 (18), 161 (20), 160 (23); calcd for $C_{19}H_{22}O_5$, 330.1467; found, 330.1470.

**Preparation of 1-Acetoxy-10-(*tert*-butyldimethylsiloxy)-8,9-(isopropylidenedioxy)-1(*R**),4,4a(*S**),9(*R**),9a-(*R**),10(*S**)-hexahydroanthracene (17a).** The alcohol **16a** (1.26 g, 3.82 mmol) and imidazole (1.62 g, 23.8 mmol) were dissolved in 6.0 mL of dry DMF and 1.70 g (11.3 mmol) of *tert*-butyldimethylchlorosilane was added. The mixture was stirred 36 h at 50–55 °C (bath temperature) and was then cooled to 25 °C. The reaction was poured into 150 mL of hexane and washed with 3 × 50 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield a pale yellow oil which slowly crystallized. Preparative layer chromatography (25% ether in hexane) gave 1.30 g (77%) of silyl ether **17a** as a colorless oil ($R_f$ 0.45) which crystallized upon standing. Recrystallization of a portion of this material from hexane gave a sample of mp 121–123 °C. IR ($CCl_4$) 1730, 1600, 1465, 1375; NMR (270 MHz, $CDCl_3$) δ 7.17 (1 H, t, $J$ = 8 Hz), 7.01 (1 H, d, $J$ = 8 Hz), 6.68 (1 H, d, $J$ = 8 Hz), 5.96 (1 H, ddd, $J$ = 10, 6, 3 Hz), 5.85 (1 H, ddd, $J$ = 10, 5, 3 Hz), 5.55 (1 H, t, $J$ = 5 Hz), 4.87 (1 H, d, $J$ = 6 Hz), 4.76 (1 H, d, $J$ = 7.5 Hz), 2.75 (1 H, td, $J$ = 7.5, 5 Hz), 2.56–2.42 (1 H, m), 2.21 (1 H, dt, $J$ = 16.5, 6 Hz), 1.71 (3 H, s), 1.65 (1 H, dm, $J$ = 16.5 Hz), 1.54 (3 H, s), 1.42 (3 H, s), 0.98 (9 H, s), 0.09 (3 H, s), 0.08 (3 H, s); UV (EtOH) 220 (7000), 273 (1900), 278 (1900); MS, $m/e$ (%) 386 (3), 269 (12), 196 (12), 195 (63), 194 (88), 167 (11), 166 (14), 165 (12), 129 (11), 117 (17). Anal. Calcd for $C_{25}H_{36}O_5Si$: C, 67.53; H, 8.16. Found: C, 67.67; H, 8.15.

**Preparation of 1-Hydroxy-10-(*tert*-butyldimethylsiloxy)-8,9-(isopropylidenedioxy)-1(*R**),4,4a(*S**),9(*R**),9a-(*S**),10(*S**)-hexahydroanthracene (26a).** To the allylic acetate **17a** (925 mg, 2.08 mmol) in 50 mL of dry toluene at −78 °C was added dropwise 2.66 mmol of diisobutylaluminum hydride as a hexane solution (2.9 mL, 0.88 M). After stirring 10 min at −78 °C, the reaction was quenched with 0.5 mL of methanol and poured into 100 mL of ether. Saturated aqueous sodium sulfate (20 mL) was added and the mixture was stirred rapidly for 5 min. The ether was decanted and the aqueous layer was stirred vigorously with an additional 50 mL of ether for 5 min. The combined ether layers were washed with 4 × 30 mL of water, dried over anhydrous sodium sulfate, and evaporated in vacuo to yield pale cream-colored crystals. Preparative layer chromatography gave 605 mg (72%) of the allylic alcohol **26a** as white crystals ($R_f$ 0.3, 30% ether in hexane). Recrystallization from hexane gave needles, mp 119–120 °C. IR ($CCl_4$) 3550, 3450, 1590, 1460, 1385, 1375; NMR (100 MHz, $CDCl_3$) δ 7.12 (1 H, t, $J$ = 8 Hz), 6.92 (1 H, d, $J$ = 8 Hz), 6.72 (1 H, d, $J$ = 8 Hz), 5.96–5.44 (2 H, m), 4.96 (1 H, d, $J$ = 8 Hz), 4.76 (1 H, d, $J$ = 4 Hz), 4.56–4.24 (1 H, m), 3.38 (1 H, d, $J$ = 12 Hz; exchanges with $D_2O$), 2.76–2.48 (1 H, m), 2.44–1.76 (3 H, m), 1.58 (3 H, s), 1.44 (3 H, s), 0.88 (9 H, s), 0.22

(3 H, s), 0.18 (3 H, s); MS, *m/e* (%) 287 (3), 217 (7) 195 (21), 129 (6). Anal. Calcd for $C_{23}H_{34}O_4Si$: C, 68.61; H, 8.51. Found: C, 68.56; H, 8.50.

**Preparation of 10-(*tert*-Butyldimethylsiloxy)-8,9-(isopropylidenedioxy)-1-oxo-1,4,4a(*S**),9(*R**),9a(*R**),10(*S**)-hexahydroanthracene (27a).** The allylic alcohol **26a** (458 mg, 1.14 mmol) was dissolved in 12 mL of dry $Me_2SO$ and 4.0 mL of acetic anhydride was added. After stirring at 25 °C for 7 h, the solution was poured into a separatory funnel containing 150 mL of hexane. This mixture was washed with 50 mL of water, 3 × 30 mL of saturated aqueous sodium bicarbonate, and 3 × 30 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to leave 448 mg of pale yellow oil. This was crystallized from 4 mL of hexane to give 374 mg of white crystals having a faint sulfide odor. Recrystallization from 1.0 mL of warm hexane cooled to −10 °C gave 352 mg (77% yield) of ketone **27a** as odorless white crystals, mp 106–107 °C. IR ($CCl_4$) 2870, 1680, 1460; NMR (270 MHz, $CDCl_3$) δ 7.24 (1 H, t, *J* = 7 Hz), 7.08 (1 H, d, *J* = 7 Hz), 6.85 (1 H, bdd, *J* = 11, 7 Hz), 6.75 (1 H, d, *J* = 7 Hz), 6.00 (1 H, dd, *J* = 11, 3 Hz), 4.83 (1 H, d, *J* = 9 Hz), 4.80 (1 H, d, *J* = 3 Hz), 3.17 (1 H, dd, *J* = 9, 4 Hz), 2.76–2.62 (1 H, m), 2.25 (1 H, dt, *J* = 20, 5 Hz), 1.76 (1 H, ddt, *J* = 20, 12, 3 Hz), 1.52 (3 H, s), 1.29 (3 H, s), 1.00 (3 H, s), 0.22 (3 H, s), 0.18 (3 H, s); MS, *m/e* (%) 400 (0.1, 342 (11), 286 (24), 285 (99), 267 (23), 251 (17), 217 (37), 211 (14), 210 (55), 201 (16), 200 (24), 182 (13), 143 (13), 115 (15). Anal. Calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05; $M_r$, 400.2070. Found: C, 68.85; H, 8.07; $M_r$, 400.2080.

**Preparation of 8,9-(Phenylborylenedioxy)-1-acetoxy-10-oxo-1(*R**),4,4a(*S**),9(*R**),9a(*R**),10-hexahydroanthracene (20).** Phenylboric acid (212 mg, 1.74 mmol) and the dihydroxy compound **14**, dissolved in 5.0 mL of dry acetone (stirred over potassium carbonate, then distilled), were stirred 3 h at 25 °C. The acetone was then removed on a rotary evaporator at aspirator pressure and the residue was warmed to 70 °C with 20 mL of hexane. The solution was decanted for a small amount of insoluble material, seeded with **20** from a previous preparation, and allowed to cool to 25 °C. The resulting white fluffy needles were separated by filtration and dried in vacuo to give 425 mg (65%) of borate ester **20**, mp 116 °C. IR ($CCl_4$) 1740, 1700, 1605, 1595, 1470, 1440, 1385, 1370, 1350, 1320; NMR (270 MHz, $CDCl_3$): δ 8.01 (2 H, dd, *J* = 8, 1.5 Hz), 7.78 (1 H, dd, *J* = 7.5, 1.5 Hz), 7.57–7.28 (5 H, m), 6.02 (1 H, ddd, *J* = 10, 5, 2.5 Hz), 5.88–5.81 (1 H, m), 5.79 (1 H, d, *J* = 6 Hz), 5.65 (1 H, t, *J* = 4.5 Hz), 3.34 (1 H, ddt, *J* = 19, 5, 1.5 Hz), 3.26 (1 H, ddd, *J* = 6, 5, 4 Hz), 3.02 (1 H, dd, *J* = 7, 5 Hz), 2.30 (1 H, ddm, *J* = 19, 7.5 Hz), 1.13 (3 H, s); MS, *m/e* (%) 331 (1), 315 (2), 314 (6), 313 (3), 312 (2), 237 (12), 236 (88), 235 (15), 209 (11), 208 (100), 207 (19). Anal. Calcd for $C_{22}H_{19}O_5B$: C, 70.61; H, 5.12. Found: C, 70.46; H, 5.13.

**Preparation of Di-*tert*-butyldichlorosilane.** Di-*tert*-butylchlorosilane[25] (80.1 g, 448 mmol) was dissolved in 400 mL of carbon tetrachloride in a 1-L flask fitted with a fritted gas dispersion tube and a reflux condenser. The solution was cooled to 5 °C by an ice bath and chlorine gas was introduced at such a rate as to maintain the temperature at 8–10 °C. (The flask was shaded from room lights, but was not in darkness.) When the temperature began to drop and the chlorine color persisted, an aliquot was removed. NMR showed disappearance of the starting material singlets at δ 4.22 and 1.08. The solution was allowed to warm to 25 °C as it was purged with dry nitrogen until colorless. The solution was concentrated by distillation through a 2.5 × 45 cm Vigreaux column. The residue was distilled through a 1 × 10 cm Vigreaux column to yield 82.6 g (86%) of di-*tert*-butyldichlorosilane as a colorless liquid, bp 85–90 °C (20 mm) (lit.[24a] bp 190 °C (729 mm)). NMR (100 MHz, $CDCl_3$) δ 1.17 (s).

**Preparation of 1-Acetoxy-8,9-(di-*tert*-butylsilylenedioxy)-10-oxo-1(*R**),4,4a(*S**),9(*R**),9a(*S**),10-hexahydroanthracene (15b).** 1-Hydroxybenzotriazole hydrate (546 mg, 4.0 mmol) was dried overnight at 0.5 mm and 25 °C. The resulting 502 mg of material was dissolved in 56 mL of dry acetonitrile with 11.50 g (39.9 mmol) of the dihydroxy compound **14**. Triethylamine (28 mL, 20 g, 200 mmol) was added via syringe followed by 9.3 g (44 mmol) of di-*tert*-butyldichlorosilane. The solution was warmed in a 65 °C oil bath, with a white precipitate forming within 10 min. After a total of 30 min at 65 °C, the mixture was cooled to 25 °C, poured into 200 mL of chloroform, and washed with 200 mL of water. The aqueous layer was extracted with 200 mL of chloroform and the combined organic layers were washed with 2 × 200 mL of water, 200 mL of saturated aqueous sodium bicarbonate, and 200 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and concentrated in vacuo to give tan crystals. Recrystallization from 600 mL of boiling hexane cooled to 25 °C gave 9.49 g of white crystals, mp 184–185 °C. The mother liquor was concentrated to 175 mL, heated, and cooled to yield an additional 3.02 g of white crystals, mp 183–184 °C. The material remaining in the mother liquor was purified by column chromatoraphy (100 g of Grace grade 62 silica gel) eluted with chloroform. The resulting yellow crystals were recrystallized from 60 mL of boiling hexane cooled to −10 °C and yielded 1.91 g of white crystals, mp 185–183 °C. The total yield of **15b** was 14.42 g (84%). IR ($CCl_4$) 1740, 1700, 1600, 1470; NMR (270 MHz, $CDCl_3$) δ 7.62 (1 H, dd, *J* = 8, 1 Hz), 7.26 (1 H, td, *J* = 8, 1 Hz), 7.11 (1 H, dd, *J* = 8, 1 Hz), 6.07–5.98 (1 H, m), 5.94 (1 H, ddd, *J* = 10, 4, 3 Hz), 5.72 (1 H, d, *J* = 6 Hz), 5.40 (1 H, dd, *J* = 5, 3 Hz), 3.28 (1 H, dd, *J* = 19, 4 Hz), 3.05 (1 H, ddd, *J* = 6, 5, 3 Hz), 2.95 (1 H, dd, *J* = 7, 5 Hz), 2.24 (1 H, ddm, *J* = 19, 7 Hz), 1.27 (3 H, s), 1.18 (9 H, s), 0.94 (9 H, s); $^{13}$CMR ($CDCl_3$) δ 195.50, 169.14, 153.50, 133.69, 131.16, 130.96, 128.17, 123.82, 123.56, 118.17, 69.54, 64.87, 43.70, 42.14, 27.14, 26.82, 23.44, 21.95, 21.04, 20.52; MS, *m/e* (%) 372 (23), 371 (100), 329 (30), 317 (60), 275 (63), 251 (55), 165 (25), 161 (61), 143 (20). Anal. Calcd for $C_{24}H_{32}O_5Si$: C, 67.25; H, 7.52; $M_r$, 428.2019. Found: C, 67.32; H, 7.59; $M_r$, 428.2012.

**Preparation of 10-Hydroxy-1-acetoxy-8,9-(di-*tert*-butylsilylenedioxy)-1(*R**),4,4a(*S**),9(*R**),9a(*S**),10(*S**)-hexahydroanthracene (16b).** The ketone **15b** (14.98 gf, 35 mmol) was placed in a dry septum-capped flask and 56 mL of 0.93 M lithium borohydride (52 mmol) in THF was added via syringe at 25 °C. Almost all of the ketone dissolved immediately and the resulting mixture was stirred at 0 °C for 48 h. The solution was then poured carefully into a vigorously stirred mixture of 175 mL of chloroform and 175 mL of 0.35 N aqueous sodium bisulfate. After hydrogen evolution ceased, the organic layer was separated and the aqueous layer was extracted with 80 mL of chloroform. The combined organic layers were washed with 175 mL of water, 80 mL of saturated aqueous sodium bicarbonate, and 2 × 80 mL of saturated aqueous sodium chloride. After drying the solution over anhydrous sodium sulfate, removal of the solvent in vacuo gave 15.46 g of white solid. Recrystallization twice from boiling *n*-heptane cooled to 25 °C gave 4.93 g of white crystals, mp 161–163 °C. The mother liquors yielded an additional 3.90 g of white crystals (twice recrystallized), mp 161–162 °C. The total crystallized yield of **16b** was 8.83 g (59%). IR ($CCl_4$) 3570, 1750, 1605, 1590, 1475, 1455, 1375; NMR (270 MHz, $CDCl_3$): δ 7.17 (1 H, td, *J* = 7, 1 Hz), 7.08 (1 H, dd, *J* = 7, 1 Hz), 6.83 (1 H, dd, *J* = 7, 1 Hz), 6.11 (1 H, dm, *J* = 10 Hz), 5.96 (1 H, dm, *J* = 10 Hz), 5.60 (1 H, t, *J* = 4.5 Hz), 5.34 (1 H, d, *J* = 7 Hz), 4.54 (1 H, dd, *J* = 12, 5 Hz), 3.20 (1 H, d, *J* = 12 Hz), 2.68 (1 H, dt, *J* = 7, 3 Hz), 2.56–2.47 (2 H, m), 2.47–2.38 (1 H, m), 1.51 (3 H, s), 1.14 (9 H, s), 0.96 (9 H, s); MS, *m/e* (%) 373 (2), 355 (28), 313 (31), 295 (20), 291 (29), 271 (10), 253 (11), 235 (11), 161 (100), 143 (10). Anal. Calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 67.05; H, 8.01.

**Preparation of 1-Acetoxy-10-(*tert*-butyldimethylsiloxy)-8,9-(di-*tert*-butylsilylenedioxy)-1(*R**),4,4a(*S**),9(*R**),9a(*S**),10(*S**)-hexahydroanthracene (17b).** Dry DMF (16 mL) was added to a 50-mL flask containing the benzylic alcohol **16b** (8.17 g, 19.0 mmol) and imidazole (4.20 g, 61.7 mmol). The *tert*-butyldimethylchlorosilane (4.28 g, 28.4 mmol) was then added and the flask was warmed in a 50 °C oil bath for 6 h with stirring of the reaction. After allowing the reaction to cool to 25 °C, the mixture was poured into a separatory funnel with 100 mL of hexane and shaken thoroughly before washing with 75 mL of water. The aqueous layer was extracted with 2 × 50 mL of hexane. The combined organic layers were washed with 2 × 75 mL of water, 75 mL of saturated aqueous sodium bicarbonate, 75 mL of water, and 50 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed in vacuo to yield a yellow oil. Addition of ~20 mL of hexane, swirling, and removal of the solvent gave 10.2 g of white powder. The crude product was recrystallized from 100 mL of boiling acetonitrile, which was allowed to cool to 25 °C and yielded

8.50 g of white needles, mp 148–150 °C. Concentration of the mother liquor in vacuo followed by recrystallization of the residue from 10 mL of acetonitrile furnished an additional 0.47 g of white needles, mp 148–150 °C. The total crystallized yield of **17b** was 8.97 g (86%). IR ($CCl_4$) 1740, 1475, 1450; NMR (270 MHz, $CDCl_3$) δ 7.24 (1 H, t, $J$ = 8 Hz), 7.10 (1 H, d, $J$ = 8 Hz), 6.86 (1 H, d, $J$ = 8 Hz), 5.83–5.75 (1 H, m), 5.73–5.61 (2 H, m), 5.11 (1 H, d, $J$ = 6 Hz), 4.73 (1 H, d, $J$ = 5 Hz), 2.62 (1 H, td, $J$ = 6, 3 Hz), 2.42–2.30 (1 H, m), 2.15 (3 H, 3), 2.04 (dm, $J$ = 18 Hz), 1.81–1.65 (1 H, m), 1.19 (9 H, s), 0.98 (9 H, s), 0.78 (9 H, s), 0.22 (3 H, s), 0.17 (3 H, s); MS, $m/e$ (%) 544 (<1), 488 (4), 487 (13), 427 (6), 409 (3), 406 (6), 354 (100), 313 (8), 161 (13). Anal. Calcd for $C_{30}H_{48}O_5Si_2$: C, 66.13; H, 8.88; $M_r$, 544.3040 Found: C, 66.16; H, 8.84; $M_r$, 544.3040.

**Preparation of 1-Hydroxy-10-(*tert*-butyldimethylsiloxy)-8,9-(di-*tert*-butylsilylenedioxy)-1(*R**),4,4a(*S**),9-(*R**),9a(*S**),10(*S**)-hexahydroanthracene (26b).** To the allylic acetate **17b** (30.46 g, 56 mmol) dissolved in 200 mL of dry toluene in a 500-mL flask fitted with an addition funnel at −75 °C (dry ice/2-propanol bath) was added dropwise a hexane solution (0.88 M, 70 mL, 61.6 mmol) of diisobutylaluminum hydride over 15 min. The reaction temperature rose to −62 °C during the addition. The solution was stirred an additional 15 min in the dry ice/2-propanol bath and then acetone (30 mL) was added. The solution was transferred to a 2-L separatory funnel with 600 mL of ether and washed with 900 mL and then 500 mL of 0.35 N aqueous sodium bisulfate. After washes with 500 mL of saturated aqueous sodium bicarbonate, 500 mL of water, and 500 mL of saturated aqueous sodium chloride, the solution was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The white crystalline residue was dissolved in 210 mL of boiling acetonitrile, allowed to cool to 25 °C, and stood overnight. Filtration yielded 25.49 g (91%) of allylic alcohol **26b** as white crystals, mp 139–140 °C. IR ($CCl_4$) 3555, 3460, 1600, 1585, 1475, 1450; NMR (100 MHz, $CDCl_3$) δ 7.48–7.18 (2 H, m), 7.02 (1 H, d, $J$ = 7 Hz), 6.06–5.68 (2 H, m), 5.42 (1 H, d, $J$ = 7 Hz), 4.79 (1 H, d, $J$ = 4 Hz), 4.79–4.50 (1 H, m), 3.58 (1 H, d, $J$ = 12 Hz), 2.84–2.56 (2 H, m), 2.44–1.46 (3 H, m), 1.16 (9 H, s), 0.96 (9 H, s), 0.86 (9 H, s), 0.20 (3 H, s), 0.17 (3 H, s); MS (ionizing voltage = 30 eV), $m/e$ (%) 502 (0.05), 487 (0.3), 445 (72), 367 (36), 341 (100), 306 (100), 219 (13). Anal. Calcd for $C_{28}H_{46}O_4Si_2$: C, 66.88; H, 9.22; $M_r$, 502.2934. Found: C, 66.79; H, 9.12; $M_r$, 502.2936.

**Preparation of 10-(*tert*-Butyldimethylsiloxy)-8,9-(di-*tert*-butylsilylenedioxy)-1-oxo-1,4,4a(*S**),9(*R**),9a(*R**),10-(*S**)-hexahydroanthracene (27b).** Dry $Me_2SO$ (150 mL, 165 g, 2.11 mol) and acetic anhydride (50 mL, 54 g, 0.53 mol) were mixed in a septum-capped 250-mL flask and allowed to stand at 25 °C for 2 h. This solution was then transferred via a double-ended needle to a flask containing the allylic alcohol **26b** (25.49 g, 50.8 mmol) dissolved in 125 mL of dry toluene. Some of the allylic alcohol precipitated at this time but redissolved during the course of the reaction. After stirring for 20 h at 25 °C, the solution was added to a 2-L separatory funnel with 400 mL of hexane and washed with 600 mL of water. The aqueous layer was extracted with 400 mL of hexane. The combined organic layers were washed with 400 mL of saturated aqueous sodium bicarbonate, 400 mL of water, and 400 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous magnesium sulfate and the solvent was removed on a rotary evaporator at aspirator pressure. Acetonitrile (75 mL) was added to the residue to induce crystallization and the solvent was removed in vacuo. Recrystallization of the crystalline residue from 150 mL of boiling acetonitrile allowed to cool slowly to 25 °C and then −10 °C gave 20.82 g (82%) of ketone **27b** as white crystals, mp 144–145 °C. IR ($CCl_4$) 1685, 1590, 1470, 1455; NMR (270 MHz, $CDCl_3$) δ 7.24 (1 H, t, $J$ = 8 Hz), 7.09 (1 H, d, $J$ = 8 Hz), 6.90 (1 H, ddd, $J$ = 10, 6, 2 Hz), 6.85 (1 H, dt, $J$ = 8, 1 Hz), 6.10 (1 H, dd, $J$ = 10, 2 Hz), 5.24 (1 H, d, $J$ = 8 Hz), 4.71 (1 H, d, $J$ = 4.5 Hz), 2.98 (1 H, dd, $J$ = 8, 4 Hz), 2.63 (1 H, dq, $J$ = 11, 4.5 Hz), 2.33 (1 H, dt, $J$ = 19, 5 Hz), 2.02 (1 H, ddt, $J$ = 19, 11, 2 Hz), 1.08 (9 H, s), 0.98 (9 H, s), 0.77 (9 H, s), 0.21 (3 H, s), 0.16 (3 H, s); UV (EtOH) 281 (15000), 272 (1800), 218 (1800); MS, $m/e$ (%) 443 (7), 312 (7), 311 (42). Anal. Calcd for $C_{28}H_{44}O_4Si_2$: C, 67.15; H, 8.86. Found: C, 67.06; H, 8.99.

**Preparation of 2-Acetoxy-6-(*tert*-butyldimethylsiloxy)-10,11-(di-*tert*-butylsilylenedioxy)-3-((4′-methoxyphenyl)-thio)-12-oxo-1,4,4a(*R**),5,5a(*S**),6(*S**),11(*R**),11a-(*R**),12,12a(*S**)-decahydronaphthacene (33).** 1-Acetoxy-2-((4′-methoxyphenyl)thio)-1-cyclobutene[46] (4.25 g, 17.0 mmol) was distilled through the vacuum pyrolysis apparatus at 0.02 mm pressure and the diene **29** was collected onto 110 mg (0.50 mmol) of 2,6-di-*tert*-butyl-4-methylphenol. The diene was transferred (with the aid of 20 mL of dry methylene chloride) via syringe to a flask containing 6.55 g (13.1 mmol) of the enone **27b**. The resulting pale yellow solution was cooled in a −15 °C bath and 0.80 mL of 1 M boron trichloride (0.8 mmol) in methylene chloride was added via syringe and produced a deep orange color. The solution was stirred for 1 h at −15 °C and 2 h at 0 °C. The reaction was then diluted with 100 mL of chloroform and washed with 2 × 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated aqueous sodium chloride. Drying over anhydrous sodium sulfate followed by removal of the solvent in vacuo gave a pale yellow oil. This was crystallized twice from boiling *n*-heptane (270 mL), allowed to cool to 25 °C, and gave 7.20 g (73%) of **33** ($R_f$ 0.6) as pale yellow crystals, mp 203–204 °C, as well as 0.27 g (4%) of the starting enone **27b** ($R_f$ 0.7). Preparative layer chromatography (20% ethyl acetate in hexane) of the material in the mother liquor gave an additional 1.05 g of the adduct **33**. Recrystallization of the additional **33** from *n*-heptane gave 0.95 g (10%) of the adduct as white crystals, mp 203–204 °C, for a total of 8.15 g (83%) of recrystallized **33**. IR ($CHCl_3$) 1750, 1710, 1595, 1495, 1470, 1450, 1370; NMR (270 MHz, $CDCl_3$) δ 7.26 (2 H, d, $J$ = 9 Hz), 7.22 (1 H, t, $J$ = 7.5 Hz), 7.05 (1 H, d, $J$ = 7.5 Hz), 6.82 (1 H, d, $J$ = 7.5 Hz), 6.77 (2 H, d, $J$ = 9 Hz), 5.18 (1 H, d, $J$ = 9.5 Hz), 4.49 (1 H, d, $J$ = 4.5 Hz), 3.76 (3 H, s), 3.28 (1 H, t, $J$ = 6.5 Hz), 3.18 (1 H, dd, $J$ = 9.5, 5 Hz), 2.89 (1 H, d, $J$ = 18 Hz), 2.63–2.48 (1 H, m), 2.45–2.28 (2 H, m), 2.18 (3 H, s), 2.01 (1 H, bdd, $J$ = 17, 12 Hz), 1.83 (1 H, dd, $J$ = 17, 5.5 Hz), 1.67 (1 H, bd, $J$ = 14 Hz), 1.45 (1 H, td, $J$ = 14, 4.5 Hz), 1.07 (9 H, s), 0.89 (9 H, s), 0.87 (9 H, s), 0.11 (3 H, s), −0.02 (3 H, s); MS, $m/e$ (%) 750 (0.5), 708 (11), 519 (4), 381 (5), 140 (7), 139 (5). Anal. Calcd for $C_{41}H_{58}O_7SSi_2$: C, 65.56; H, 7.78; $M_r$, 750.3441. Found: C, 65.48; H, 7.74; $M_r$, 750.3406.

**Preparation of 10,11-Dihydroxy-2-acetoxy-6-(*tert*-butyldimethylsiloxy)-3-((4′-methoxyphenyl)thio)-12-oxo-1,4,4a-(*R**),5,5a(*S**),6(*S**),11(*R**),11a(*R**),12,12a(*S**)-decahydronaphthacene (34).** A plastic syringe and needle were used to add 0.88 g of pyridinium poly(hydrogen fluoride) (70% hydrogen fluoride, ~30 mmol of fluoride) to 20 mL of dry tetrahydrofuran containing pyridine (3.13 g, 40 mmol) and a stock solution (~1.2 *N*) of pyridinium fluoride was produced. The silylene derivative **33** (2.0 g, 2.67 mmol) was dissolved in 5.0 mL of dry tetrahydrofuran and 0.50 mL (0.49 g, 6.2 mmol) of pyridine. A portion of the stock solution (6.8 mL, ~8.2 mmol of fluoride) was added and the reaction was stirred at 25 °C for 1.5 h. The reaction was then diluted with 80 mL of ethyl acetate and washed with 2 × 20 mL of saturated aqueous sodium bicarbonate and 2 × 20 mL of saturated aqueous sodium chloride. After drying the solution over anhydrous sodium sulfate, the solvent was removed in vacuo to leave a pale yellow crystalline solid. Recrystallization from 20 mL of warm toluene followed by cooling to 25 °C gave 1.18 g (72%) of **34** as white needles, mp 103–104 °C. The mother liquor was concentrated (aspirator pressure) to a volume of 5 mL, warmed to dissolve the solid, and allowed to cool to 25 °C to yield an additional 260 mg (16%) of **34** as white needles, mp 103–104 °C, for a total yield of 88%. IR ($CCl_4$) 3500–3100, 1750, 1700, 1585, 1490, 1465, 1365; NMR (270 MHz, $CDCl_3$) δ 7.28 (2 H, d, $J$ = 9 Hz), 7.16 (1 H, t, $J$ = 7 Hz), 6.89 (1 H, d, $J$ = 7 Hz), 6.82 (2 H, d, $J$ = 9 Hz), 6.80 (1 H, d, $J$ = 7 Hz), 5.25 (1 H, t, $J$ = 7 Hz, collapses to d, $J$ = 7 Hz, upon addition of $D_2O$), 4.84 (1 H, d, $J$ = 4 Hz; exchanges with $D_2O$), 4.62 (1 H, d, $J$ = 4.5 Hz), 3.05 (1 H, t, $J$ = 7 Hz), 3.79 (3 H, s), 2.87–2.75 (2 H, m), 2.65–2.48 (2 H, m), 2.39 (1 H, bdd, $J$ = 18, 8 Hz), 2.20 (3 H, s), 2.07 (1 H, dd, $J$ = 17, 5 Hz), 1.97–1.68 (3 H, m), 0.84 (9 H, s), 0.01 (3 H, s), −0.05 (3 H, s); MS, $m/e$ (%) 610 (0.1), 592 (1), 550 (6). Anal. Calcd for $C_{33}H_{42}O_7SSi$: C, 64.88; H, 6.93. Found: C, 64.94; H, 6.91.

**Preparation of 10,12-Dihydroxy-2-acetoxy-6-(*tert*-butyldimethylsiloxy)-3-((4′-methoxyphenyl)thio)-11-oxo-1,4,4a-**

(46) The enol acetylation was performed as described in ref 9c except that 6 mol % of DMAP was added to catalyze the reaction.

**(R*),5,5a(S*),6(S*),11,12a(S*)-octahydronaphthacene (35).** The benzylic alcohol **34** (1.00 g, 1.64 mmol) was dissolved in 100 mL of acetone in an Erlenmeyer flask and 5.00 g (57.5 mmol) of manganese dioxide was added. The flask was stoppered and stirred at 25 °C for 45 min. The suspension was then filtered through a pad of finely ground sand in a sintered glass filter funnel and the solid was washed with 4 × 25 mL of acetone. The acetone was removed on a rotary evaporator at aspirator pressure and the residue was passed down a short chromatography column (1.5 × 8 cm, 5 g of silica gel) with 40–45 mL of 49:49:2 cyclohexane/chloroform/ethyl acetate. Removal of the solvent in vacuo and recrystallization of the residue from 50 mL of boiling *n*-heptane allowed to cool to 25 °C gave 762 mg (76%) of **35** as fine yellow needles, mp 178–179 °C. IR ($CHCl_3$) 1750, 1610, 1580, 1490, 1460, 1370, 1350; NMR (270 MHz, $CDCl_3$) δ 15.04 (1 H, s), 11.77 (1 H, s), 7.29 (1 H, dd, *J* = 8, 7.2 Hz), 7.18 (2 H, d, *J* = 9 Hz), 6.86 (1 H, dd, *J* = 8, 1 Hz), 6.72 (2 H, d, *J* = 9 Hz), 6.64 (1 H, dd, *J* = 7.5, 1 Hz), 4.36 (1 H, d, *J* = 2 Hz), 3.71 (3 H, s), 2.98–2.76 (3 H, m), 2.60 (1 H, dm, *J* = 18 Hz), 2.46–2.35 (1 H, m), 2.19 (3 H, s), 2.08 (2 H, bd, *J* = 7 Hz), 1.98 (1 H, ddd, *J* = 14, 10, 4 Hz), 1.74 (1 H, dt, *J* = 12, 5 Hz), 0.72 (9 H, s), 0.01 (3 H, s), −0.34 (3 H, s); MS, *m/e* (%) 608 (3), 566 (6), 283 (5), 249 (16), 248 (70), 139 (44), 109 (18). Anal. Calcd for $C_{33}H_{40}O_7SSi$: C, 65.10; H, 6.62; $M_r$, 608.2263. Found: C, 64.98; H, 6.62; $M_r$, 608.2252.

**Preparation of 10,11-Dihydroxy-2-acetoxy-3-((4′-methoxyphenyl)thio)-12-oxo-1,4,4a(R*),5,12,12a(S*)-hexahydronaphhacene (36).** The benzylic silyl ether **35** (1.73 g, 2.84 mmol) was suspended in 17 mL of glacial acetic acid and 1.7 mL (2.5 g, 22 mmol) of trifluoroacetic acid was added. The mixture was heated with stirring in a 95 °C oil bath for 40 min during which time silyl ether **35** dissolved and elimination product **36** precipitated. The mixture was cooled to 25 °C, dissolved in 100 mL of chloroform, and washed with 2 × 100 mL of water, 2 × 50 mL of saturated aqueous sodium bicarbonate, and 50 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and concentrated in vacuo to give 1.35 g (100%) of **36** as yellow crystals, mp 215–216 °C. This material was >95% pure as determined from its 270-MHz NMR spectrum. Recrystallization of a sample from boiling toluene gave yellow needles of mp 218 °C. IR ($CHCl_3$) 3400, 1750, 1635, 1595, 1585, 1495, 1450, 1385; NMR (270 MHz, $CDCl_3$) δ 16.05 (1 H, s), 9.81 (1 H, s), 7.43 (1 H, t, *J* = 7.5 Hz), 7.21 (2 H, d, *J* = 8.5 Hz), 7.07 (1 H, dd, *J* = 7, 1 Hz), 6.90 (1 H, s), 6.80 (1 H, dd, *J* = 7, 1 Hz), 6.75 (2 H, d, *J* = 8.5 Hz), 3.73 (3 H, s), 3.12 (1 H, q, *J* = 5 Hz), 3.01 (2 H, d, *J* = 5 Hz), 2.94 (1 H, bdd, *J* = 18, 5 Hz), 2.90–2.74 (2 H, m), 2.32–2.18 (1 H, m), 2.22 (3 H, s), 2.01 (1 H, ddt, *J* = 17, 7, 1.5 Hz); MS, *m/e* (%) 477 (3), 476 (14), 434 (34), 326 (18), 226 (37), 201 (20), 200 (20), 197 (20), 140 (12), 139 (33), 121 (27), 108 (22). Anal. Calcd for $C_{27}H_{24}O_6S$: C, 68.05; H, 5.08; $M_r$, 476.1293. Found: C, 68.27; H, 5.20; $M_r$, 476.1291.

**Preparation of 2-Acetoxy-6-(*tert*-butyldimethylsiloxy)-10,11-(di-*tert*-butylsilylenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-3-((4′-methoxyphenyl)thio)-1,4,4a-(R*),5,5a(S*),6(S*),11(R*),11a(R*),12,12a(S*)-decahydronaphthacene (37).** The ketone **33** (3.75 g, 5.00 mmol), 2,2-dimethyl-1,3propanediol (18.2 g, 175 mmol), and benzene (80 mL) were placed in a flask fitted with a Dean–Stark trap containing 3 Å molecular sieves. The mixture was refluxed for 1 h before the addition of 580 mg (2.5 mmol) of camphorsulfonic acid. After 5 h at reflux, the mixture was cooled in an ice bath, diluted with 100 mL of methylene chloride, and washed with 2 × 100 mL of saturated aqueous sodium bicarbonate, 2 × 100 mL of water, and 2 × 100 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The crude product was passed down a 5 × 10 cm chromatography column (50 g of silica gel) by using 80:20:2 hexane/methylene chloride/ethyl acetate. After removing the solvent in vacuo, the residue was purified on a Waters Prep 500 HPLC instrument by using the same solvent mixture. This gave 2.58 g (62%) of the ketal **37**, the first material to elute, as a brittle white foam which resisted crystallization. IR ($CHCl_3$) 1745, 1590, 1500, 1470, 1450, 1370; NMR (270 MHz, $CDCl_3$) δ 7.30 (2 H, d, *J* = 9 Hz), 7.19 (1 H, t, *J* = 8 Hz), 7.06 (1 H, d, *J* = 8 Hz), 6.85 (1 H, d, *J* = 8 Hz), 6.78 (2 H, d, *J* = 9 Hz), 5.06 (1 H, d, *J* = 7 Hz), 4.63 (1 H, d, *J* = 5 Hz), 3.79 (3 H, s), 3.70 (1 H, d, *J* = 12 Hz), 3.60 (1 H, d, *J* = 12 Hz), 3.42 (2 H, t, *J* = 12 Hz), 3.31 (1 H, dd, *J* = 8, 6 Hz), 3.04 (1 H, bdd, *J* = 7, 3 Hz), 2.89 (1 H, d, *J* = 19 Hz), 2.59–2.19 (5 H, m), 2.18 (3 H, s), 1.73 (1 H, dd, *J* = 16, 5 Hz), 1.49 (1 H, td, *J* = 13, 5 Hz), 1.31 (3 H, s), 1.13 (9 H, s), 0.87 (9 H, s), 0.79 (9 H, s), 0.76 (3 H, s), 0.11 (3 H, s), −0.03 (3 H, s); MS, *m/e* (%) 836 (0.4), 245 (0.5), 143 (17); calcd for $C_{46}H_{68}O_8SSi_2$: 836.4173; found: 836.4173.

**Preparation of 6-(*tert*-Butyldimethylsiloxy)-10,11-(di-*tert*-butylsilylenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-2-oxo-1,2,4a(R*),5,5a(S*),6(S*),11(R*),11a-(R*),12,12a(S*)-decahydronaphthacene (38).** To a solution of the sulfide **37** (475 mg, 0.568 mmol) in 10.0 mL of dry methylene chloride at −78 °C was added a solution of *m*-chloroperoxybenzoic acid (85%, 120 mg (102 mg), 0.59 mmol) in 3.0 mL of dry methylene chloride over a 5 min period. The mixture was stirred at −78 °C for 15 min and then added to a rapidly stirred mixture of 35 mL of methylene chloride and 35 mL of saturated aqueous sodium bicarbonate solution. The organic layer was washed with 50 mL of 10% aqueous sodium sulfite, 2 × 40 mL of saturated aqueous sodium bicarbonate, and 40 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and concentrated in vacuo to give 474 mg of the sulfoxide as a colorless glass.

Methyllithium (1.7 *M*, 7.1 mL, 12 mmol) was added over a 5 min period via syringe to a solution of the crude sulfoxide in 10.0 mL of dry THF at −78 °C. After 5 min at −78 °C, the solution was transferred through a double-ended needle into an Erlenmeyer flask containing a stirred mixture of 100 mL of ether and 50 mL of 4 N aqueous ammonium chloride. The organic layer was separated and washed with 2 × 40 mL of saturated aqueous sodium bicarbonate and 40 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed in vacuo to give 430 mg of crude β-keto sulfoxide as an almost colorless glass which slowly crystallized.

The crude β-keto sulfoxide in 50 mL of xylene containing 500 μL (460 mg, 5.5 mmol) of dihydropyran and 1.5 g (15 mmol) of calcium carbonate was heated to reflux for 3.5 h. After cooling to 25 °C, the solution was washed with 2 × 30 mL of saturated aqueous sodium bicarbonate and 30 mL of saturated aqueous sodium chloride, then dried over anhydrous sodium sulfate, and evaporated at a pressure of ~1 mm. Preparative layer chromatography (5% ether in methylene chloride) gave 234 mg (63%) of the enone **38** as white crystals ($R_f$ 0.4). Recrystallization of a portion of this material from warm *n*-heptane gave white crystals, mp 278–280 °C. IR ($CHCl_3$) 1675, 1600, 1585, 1470, 1445; NMR (270 MHz, $CDCl_3$) δ 7.39 (1 H, d, *J* = 8 Hz), 7.23 (1 H, t, *J* = 8 Hz), 6.99 (1 H, d, *J* = 8 Hz), 6.32–6.20 (2 H, m), 4.89 (1 H, d, *J* = 6.5 Hz), 4.56 (1 H, d, *J* = 5 Hz),3.46–3.29 (3 H, m), 3.26 (1 H, d, *J* = 11 Hz), 3.13 (2 H, bd, *J* = 11 Hz), 2.67–2.58 (2 H, m), 2.20 (1 H, dd, *J* = 17, 6 Hz), 2.20–2.10 (1 H, m), 1.87 (1 H, td, *J* = 14, 6 Hz), 1.73 (1 H, dm, *J* = 12 Hz), 1.32 (3 H, s), 1.29 (9 H, s), 1.12 (9 H, s), 0.95 (9 H, s), 0.37 (3 H, s), 0.28 (3 H, s), 0.23 (3 H, s); MS, *m/e* (%) 656 (2), 655 (7), 654 (17), 445 (12), 413 (5), 220 (10), 141 (5). Anal. Calcd for $C_{37}H_{58}O_6Si_2$: C, 67.84; H, 8.93; $M_r$, 654.3771. Found: C, 67.82; H, 8.78; $M_r$, 654.3772.

**Preparation of 6-(*tert*-Butyldimethylsiloxy)-3,4-(isopropylidenedioxy)-10,11-(di-*tert*-butylsilylenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-2-oxo-1,2,3-(R*),4(R*),4a(S*),5,5a(S*),6(S*),11(R*),11a(R*),12,12a-(S*)-dodecahydronaphthacene (40).** A solution of osmium tetroxide (411 mg, 1.62 mmol) in 2.0 mL of pyridine was added to a solution of the enone (964 mg, 1.47 mmol) in 8 mL of dry pyridine. The reaction immediately became dark and slightly warm to the touch. After 2 h of stirring, tetrahydrofuran (20 mL) was added followed by a solution of 1.5 g (14 mmol) of sodium bisulfite dissolved in 10 mL of water. The resulting mixture was stirred 0.5 h at 25 °C. The reaction was diluted with 50 mL of ethyl acetate and washed with 50 mL of water, 2 × 25 mL of saturated aqueous sodium bicarbonate, and 25 mL of saturated aqueous sodium chloride. The pale yellow solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure. This material (1.35 g), containing residual pyridine, was dissolved in 25 mL of ethyl acetate and washed with 25 mL of 0.35 N sodium bisulfate and 2 × 25 mL of saturated aqueous sodium bicarbonate. Drying over anhydrous sodium sulfate and removal of the solvent in vacuo gave 985 mg of crude diol **39** as

a brittle tan foam. Analytical TLC showed a single spot ($R_f$ 0.5, 10% acetone in chloroform).

The crude **39** (~1.4 mmol) was dissolved in 20 mL (17 g, 160 mmol) of 2,2-dimethoxypropane and 25 mg (0.11 mmol) of camphorsulfonic acid was added. After stirring at 25 °C for 4 h, the solution was diluted with 50 mL of ethyl acetate and washed with 2 × 25 mL of saturated aqueous sodium bicarbonate and 25 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The residue was purified by preparative layer chromatography (5% ether in methylene chloride) to give 923 mg (86% based on enone **38**) of isopropylidene derivative **40** ($R_f$ 0.5) as an almost colorless foam. Crystallization from 8 mL of warm *n*-heptane cooled slowly to 0 °C gave 611 mg of white needles, mp 198–200 °C. The mother liquor was concentrated to a volume of 2 mL, warmed to dissolve the solid, and cooled slowly to 0 °C to yield an additional 160 mg of **40** as white needles, mp 198–200 °C. The total yield of recrystallized material was 771 mg (72% based on enone **38**). IR ($CCl_4$) 1545, 1480, 1460, 1380; NMR (270 MHz, $CDCl_3$) δ 7.24 (1 H, t, $J$ = 7 Hz), 7.14 (1 H, d, $J$ = 7 Hz), 6.88 (1 H, d, $J$ = 7 Hz), 5.09 (1 H, d, $J$ = 7 Hz), 4.75 (1 H, d, $J$ = 5.5 Hz), 4.66 (1 H, dd, $J$ = 9, 8 Hz), 4.53 (1 H, d, $J$ = 8 Hz), 3.68 (2 H, bt, $J$ = 11 Hz), 3.62–3.50 (1 H, m), 3.43 (2 H, d, $J$ = 11 Hz), 3.12–3.02 (2 H, m), 2.41 (1 H, dd, $J$ = 17, 9 Hz), 2.43–2.30 (1 H, m), 2.03–1.86 (2 H, m), 1.50 (1 H, td, $J$ = 13, 5 Hz), 1.46 (3 H, s), 1.32 (3 H, s), 1.21 (3 H, s), 1.14 (9 H, s), 1.01 (9 H, s), 0.80 (9 H, s), 0.76 (3 H, s), 0.22 (3 H, s), 0.19 (3 H, s); MS, *m/e* (%) 730 (2), 729 (9), 728 (22), 671 (12), 670 (14), 614 (29), 613 (77), 527 (29), 413 (14), 245 (16), 151 (14). Anal. Calcd for $C_{40}H_{64}O_8Si_2$: C, 65.89; H, 8.85; $M_r$, 728.4139. Found: C, 65.98; H, 8.80; $M_r$, 728.4122.

**Preparation of (*E*)- and (*Z*)-6-(*tert*-Butyldimethylsiloxy)-2-(1′-methoxyethylidene)-3,4-(isopropylidenedioxy)-10,11-(di-*tert*-butylsilylenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-1,2,3(*S**),4(*R**),4a(*S**),5,5a(*S**),6-(*S**),11(*R**),11a(*R**),12,12a(*S**)-dodecahydronaphthacene (44).** Lithium diisopropylamide was prepared by the addition of a hexane solution of *n*-butyllithium (275 μL, 1.5 M, 0.41 mmol) to 2.4 mL of THF containing 66 μL (48 mg, 0.47 mmol) of diisopropyl amine at 0 °C. After 10 min, a solution of 150 mg (0.58 mmol) of (1-methoxyethyl)diphenylphosphine oxide[47] in 1.2 mL of THF was added via a double-ended needle over a 5-min period. After 10 min, the deep red solution was cooled to −100 °C (methanol/liquid nitrogen bath). The ketone **40** (150 mg, 0.206 mmol), dissolved in 1.2 mL of THF cooled to −100 °C, was added over ~2 min via a double-ended needle. The solution was stirred for 30 min as the bath was allowed to warm to −78 °C. The excess phosphine oxide anion was quenched by the careful addition (via syringe) of 0.4 N benzoic acid in THF until the solution faded to pale orange. Then HMPA (450 μL) was added and the cooling bath was removed. The reaction was stirred at 25 °C for 1 h before being taken up in 30 mL of ether and washed with 2 × 10 mL of saturated aqueous sodium bicarbonate, 2 × 10 mL of water, and 10 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and the solvent was removed in vacuo. Preparative layer chromatography (30% ether in hexane) gave 37 mg (25%) of the starting ketone **40** ($R_f$ 0.42) and 105 mg (66%) of **44** ($R_f$ 0.5 to 0.65) as a 2:1 mixture of isomers, separable by preparative layer chromatography using 20% ether in cyclohexane. The major, less mobile isomer of **44** (66% of the mixture) was recrystallized from warm *n*-heptane to give white crystals, mp 158–160 °C. IR ($CHCl_3$) 1675, 1605, 1590, 1475, 1450, 1380, 1370; NMR (270 MHz, benzene-$d_6$) δ 7.52 (1 H, d, $J$ = 8 Hz), 7.27 (1 H, t, $J$ = 8 Hz), 7.02 (1 H, d, $J$ = 8 Hz), 5.66 (1 H, d, $J$ = 5.5 Hz), 4.92 (1 H, d, $J$ = 7 Hz), 4.62 (1 H, d, $J$ = 4.5 Hz), 4.55 (1 *H*, dd, $J$ = 11, 5.5 Hz), 3.53–3.46 (2 H, m), 3.41 (3 H, s), 3.36 (2 H, bd, $J$ = 12 Hz), 3.21 (1 H, d, $J$ = 16 Hz), 3.06 (1 H, dd, $J$ = 11, 2 Hz), 2.72 (1 H, dm, $J$ = 5 Hz), 2.57–2.30 (4 H, m), 1.81 (3 H, bs), 1.72 (1 H, td, $J$ = 13, 5 Hz), 1.49 (3 H, s), 1.48 (3 H, s), 1.27 (9 H, s), 1.15 (9 H, s), 1.13 (3 H, s), 0.88 (9 H, s), 0.42 (3 H, s), 0.39 (3 H, s), 0.31 (3 H, s); MS, *m/e* (%) 772 (6), 771 (14), 770 (31), 638 (10), 323 (11), 115 (11). Anal. Calcd for $C_{43}H_{70}O_8Si_2$: C, 66.97; H, 9.15; $M_r$, 770.4609. Found: C, 67.10; H, 9.22; $M_r$, 770.4607.

The minor, more mobile isomer of **44** (34% of the mixture) was recrystallized from warm *n*-heptane to give white crystals which begin to decompose at 195 °C, with melting ~215 °C. IR ($CHCl_3$) 1675, 1610, 1590, 1475, 1450, 1380, 1370; NMR (270 MHz, benzene-$d_6$) δ 7.51 (1 H, d, $J$ = 7.5 Hz), 7.27 (1 H, t, $J$ = 7.5 Hz), 7.02 (1 H, d, $J$ = 7.5 Hz), 5.01 (1 H, d, $J$ = 5.5 Hz), 4.96 (1 H, d, $J$ = 6.5 Hz), 4.67 (1 H, d, $J$ = 5 Hz), 4.65 (1 H, dd, $J$ = 11, 6 Hz), 3.78 (1 H, dd, $J$ = 17, 1.5 Hz), 3.54–3.37 (4 H, m), 3.26 (3 H, s), 3.19 (1 H, dd, $J$ = 11, 1.5 Hz), 2.76–2.70 (1 H, m), 2.59–2.29 (4 H, m), 1.91 (3 H, d, $J$ = 1.5 Hz), 1.75 (1 H, td, $J$ = 13, 5 Hz), 1.45 (3 H, s), 1.39 (3 H, s), 1.29 (3 H, s), 1.28 (9 H, s), 1.17 (9 H, s), 0.87 (9 H, s), 0.46 (3 H, s), 0.39 (3 H, s), 0.32 (3 H, s); MS, *m/e* (%) 772 (13), 771 (42), 770 (100), 655 (15), 638 (17), 323 (10). Anal. Calcd for $C_{43}H_{70}O_8Si_2$: C, 66.97; H, 9.15; $M_r$, 770.4609. Found: C, 67.05; H, 9.11; $M_r$, 770.4516.

**Preparation of 2-Acetyl-6-(*tert*-butyldimethylsiloxy)-3,4-(isopropylidenedioxy)-10,11-(di-*tert*-butylsilylenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-3(*S**),4-(*R**),4a(*S**),5,5a(*S**),6(*S**),11(*R**),11a(*R**),12,12a(*S**)-decahydronaphthacene (45).** The mixture of enol ethers **45** (105 mg, 0.136 mmol) was dissolved in 5.0 mL of dry methylene chloride in a 25-mL round-bottom flask and a solution of 0.8 mg (0.003 mmol) of methylene blue in 400 μL of methylene chloride was added. Oxygen was passed through the solution as it was irradiated by a tungsten–halogen projector lamp for 25 min. Then a solution of 55 mg (0.21 mmol) of triphenylphosphine in methylene chloride was added and the solution was allowed to stand for 30 min. The solvent was removed in vacuo and the residue was purified by preparative layer chromatography (20% ethyl acetate in hexane). This gave 54 mg (53%) of ketone **45** ($R_f$ 0.50) as a colorless glass. Crystallization from warm *n*-heptane gave white crystals, mp 230–233 °C. IR ($CHCl_3$) 1675, 1605, 1590, 1475, 1400, 1375; NMR (270 MHz, benzene-$d_6$) δ 7.58 (1 H, d, $J$ = 5 Hz), 7.47 (1 H, d, $J$ = 8 Hz), 7.23 (1 H, t, $J$ = 8 Hz), 6.98 (1 H, d, $J$ = 8 Hz), 5.25 (1 H, d, $J$ = 6 Hz), 4.95 (1 H, d, $J$ = 6.5 Hz), 4.67 (1 H, d, $J$ = 5 Hz), 4.61 (1 H, dd, $J$ = 11.5, 6 Hz), 4.15 (1 H, t, $J$ = 6 Hz), 3.42 (1 H, d, $J$ = 11 Hz), 3.38–3.27 (2 H, m), 3.07 (1 H, dd, $J$ = 11, 2 Hz), 2.68–2.61 (1 H, m), 2.55–2.28 (3 H, m), 2.11 (3 H, s), 1.82 (1 H, td, $J$ = 14, 5 Hz), 1.41 (3 H, s), 1.38 (3 H, s), 1.31 (9 H, s), 1.18 (9 H, s), 1.03 (3 H, s), 0.84 (9 H, s), 0.39 (3 H, s), 0.37 (3 H, s), 0.33 (3 H, s); MS, *m/e* (%) 757 (4), 756 (17), 755 (44), 754 (69), 739 (3), 696 (4), 639 (4), 245 (13). Anal. Calcd for $C_{42}H_{66}O_8Si_2$: C, 66.80; H, 8.81; $M_r$, 754.4296. Found: C, 66.77; H, 8.97; $M_r$, 754.4251.

**Preparation of 2-Acetyl-10,11-dihydroxy-6-(*tert*-butyldimethylsiloxy)-3,4-(isopropylidenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-3(*S**),4(*R**),4a(*S**),5,5a-(*S**),6(*S**),11(*R**),11a(*R**),12,12a(*S**)-decahydronaphthacene (47).** A plastic syringe and needle were used to add 1.00 g of pyridinium poly(hydrogen fluoride) (70% hydrogen fluoride, ~35 mmol of fluoride) to 20 mL of dry THF containing pyridine (5.0 mL, 4.9 g, 62 mmol), giving a stock solution (~1.4 N) of pyridinium hydrofluoride. The silylene derivative **45** (54 mg, 0.072 mmol) was dissolved in 2.0 mL of the pyridinium hydrofluoride solution (~2.4 mmol of fluoride) and the solution was stirred for 24 h at 25 °C. The reaction was diluted with 20 mL of ethyl acetate and washed with 2 × 10 mL of saturated aqueous sodium bicarbonate, 10 mL of water, and 10 mL of saturated aqueous sodium chloride. The solution was dried over anhydrous sodium sulfate and solvent was removed in vacuo to give 48 mg of colorless glass. The purity of this material was estimated to be >90% from inspection of its 270-MHz NMR spectrum. Crystallization from boiling toluene allowed to cool to 25 °C gave an analytical sample of dihydroxy compound **47** as white crystals, mp 197–198 °C (with decomposition). IR ($CHCl_3$) 3510, 3450–3200, 3005, 2960, 2930, 2900, 2860, 1675, 1590, 1460, 1370; NMR (270 MHz, benzene-$d_6$) δ 8.10 (1 H, s), 7.45 (1 H, d, $J$ = 7 Hz), 7.30 (1 H, t, $J$ = 7 Hz), 7.22 (1 H, d, $J$ = 5 Hz), 5.08 (1 H, d, $J$ = 5.5 Hz), 4.73 (1 H, dd, $J$ = 7, 2 Hz), 4.52 (1 H, d, $J$ = 5 Hz), 4.44 (1 H, dd, $J$ = 11, 5.5 Hz), 3.72–3.03 (2 H, m), 2.93 (2 H, dm, $J$ = 12 Hz), 2.53–2.47 (1 H, m), 2.31–2.20 (2 H, m), 2.18 (3 H, s), 2.02–1.92 (1 H, m), 1.47 (1 H, td, $J$ = 14, 5 Hz), 1.37 (3 H, s), 1.34 (3 H, s), 1.13 (9 H, s), 0.89 (3 H, s), 0.30 (3 H, s), 0.28 (3 H, s), 0.26 (3 H, s), one of the

(47) The phosphine oxide **46** was prepared as described.[39a] Purification by silica gel chromatography eluting with 10% acetone in methylene chloride gave crystalline product which was recrystallized from a small volume of hexane and toluene.

aromatic protons was apparently obscured by the benzene residual signal; MS, *m/e* (%) 614 (0.1), 599 (1), 598 (3), 597 (7), 596 (26), 387 (22), 349 (19), 257 (6). Anal. Calcd for $C_{34}H_{50}O_8Si$: C, 66.41; H, 8.20; $M_r$, 614.3275. Found: C, 66.38; H, 8.08; $M_r$, 614.3275.

**Preparation of 2-Acetyl-6-(*tert*-butyldimethylsiloxy)-3,4-(isopropylidenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-10-hydroxy-11-oxo-3(*S**),4(*R**),4a(*S**),5,5a-(*S**),6(*S**),11a(*R**),12,12a(*S**)-decahydronaphthacene (48).** To a solution of 62 mg (0.1008 mmol) of diol **47** in 6.5 mL of acetone was added 53 mg (0.61 mmol) of activated manganese dioxide. Additional portions of 18 mg (0.207 mmol) and 9 mg (0.104 mmol) of manganese dioxide were added after one and two day intervals respectively. After two more days of vigorous stirring, the mixture was filtered through a short column of silica gel eluting with acetone. The crude residue obtained upon evaporation of solvent was chromatographed on silica gel and eluted with 35% ethyl acetate in hexane to give 30 mg (48%) of recovered starting material and 29.8 mg (48%, 93% based upon recovered starting material) of the ketone **48**. IR ($CCl_4$) 1680, 1635, 1613, 1450; NMR (270 MHz, $CDCl_3$) $\delta$ 0.24 (3 H, s), 0.25 (3 H, s), 0.74 (3 H, s), 1.03 (9 H, s), 1.05 (3 H, s), 1.32 (3 H, s), 1.38 (3 H, s), 1.93 (1 H, m), 2.21 (1 H, bd, $J$ = 15 Hz), 2.39 (3 H, s), 2.68 (1 H, m), 2.92 (1 H, t, $J$ = 6 Hz), 3.30–3.73 (5 H, m), 4.25 (1 H, dd, $J$ = 6 Hz, 11 Hz), 4.95 (1 H, d, $J$ = 6 Hz), 5.12 (1 H, d, $J$ = 5 Hz), 6.87 (1 H, d, $J$ = 9 Hz), 7.07 (1 H, d, $J$ = 7 Hz), 7.41 (1 H, d, $J$ = 6.5 Hz), 7.50 (1 H, t, $J$ = 8 Hz); MS, *m/e* (%) 612 (3), 430 (2), 41 (51), 39 (14); Calcd for $C_{34}H_{48}O_8Si$: 612.3118; found: 612.3117.

**Preparation of 2-Acetyl-10-acetoxy-6-(*tert*-butyldimethylsiloxy)-3,4-(isopropylidenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-11-oxo-3(*S**),4(*R**),4a-(*S**),5,5a(*S**),6(*S**),11a(*R**),12,12a(*S**)-decahydronaphthacene (49).** A solution of 36 mg (0.0587 mmol) of ketone **48** in 1 mL of distilled acetic anhydride and 0.5 mL of pyridine stood at room temperature for 48 h. After evaporation in vacuo, the residue was purified by flash chromatography eluting with 45% $C_2H_5OAc$ in hexane to give 37.6 mg (98% yield) of the acetate **49**. IR ($CCl_4$) 2860, 1773, 1700, 1685, 1605, 1465, 1370; NMR (270 MHz, $CDCl_3$) $\delta$ 0.25 (3 H, s), 0.26 (3 H, s), 0.71 (3 H, s), 1.03 (9 H, s), 1.32 (3 H, s), 1.37 (3 H, s), 1.95 (1 H, m), 2.20 (1 H, bd, $J$ = 15 Hz), 2.36 (3 H, s), 2.37 (3 H, s), 2.72 (1 H, m), 3.09 (1 H, t, $J$ = 5.5 Hz), 4.22 (1 H, dd, $J$ = 6, 11 Hz), 4.94 (1 H, d, $J$ = 5.5 Hz), 5.20 (1 H, d, $J$ = 5 Hz), 6.99 (1 H, d, $J$ = 8 Hz), 7.45 (1 H, d, $J$ = 5.5 Hz), 7.57 (1 H, d, $J$ = 8 Hz); MS, *m/e* (%) 654 (1), 653 (3); calcd for $C_{36}H_{50}O_9Si$: 654.3224; found: 654.3224.

**Preparation of 2-Acetyl-10-acetoxy-3,4-(isopropylidenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-6-hydroxy-11-oxo-3(*S**),4(*R**),4a(*S**),5,5a(*S**),6(*S**),11a-(*R**),12,12a(*S**)-decahydronaphthacene (50).** A solution obtained by adding 1.7 mL of a 0.2 M solution (0.34 mmol) of benzoic acid in THF to 2.3 mL of a 0.2 M solution (0.46 mmol) of tetrabutylammonium fluoride in THF was added to 74.5 mg (0.114 mmol) of acetate **49**. After 12 h, the mixture was passed through a silica gel column and eluted with 80% ethyl acetate in hexane. The eluate was concentrated and purified by flash chromatography to give 60.2 mg (97% yield) of alcohol **50**. IR ($CCl_4$) 3615, 3475, 1780, 1690, 1610, 1465, 1375; NMR (270 MHz, $CDCl_3$) $\delta$ 1.35 (3 H, s), 1.42 (3 H, s), 2.37 (3 H, s), 2.40 (3 H, s), 4.38 (1 H, m), 5.02 (1 H, d, $J$ = 5 Hz), 7.03 (1 H, d, $J$ = 9 Hz), 7.60 (1 H, t, $J$ = 8 Hz); MS, *m/e* (%) 540 (0.2), 122 (7), 105 (9); calcd for $C_{30}H_{36}O_9$ 540.2359; found: 540.2357.

**Preparation of 2-Acetyl-10,11-diacetoxy-3,4-(isopropylidenedioxy)-12,12-(2′,2′-dimethylpropane-1′,3′-diyldioxy)-3(*S**),4(*R**),4a(*S**),5,12,12a(*S**)-hexahydronaphthacene (52).** Alcohol **50** (3.3 mg, 0.0061 mmol) was dissolved in 195 $\mu$L of a 0.25 M solution (0.0488 mmol) of triethylamine in methylene chloride. Upon cooling to 0 °C, 98 $\mu$L of a 0.25 M solution (0.0245 mmol) of methanesulfonyl chloride in methylene chloride was added. The mixture was stirred 5 min at 0 °C and 1.3 h at room temperature. After dilution with ethyl acetate, the organic solution was washed twice with sodium bicarbonate and twice with saturated aqueous sodium chloride solution. After drying ($Na_2SO_4$) and concentration in vacuo, the residue was further dried at 0.002 Torr for 3 h. IR ($CCl_4$) 1775, 1700, 1685, 1605, 1365; NMR ($CDCl_3$, 270 MHz) $\delta$ 0.72 (3 H, s), 1.03 (3 H, s), 1.35 (3 H, s), 1.40 (3 H, s), 2.02 (1 H, m), 2.17 (1 H, br d, $J$ = 14 Hz), 2.37 (3 H, s), 2.38 (3 H, s), 3.05 (1 H, m), 3.15 (1 H, t, $J$ = 6 Hz), 3.29 (3 H, s), 4.26 (1 H, dd, $J$ = 6, 11.5 Hz), 4.95 (1 H, d, $J$ = 5.5 Hz), 6.24 (1 H, d, $J$ = 6 Hz), 7.09 (1 H, d, $J$ = 8 Hz), 7.44 (1 H, d, $J$ = 5 Hz), 7.53 (1 H, d, $J$ = 8 Hz), 7.66 (1 H, t, $J$ = 8 Hz).

A solution of 20 mg (0.0349 mmol) of tetrabutylammonium oxalate[42] and 100 $\mu$L of lutidine in 1 mL of methylene chloride that was degassed by bubbling argon through it was added to the above mesylate at room temperature. After 6 h, 100 $\mu$L of acetic anhydride and 50 $\mu$L of pyridine were added. After stirring 20 h, the reaction was filtered through a short silica gel column eluting with 80% ethyl acetate in hexane. Upon concentration, the residue was purified by flash chromatography with 65% ethyl acetate in hexane to give 2.4 mg (70% yield) of **52**. IR ($CHCl_3$) 1755, 1670, 1370; NMR ($CDCl_3$) $\delta$ 0.89 (s, 3 H), 1.40 (s, 3 H), 1.45 (s, 6 H), 2.13 (s, 3 H), 2.39 (s, 3 H), 2.42 (s, 3 H), 2.51 (d, $J$ = 10 Hz, 1 H), 2.93 (m, 1 H), 3.16 (t, $J$ = 10 Hz, 1 H), 3.59 (dd, $J$ = 10, 1 Hz, 1 H), 3.59 (dd, $J$ = 11, 1 Hz, 1 H), 3.77 (d, $J$ = 10 Hz, 1 H), 3.90 (d, $J$ = 11 Hz, 1 H), 4.00 (d, $J$ = 3 Hz, 1 H), 4.46 (dd, $J$ = 6, 3 Hz, 1 H), 5.13 (d, $J$ = 6 Hz, 1 H), 6.71 (s, 1 H), 7.04 (d, $J$ = 6.5 Hz, 1 H), 7.40 (t, $J$ = 6.5 Hz, 1 H), 7.43 (s, 1 H), 7.59 (d, $J$ = 6.5 Hz, 1 H).

**Preparation of 2-Acetyl-10,11-diacetoxy-3,4-(isopropylidenedioxy)-12-(3′-acetoxy-2′,2′-dimethylpropan-1′-yloxy)-3(*S**),4(*R**),4a(*S**),5-tetrahydronaphthacene (54).** A solution of 39 mg (0.0681 mmol) of tetra-*n*-butylammonium oxalate, 50 $\mu$L of pyridine, and 50 $\mu$L of DBU in 1 mL of dry acetone that has been degassed by bubbling argon through it was added to the crude mesylate which had been prepared as above starting from 4.8 mg (0.00888 mmol) of alcohol **50**. After 40 min under argon, 200 $\mu$L of acetic anhydride was added and stirring continued an additional 1.5 h. The reaction mixture was diluted by addition of 1 mL of a 3:2 (v:v) mixture of ethyl acetate and hexane and the resultant solution evaporated in vacuo to one-half its volume. This process was repeated three times to remove the acetone. The resultant mixture was passed through a short column of silica gel washing with 3:2 ethyl acetate–hexane. After concentration in vacuo, the residue was purified by flash chromatography eluting with 55% ethyl acetate in hexane to give 3.2 mg of **54** (93% yield). IR ($CHCl_3$) 1775, 1740, 1670, 1600, 1580, 1370; NMR ($CDCl_3$) $\delta$ 1.08 (s, 6 H), 1.47 (s, 3 H), 1.52 (s, 3 H), 2.02 (s, 3 H), 2.40 (s, 3 H), 2.47 (s, 3 H), 2.48 (s, 3 H), 2.55–2.71 (m, 2 H), 3.35–3.42 (1 H), 3.37 (d, $J$ = 9 Hz, 1 H), 3.92–3.99 (1 H), 3.94 (d, $J$ = 9 Hz, 1 H), 4.00 (d, $J$ = 10 Hz, 1 H), 4.07 (d, $J$ = 10 Hz, 1 H), 5.14 (d, $J$ = 5 Hz, 1 H), 7.11 (dd, $J$ = 7.5, 1 Hz, 1 H), 7.49 (t, $J$ = 7.5 Hz, 1 H), 7.65 (d, $J$ = 1 Hz, 1 H), 7.70 (d, $J$ = 7.5 Hz, 1 H), 8.01 (s, 1 H); calcd for $C_{34}H_{38}O_{10}$: 606.2465; found: 606.2462.

**Preparation of 2-Acetyl-3,4,10,11-tetraacetoxy-12-(3′-acetoxy-2′,2′-dimethylpropan-1′-yloxy)-3(*S**),4(*R**),4a-(*S**),5-tetrahydronaphthacene (55).** A solution of 2.2 mg (0.00363 mmol) of acetonide **54** in 300 $\mu$L of a 0.05 M solution of camphorsulfonic acid in 9:1 (v:v) acetone–water was stirred at room temperature for 18 h under argon. The reaction was diluted with ethyl acetate and filtered through a short column of silica gel with ethyl acetate. After concentration in vacuo, flash chromatography with ethyl acetate gave 0.5 mg (23% recovery) of starting material and 1.3 mg (63%, 82% yield based upon recovered starting material) of diol. IR ($CHCl_3$) 3560, 1765, 1735, 1655, 1590, 1375; NMR ($CDCl_3$) $\delta$ 1.10 (s, 6 H), 2.04 (s, 3 H), 2.38 (s, 3 H), 2.45 (s, 3 H), 2.47 (s, 3 H), 2.57 (t, $J$ = 15 Hz, $H_5$ axial), 2.77 (dt, $J \sim$ 13, 4 Hz, $H_{4a}$), 3.33 (d, $J$ = 10 Hz, 1 H), 3.46 (dd, $J$ = 15, 4 Hz, $H_5$ equatorial), 3.54 (dd, $J \sim$ 10, 4 Hz, $H_4$), 3.96 (d, $J$ = 10 Hz, 1 H), 4.03 (d, $J$ = 10 Hz, 1 H), 4.09 (d, $J$ = 10 Hz, 1 H), 4.86 (br s, $H_3$), 7.12 (d, $J$ = 7.5 Hz, 1 H), 7.50 (t, $J$ = 7.5 Hz, 1 H), 7.67 (s, 1 H), 7.72 (d, $J$ = 7.5 Hz, 1 H), 7.89 (s, 1 H); MS, *m/e* 566 (1.2), 129 (45); calcd for $C_{31}H_{34}O_{10}$: 566.2152; found: 566.2150. The above diol (3.2 mg, 0.00565 mmol) was acetylated by stirring in a solution of 200 $\mu$L of acetic anhydride and 100 $\mu$L of pyridine for 2 h at room temperature. After evaporation in vacuo, flash chromatography (90% ethyl acetate in hexane) gave 3.5 mg (95% yield) of pentaacetate **55**. IR($CHCl_3$) 1765, 1745, 1670, 1590, 1370; NMR ($CDCl_3$) $\delta$ 1.09 (s, 3 H), 1.12 (s, 3 H), 1.99 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 2.40 (s, 3 H), 2.42 (s, 3 H), 2.46 (s, 3 H), 2.55 (t, $J$ = 15 Hz, $H_5$ axial), 2.98 $\sim$ 3.13 (m, $H_5$ equatorial), 3.07 (m, $H_{4a}$), 3.30 (d, $J$ = 9.6 Hz, 1 H), 4.02 (d, $J$ = 11.0 Hz, 1 H), 4.08 (d, $J$ = 11.0 Hz, 1 H), 4.90 (dd, $J$ = 11.2, 3.2 Hz, 1 H), 6.33 (d, $J$ = 3.0 Hz, 1 H), 7.12 (d, $J$ = 8.1 Hz, 1 H), 7.49 (t, $J$ = 8.1 Hz, 1 H), 7.63 (s, 1 H), 7.68 (d, $J$ = 8.1 Hz, 1 H), 7.99

(s, 1 H); MS, *m/e* (%) 650 (2.6), 649 (9), 377 (18), 342 (8), 334 (6), 333 (11), 319 (5), 318 (29), 317 (25), 130 (18), 129 (63); calcd for $C_{35}H_{38}O_{12}$: 650.2363; found: 650.2364.

**Preparation of 2-Acetyl-3,4,10,11,12-pentaacetoxy-3-(*S**),4(*R**),4a(*S**),5-tetrahydronaphthacene (12a-Deoxypillaromycinone Pentaacetate, 56).** A solution of 0.69 mg (0.00388 mmol) of NBS in 45 μL of acetic acid and 5 μL of water was added to 2.3 mg (0.00353 mmol) of pentaacetate **55** at 0 °C. After 40 min at 0 °C, the solvent was removed in a stream of nitrogen. Acetic anhydride (250 μL) was added to the residue, and after stirring 30 min at room temperature, 100 μL of pyridine was added also. After 1.5 h, the mixture was evaporated in vacuo and the residue purified by flash chromatography and elution with ethyl acetate to give 1.6 mg (80% yield) of crystalline **56**, mp 211–212 °C. IR ($CHCl_3$) 1770, 1745, 1670, 1600, 1366; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.13 (s, 3 H), 2.38 (s, 6 H), 2.42 (s, 6 H), 2.77 (t, $J$ = 15.6 Hz, $H_5$ axial), 3.08 ~ 3.20 (m, 2 H, $H_5$ equatorial and $H_{4a}$), 4.95 (dd, $J$ = 11, 3 Hz, $H_4$), 6.32 (d, $J$ = 3 Hz, $H_3$), 7.11 (d, $J$ = 8 Hz, 1 H), 7.48 (t, $J$ = 8 Hz, 1 H), 7.60 (s, 1 H), 7.64 (s, 1 H), 7.67 (d, $J$ = 8 Hz, 1 H); NMR ($C_6D_6$) δ 2.56 (t, $J$ = 14.5 Hz, 1 H), 2.87 (dd, $J$ = 14.5, 5 Hz, 1 H), 3.11 (ddd, $J$ = 14.5, 12, 5 Hz, 1 H), 5.01 (dd, $J$ = 12, 3 Hz, 1 H), 6.60 (d, $J$ = 3 Hz, 1 H); MS, *m/e* (%) 565 (3), 564 (11), 463 (13), 462 (53), 421 (8), 420 (33), 404 (6), 379 (18), 378 (100), 377 (7), 376 (15), 361 (9), 360 (8), 344 (8), 343 (25), 336 (6), 335 (10), 334 (9), 320 (14), 319 (63), 318 (60), 302 (7); calcd for $C_{30}H_{28}O_{11}$: 564.1631; found: 564.1633.

**Acknowledgment.** We thank the National Cancer Institute of the National Institutes of Health for their generous support of our programs. C.G.C. thanks the NSF for the award of a predoctoral fellowship and D. H. thanks CNRS-France and NATO for support during his stay in these laboratories.

**Registry No.** **12**, 86668-63-5; **14**, 86668-37-3; **15a**, 73794-51-1; **15b**, 81418-04-4; **16a**, 86668-38-4; **16b**, 86668-39-5; **17a**, 86668-40-8; **17b**, 86668-41-9; **20**, 86668-42-0; **26a**, 86668-43-1; **26b**, 86668-44-2; **27a**, 86668-45-3; **27b**, 86668-46-4; **29**, 65174-13-2; **33**, 81418-09-9; **34**, 81418-10-2; **35**, 86668-47-5; **36**, 86668-48-6; **37**, 86668-49-7; **37** sulfoxide, 86668-64-6; **37** β-keto sulfoxide, 86668-65-7; **38**, 86668-50-0; **39**, 86668-51-1; **40**, 86668-52-2; (*E*)-**44**, 86668-53-3; (*Z*)-**44**, 86708-55-6; **45**, 86668-54-4; **47**, 86668-55-5; **48**, 86668-56-6; **49**, 86668-57-7; **50**, 86668-58-8; **51**, 86668-59-9; **52**, 86668-60-2; **54**, 86668-61-3; **54** diol, 86668-66-8; **55**, 86668-62-4; **56**, 86688-41-7; juglone, 481-39-0; (*E*)-1-acetoxy-1,3-butadiene, 35694-20-3; di-*tert*-butylchlorosilane, 56310-18-0; di-*tert*-butyldichlorosilane, 18395-90-9; 1-acetoxy-2-[(4-methoxyphenyl)thio]cyclobutene, 65174-11-0; (1-methoxyethyl)diphenylphosphine oxide, 64304-77-4.

# Synthetic Approaches to Rhodomycinone and Olivin

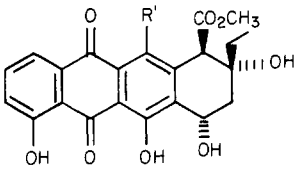
George A. Kraus* and Michael D. Hagen

*Department of Chemistry, Iowa State University, Ames, Iowa 50011*

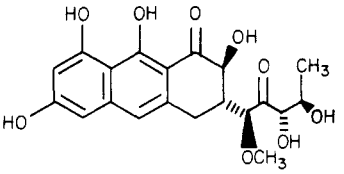
*Received February 1, 1983*

Intermediates for the synthesis of olivin and rhodomycinone were prepared by a sequence involving a Diels–Alder reaction followed by a Friedel–Crafts cyclization. In all cases optimal yields were obtained by regioselective methanolysis of anhydrides **9**, **10**, and **21** followed by treatment of the crude ester acids with trifluoroacetic anhydride. An added advantage of the latter reaction is that aromatization also occurs.

The important biological activity exhibited by compounds **1–3** has prompted considerable synthetic attention.[1] Several imaginative and successful approaches to **1** have been reported.[2] In contrast, comparatively few



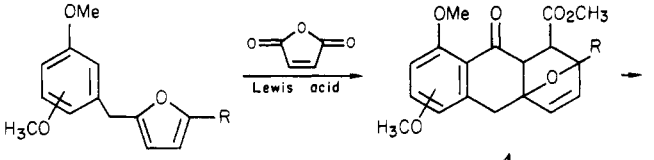
1 (aklavinone), R′ = H
2 (rhodomycinone), R′ = OH



3 (olivin)

approaches to the related molecules **2** and **3** have been published.[3] In this paper we will describe a direct and efficient approach to both **2** and **3**. The approach solves the regiochemical control problems associated with compound **3**.

Our strategy centered around a tandem Diels–Alder/Friedel–Crafts acylation sequence. Since certain Lewis acids catalyze both reactions,[4] we anticipated that the one-pot transformation depicted in eq 1 might occur.




2 or 3 (1)

Additionally, the stereochemistry developed in the Diels–Alder step would ultimately lead to the stereoselective introduction of functionality in the A ring. Furans **5** and **6** were prepared (eq 2) by the efficient reductive sequence developed by Hall and co-workers.[5] The acid-catalyzed reaction was attempted under a variety of conditions (**5**: $AlCl_3$, −78 °C, 0 °C, 25 °C; $BF_3$ $Et_2O$, −78 °C; $AgO_3SCF_3$, 0 °C). Extensive decomposition was invariably observed. We suspected that the oxabicyclo[2.2.1]heptene subunit formed in the Diels–Alder reaction was unstable to Lewis acids. This proved to be the case, since adducts

(1) For excellent reviews of biological properties and syntheses of anthracyclines, see: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley-Interscience: Somerset, NJ, 1979; Vol. 1. Arcamone, F. *Top. Antibiot. Chem.* **1978**, *2*, 89.

(2) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatkeyama, S.; Sekizaki, H.; Kishi, Y. *Ibid.* **1981**, *103*, 4248. Confalone, P. N.; Pizzolat, G. J. *Ibid.* **1981**, *103*, 4251. Li, R.; Wu, Y. L. *Ibid.* **1981**, *103*, 7007. Boeckman, R. K., Jr.; Sum, F.-W. *Ibid.* **1982**, *104*, 4604.

(3) Hatch, R. P.: Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. Franck, R. W.; John, T. V. *Ibid.* 1980, *45*, 1172. Thiem, J.; Wessel, H.-P. *Tetrahedron Lett.* **1980**, 3571; *Liebigs Ann. Chem.* **1981**, 2216. Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045. Krohn, K. *Tetrahedron Lett.* **1981**, *22*, 3219 and references therein.

(4) Lewis acids known to catalyze Diels–Alder reactions and also Friedel–Crafts acylations: $AlCl_3$, $BF_3$·$Et_2O$, $SnCl_4$, $ZnCl_2$.

(5) Zilenovski, J. S. R.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 1159.

0022-3263/83/1948-3265$01.50/0 