Synthetic and Biological Studies of Compactin and Related Compounds. 3. Synthesis of the Hexalin Portion of Compactin[1]

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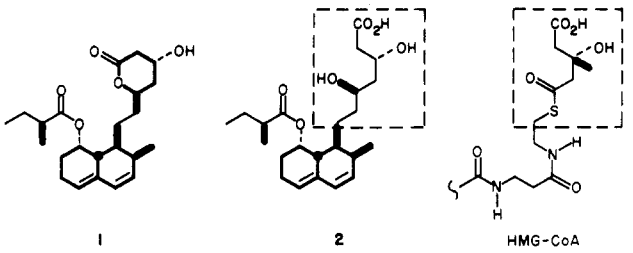
Several synthons for the hexalin moiety of compactin (**1**) have been prepared, and a procedure for production of the key alcohol **5** in enantiomerically homogeneous form is presented. Diels–Alder reaction of ethyl (*Z*)-crotonate and Danishefsky's diene affords cycloadduct **6** (78%). Hydride reduction followed by silylation of the resulting primary alcohol gives enone **8** (72%). Two-step cyclohexene annelation furnishes enone **11** (42–55%), which is elaborated to diene **21** by using a modification of the Shapiro olefin synthesis (three steps, 60%). Dithiane hydrolysis followed by L-Selectride (Aldrich) reduction of the resulting ketone affords axial alcohol **28**. Compound **28** possesses the correct relative stereochemistry at the four contiguous asymmetric carbon atoms in the hexalin portion of **1**, and the synthesis is suitable for large-scale preparation (ten steps, 10–14%, no isomer separations). Functional group manipulations give synthons **36–39**. Acid-catalyzed dehydration of allylic alcohol **19** affords diene isomer **20** (11:1). A simple procedure for the preparation of large quantities of ethyl (*Z*)-crotonate is also presented.

In 1976, the isolation of compactin (ML236B) was reported independently by Endo and co-workers[4] and workers at Beecham Pharmaceuticals.[5] Since that time, there has been intense effort directed toward the synthesis of compactin (**1**)[1,6,7,10] and other naturally occurring mevinic acids.[8] The mevinic acids are potent inhibitors of HMG CoA reductase, the enzyme which controls the rate-limiting step in cholesterol biosynthesis. Compounds which influence the activity of this enzyme are of potential importance as hypocholesterolemic drugs. Indeed, recent clinical trials have demonstrated that compactin effectively reduces serum cholesterol levels in patients with hypercholesterolemia.[9] It is known that the enzyme binds HMG CoA itself[4c] and that the active form of compactin is the open-chain dihydroxy acid **2**.[4b] It is reasonable to hypothesize that the upper portion of the molecule is bound by the enzyme in the same region as the hydroxymethylglutaryl portion of HMG CoA. The function of the hexalin moiety is less clear.



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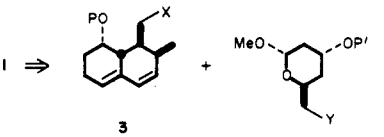
We have been engaged in a project aimed at a total synthesis of **1** and analogues designed to provide information on the molecular basis of the inhibitory action of **1**. Our convergent approach to **1** involves assembly of an appropriately substituted hexalin unit of the general form **3** and a lactone synthon which may then be coupled to form the ethylene linkage present in compactin. We have also been interested in the preparation and biological activity of glutarate esters of the form **4**, which bear a close



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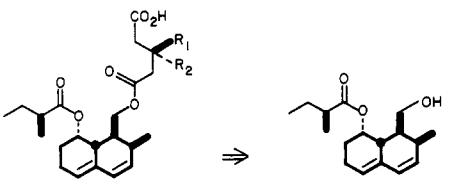
structural resemblance to the HMG portion of HMG CoA and possess the hexalin moiety of **1**. Herein, we report the synthesis of several hexalin subunits (**3**) and the key optically active alcohol **5**.[10] In a subsequent publication, we will discuss the preparation and biological evaluation of several esters of the general form **4**.



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(1) For part 2, see: Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994.

(2) Current address: Department of Chemistry, University of Akron, Akron, OH 44325.

(3) Current address: Chemical Research, Parke-Davis, 118 Howard Avenue, Holland, MI 49423.

(4) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiotics* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (c) Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31.

(5) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1165.

(6) Total syntheses. Compactin: (a) Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. (b) Hirama, M.; Uei, M. *Ibid.* **1982**, *104*, 4251. (c) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *Ibid.* **1983**, *105*, 1403. (d) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501. (e) Girotra, N. N.; Wendler, N. L. *Ibid.* **1983**, *24*, 3687. Mevinolin: Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811.

(7) Synthetic studies: (a) Danishefsky, S.; Kerwin, J. F., Jr., Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (c) Deutsch, E. A.; Snider, B. B. *Ibid.* **1982**, *47*, 2682. (d) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (e) Yang, Y.-L.; Falck, J. R. *Ibid.* **1982**, *23*, 4305. (f) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750. (g) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373. (h) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. (i) Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701. (j) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Ibid.* **1984**, *25*, 1655. (k) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Ibid.* **1984**, *25*, 2101. (l) Prasad, K.; Repic, O. *Ibid.* **1984**, *25*, 2435.

(8) Mevinolin: (a) Alberts, A. W.; Chen, J.; Kuraon, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957. (b) Endo, A. *J. Antibiotics* **1979**, *32*, 852. Dihydrocompactin: Lam, Y. K. T.; Gullo, V. P.; Goegelman, R. T.; Jorn, D.; Huang, L.; DeRiso, C.; Monaghan, R. L.; Putter, I. *J. Antibiotics* **1981**, *34*, 614. Dihydromevinolin: Albers-Schonberg, G.; Joshua, H.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Patchett, A. A. *J. Antibiotics* **1981**, *34*, 507.

(9) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *New Engl. J. Med.* **1981**, *305*, 478.

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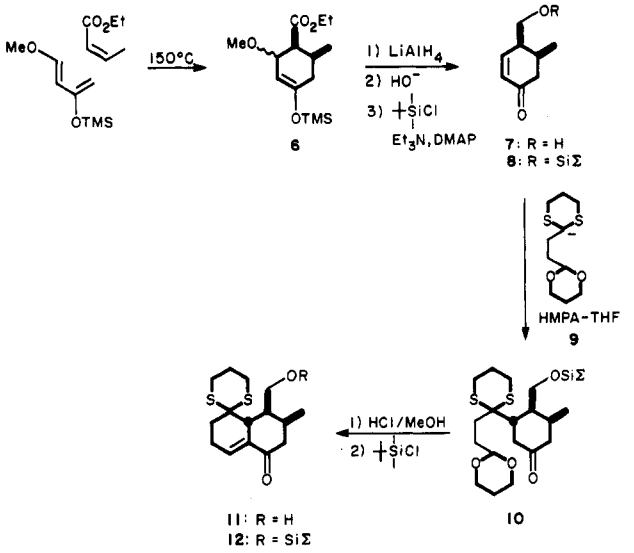
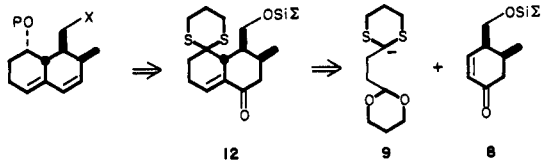
Scheme I



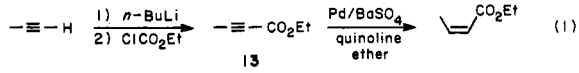
Results and Discussion

The general retrosynthetic analysis of the hexalin portion of **1** involves use of a cyclohexene annelation procedure developed earlier by us for this purpose.[11] Conjugate addition of dithiane anion **9** to enone **8** followed by acid-



mediated intramolecular aldol condensation is expected to afford dithiane enone **12**. The enone functionality in **12** could then be transformed into the compactin diene and the dithiane moiety to a suitably protected axial hydroxyl group.

The synthesis of enone **12** is summarized in Scheme I. Our approach to the hexalin system requires the ready availability of ethyl (*Z*)-crotonate. In preliminary studies we employed methyl (*Z*)-crotonate, prepared by a three-step sequence from methyl ethyl ketone.[12] However, we found this procedure to be awkward and low yielding (10–20%). Consequently, we have developed an alternative procedure which furnishes ethyl (*Z*)-crotonate in excellent yield (eq 1). Lithiation of propyne followed by quenching

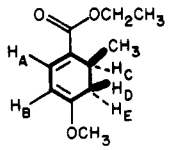


with ethyl chloroformate gives butynoate **13**. Hydrogenation of **13**, employing a poisoned catalyst, affords ethyl (*Z*)-crotonate in a yield of 90–100% for the two-step sequence. Capillary gas chromatographic analysis indicates that the product obtained is greater than 58:1 cis/trans.

Thermal cycloaddition of ethyl (*Z*)-crotonate and Danishefsky's diene[13] provides adduct **6** as a 1:1 mixture of epimers at the methoxy-bearing carbon (78% yield). This reaction is performed typically on a scale of 0.2–0.5 mol. In general, crude ethyl (*Z*)-crotonate may be utilized. However, on a few occasions this reaction has afforded no

(10) For preliminary results, see: Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popják, G. *Tetrahedron Lett.* **1982**, *23*, 4747.
(11) Thomas, J. A.; Heathcock, C. H. *Tetrahedron Lett.* **1980**, *21*, 3255.
(12) Rappe, C. *Org. Synth.* **1973**, *53*, 123.
(13) Danishefsky, S.; Kitahara, T.; Van, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

Table I. ^{1}H NMR Spectrum of Compound 14



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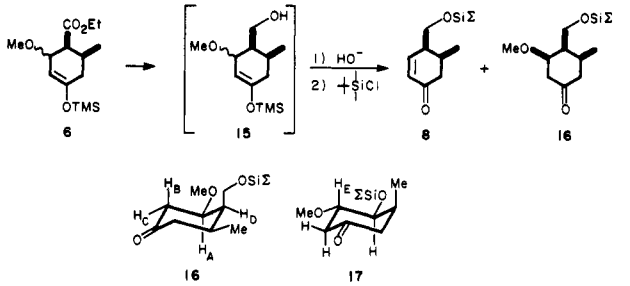
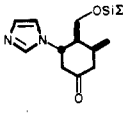
chemical shift, multiplitiy, coupling constant(s) (Hz)	assignment
7.08, d, J = 6.6	H_A
5.08, dd, J = 6.6, 2.1	H_B
4.19, 4.20, 2q, J = 7.1	OCH_2CH_3
3.65, s	OCH_3
2.89, ddq, J = 8.8, 6.9, 1.0	H_C
2.73, ddd, J = 16.7, 8.8, 2.1	H_D, H_E
2.03, dd, J = 16.7, 1.0	H_D, H_E
1.29, t, J = 7.1	OCH_2CH_3
1.01, d, J = 6.9	CH_3

adduct **6**. Instead, the major product isolated is diene ester **14**. The structure of compound **14** was assigned on the basis of a series of ^{1}H NMR decoupling experiments. A summary of the ^{1}H NMR data is presented in Table I. The carbonyl absorption (1690 cm^{-1}) in the infrared spectrum of **14** is also consistent with the δ-alkoxy dienoate structure. Compound **14** exhibits λ_{max} at 319 nm (MeOH ε 8900) in its ultraviolet spectrum, and the calculated value is 323 nm.[14] Finally, the compound shows a molecular ion of m/z 196.1093 in its high resolution mass spectrum, in agreement with the molecular formula of **14**, $C_{11}H_{16}O_3$. Byproduct **14** has not been observed when distilled ethyl crotonate is employed for the cycloaddition reaction.

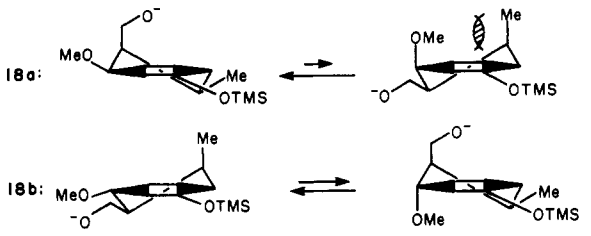
Lithium aluminum hydride reduction of ester **6** followed by a modified Fieser workup[15] and silylation[16,39] of the resulting alcohol affords enone **8** (72% yield from **6** after distillation). It is interesting to note that the initial reduction products derived from the epimeric mixture **6** are transformed by the action of base into enone **7** at substantially different rates. After the addition of **6** to an ethereal suspension of $LiAlH_4$, thin-layer chromatographic (TLC) analysis indicates the presence of two new major compounds which are assumed to be the epimeric silyl enol ethers **15**; no **6** remains. The reaction mixture is treated with base, and the two enol ethers gradually hydrolyze with simultaneous loss of methanol to give, after silylation, enone **8**. The product obtained contains less than 10% of β-methoxy ketone **16**. However, premature isolation of the material from the basic hydrolysis medium results in



(14) Reference 29 (p 257) in: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds"; Wiley: New York, 1974.
(15) Fieser workup refers to the procedure found in: Mičović, V. M.; Mihailović, M. L. J. *J. Org. Chem.* **1953**, *18*, 1190.
(16) If imidazole is used as the base, one obtains substantial amounts of the following Michael adduct.



Scheme II

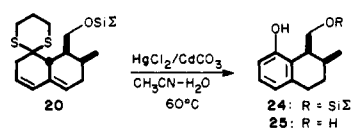


a larger proportion of contaminant **16**. The relative stereochemistry of compound **16** is assigned on the basis of its ^1H NMR spectrum. The proton on the methoxy-bearing carbon, H_A, appears as a ddd at 3.71 ppm. The coupling constants of 7.4, 3.7, and 3.7 Hz are more consistent with structure **16** than the alternative, **17**. The resonance for H_E in compound **17** would be expected to show two large (axial–axial) and one smaller (axial–equatorial) coupling constants. The conformational equilibria for the initial reduction products obtained from the epimeric mixture **6** are shown in Scheme II. If one assumes that the methoxy group must be in a pseudoaxial orientation for concommitant loss of methoxide with hydrolysis,[17] which is reasonable on the basis of stereoelectronic considerations, it seems clear that **18b** will undergo such an elimination with greater facility than **18a**, since the required conformation in the latter case necessitates an unfavorable 1,3-diaxial interaction. Presumably, β-methoxy ketone **16** arises from simple enol ether hydrolysis of the all-cis epimer of **15** (derived from **18a**) during subsequent manipulations, if the base-mediated hydrolytic elimination is not carried out to completion.

Conjugate addition of dithiane anion **9** to enone **8**, in the presence of HMPA, furnishes keto acetal **10** (57–74% yield). Attack of the anion occurs exclusively on the less-hindered face of the molecule. Intramolecular aldol condensation of **10** under dehydrating conditions furnishes crystalline enone **11** which no longer possesses the silyl protecting group (74% yield).

With compound **11** readily available, we addressed the problem of introducing the diene functionality of **1** (Scheme III). Protection of the primary hydroxyl group with *tert*-butylchlorodimethylsilane[18] followed by reduction with sodium borohydride ($CeCl_3$, MeOH)[19] affords equatorial alcohol **19**. Diene isomers **20** and **21** are obtained in a ratio of 11:1 by heating a dichloroethane solution of alcohol **19** with 10 mol % of pyridinium *p*-toluenesulfonate (PPTS).[20]

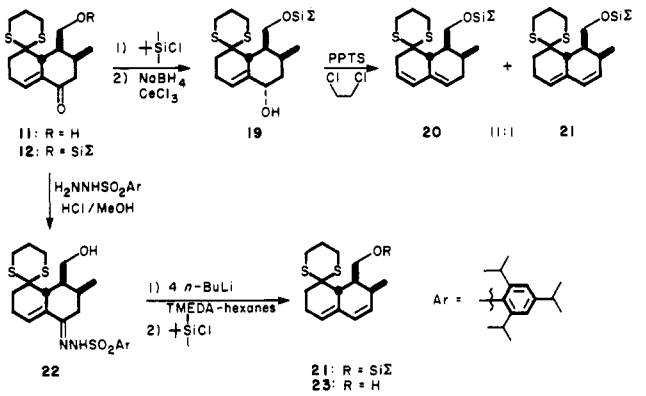
Attempted hydrolysis of the dithiane moiety in **20** provided the first piece of evidence suggesting that the diene chromophore in the major dehydration product is isomeric to that of the natural product. When **20** is heated with mercury(II) chloride and cadmium carbonate (80% CH_3CN–H_2O, 60 °C, 3 h),[21] phenols **24** and **25** are produced (eq 2). It is known that during mercury-induced dithiane



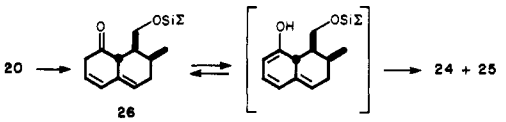
(2)

hydrolyses, the reaction medium becomes acidic.[22] Under

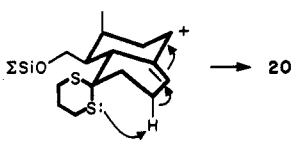
Scheme III



such conditions, one might expect that enolization of the first-formed ketone **26** would lead to the observed aromatization. Comparison of the vinyl regions of the ^1H

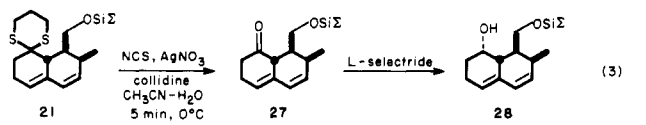


NMR spectra of isomers **20** and **21** with that of natural compactin demonstrates that the minor product is indeed the desired isomer. The high degree of selectivity obtained in this dehydration, albeit in the undesired manner, poses an interesting mechanistic problem. The preferred direction of elimination may result from intramolecular proton abstraction by the axial sulfur atom in the intermediate allylic cation.



The 3,4-double bond of the hexalin skeleton is cleanly introduced by using a modification[23] of the Shapiro olefin synthesis. Enone **11** is converted to triisopropylbenzenesulfonyl hydrazone **22** (81% yield) which is transformed smoothly to diene **21** by sequential treatment with 400 mol % of *n*-butyllithium and reprotection of the primary alcohol (74% yield, after recrystallization). The material obtained is identical with the minor product isolated previously from the dehydration of alcohol **19**.

Dithiane hydrolysis (NCS, silver nitrate, collidine)[22] followed by L-Selectride[24] (Aldrich) reduction of the resulting ketone **27** furnishes axial alcohol **28** (74% yield), which possesses the proper relative stereochemistry at the four contiguous asymmetric centers present in the hexalin portion of **1** (eq 3). The signal for the ring juncture proton

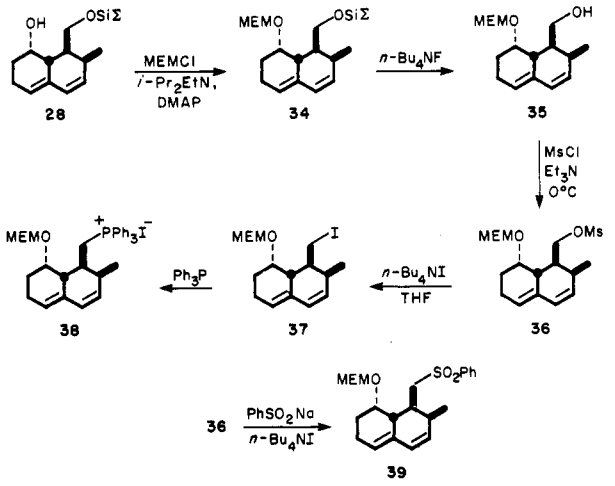


(3)

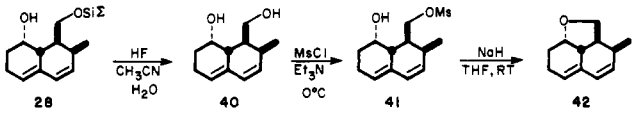
in ketone **27** occurs as a doublet at 3.01 ppm. The coupling constant of 11.5 Hz (to the proton on the (silyloxy)-methyl-bearing carbon) provides spectroscopic evidence for the stereochemical assignments at these two centers. It is also noteworthy that when the dithiane moiety of diene **20** is hydrolyzed under the bufferred conditions

(17) Similar observations are reported in ref 13.
(18) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(19) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(20) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(21) Wolfrom, M. L. *J. Am. Chem. Soc.* **1929**, *51*, 2188.
(22) Corey, E. J.; Ericson, B. W. *J. Org. Chem.* **1971**, *36*, 4144.
(23) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.
(24) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

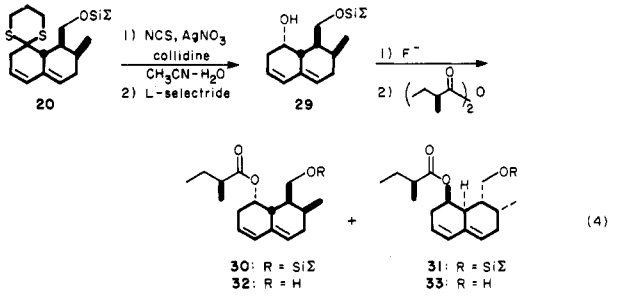
Scheme IV



Scheme V

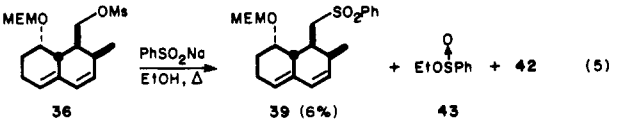


developed by Corey[22] aromatization is not observed, and subsequent L-Selectride reduction furnishes alcohol **29** in an overall yield of 46%. Acylation with (*S*)-2-methylbutyric anhydride followed by desilylation gives diastereomers **32** and **33** (89% yield), in which the diene chromophore is isomeric to that of **1** (eq 4).

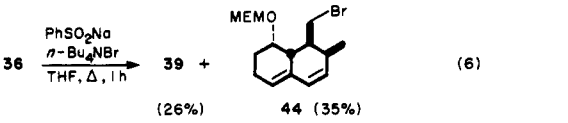


The conversion of alcohol **28** to several compounds of the general form **3** is summarized in Scheme IV. Protection of the secondary alcohol as its (2-methoxyethoxy)methyl (MEM) ether[25] (91% yield) and desilylation (quantitative yield) gives alcohol **35** which is converted to its methanesulfonate ester **36** in the standard manner (96% yield). Compounds in this series that possess a good leaving group on the methyl at the 1-position of the hexalin are somewhat prone to loss of the MEM protecting group with concommitant formation of ether **42** if not handled carefully. Compound **42** is prepared unambiguously as shown in Scheme V. Desilylation of **28** affords diol **40** (97% yield). Selective mesylation of the primary hydroxyl (15 min, 0 °C) followed by treatment with sodium hydride gives cyclic ether **42** (87% yield). The facility with which this cyclization occurs is interesting considering the trans relationship of the C-1 and C-8 substituents of the hexalin system.

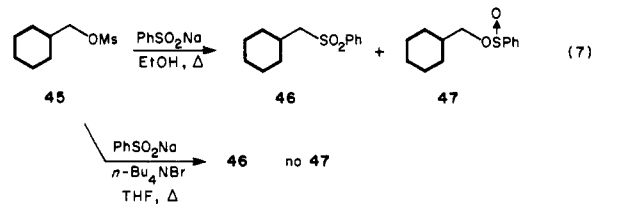
Our initial attempt to prepare sulfone **39** by displacement of the corresponding methanesulfonate ester ($PhSO_2Na$, EtOH)[26] gave the desired product in poor yield (6%), along with a substantial quantity of ether **42** and sulfinate ester **43** (eq 5). Prompted by a report that



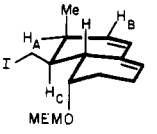
sulfones may be formed in good yield from the corresponding halides and tetrabutylammonium sulfinates, we investigated a modification of the previously described procedure.[27] Heating a mixture of tetra-*n*-butylammonium bromide, sodium benzenesulfinate, and compound **36** in refluxing THF furnishes the desired sulfone. During the course of the reaction, TLC analysis indicates the formation of a transient product of relatively high R_f which we postulated to be the bromide **44**. Indeed, when the reaction of **36** with sodium benzenesulfinate/tetra-*n*-butylammonium bromide is interrupted prior to completion, a mixture of sulfone **39** and bromide **44** is obtained (eq 6). We have found that higher yields of sulfone are



obtained when tetra-*n*-butylammonium iodide is employed as the coreagent. Thus, crystalline **39** is obtained from **36** in 53% yield. This method of preparing sulfones may be of utility when a situation is encountered in which O-alkylation of the ambident sulfinate anion is competitive with the desired S-alkylation. In model studies, it was observed that methanesulfonate ester **45** gives a poor mixture of sulfone **46** and O-alkylated product **47** upon treatment with sodium benzenesulfinate in refluxing ethanol (eq 7). However, reaction of **45** with sodium benzenesulfinate/tetra-*n*-butylammonium bromide affords only **46** uncontaminated by isomer **47** as evidenced by the ^1H NMR spectrum of the crude product mixture.



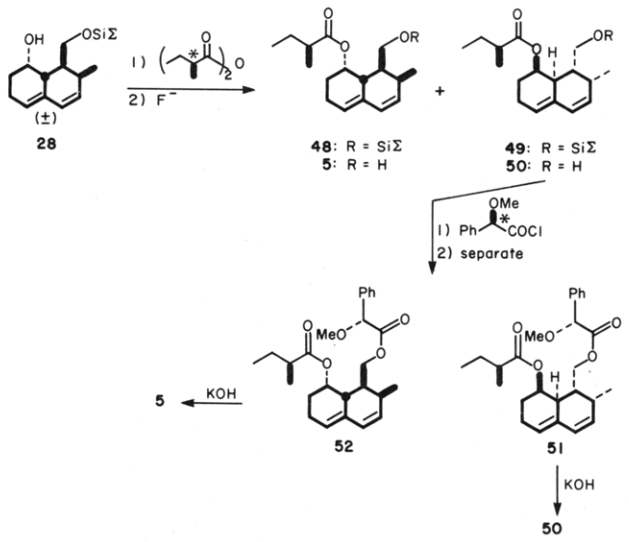
Treatment of **36** with tetra-*n*-butylammonium iodide in refluxing tetrahydrofuran affords crystalline iodide **37** in 91% yield. Indeed, we have found tetrabutylammonium halides to be excellent and mild reagents for the preparation of primary iodides and bromides which possess sensitive functionality.[28,29] Spectroscopic evidence for the relative stereochemistry of the C-2 methyl group in **37** was



obtained from a series of ^1H NMR decoupling experiments. Irradiation of the multiplet centered at 2.68 ppm (H_A) causes the methyl doublet at 0.88 ppm to become a singlet and the double doublet at 5.74 ppm (H_B) to become a

(25) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(26) Oxley, P.; Partridge, M. W.; Robson, T. D.; Short, W. F. *J. Chem. Soc.* **1943**, 763.
(27) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519.
(28) Finkelstein, B. L., unpublished results.
(29) For related examples, see: (a) Binkely, R. W.; Hehemann, D. G. *J. Org. Chem.* **1978**, *43*, 3244. (b) Brändström, A.; Kolind-Andersen, H. Acta *Chem. Scand. Ser. B* **1975**, *B29*, 201.

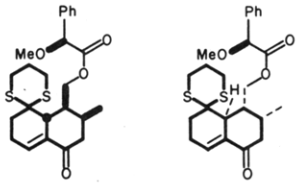
Scheme VI



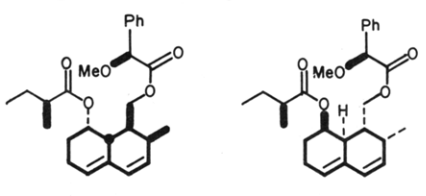
doublet (J = 9.3 Hz). Irradiation of the methyl doublet causes the multiplet (H_A) to collapse to a double doublet (J = 5.0, 5.0 Hz). The equatorial–axial coupling constant (J_{AC} = 5.0 Hz) together with the earlier establishment of H_C as axial in ketone **27** supports the stereochemical assignment at C-2.

Heating **37** with triphenylphosphine at 100 °C affords phosphonium salt **38** in 55% yield.

We next turned out attention to the preparation of optically active alcohol **5** (Scheme VI). Acylation of racemic **28** with (*S*)-2-methylbutyric anhydride[6a] followed by silyl ether cleavage gives a diastereomeric mixture of **5** and **50** in quantitative yield. We were unable to separate this mixture by HPLC. In early work, we observed that the *O*-methylmandelates **53** and **54** are separable by HPLC.



Work by Sih[6a] suggests that the ester linkage in compounds **5** and **50** should be sluggish toward mild hydrolytic conditions. Treatment of the mixture of **5** and **50** with (*R*)-*O*-methylmandelyl chloride[30] furnishes diesters **51** and **52** (88% yield) which are separable by HPLC. After separation, the individual esters (**51** and **52**) are treated with 200 mol % of potassium hydroxide to obtain alcohols **5** and **50**, respectively (quantitative yield). No product derived from cleavage of the 2-methylbutyrate ester side chain is observed. We have found that the esters derived from the S antipode of *O*-methylmandelic acid (**55** and **56**)



(prepared from the mixture of **5** and **50** in 94% yield) are separated with greater facility than the corresponding esters **51** and **52**. The stereostructure of alcohol **5** was

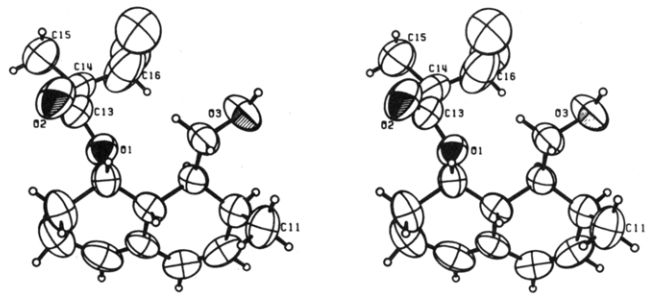


Figure 1. ORTEP stereoscopic depiction of alcohol **5**.

confirmed by single-crystal X-ray analysis; an ORTEP drawing of the structure is shown in Figure 1.

In summary, alcohol **28** which possesses the proper relative stereochemistry of the hexalin portion of **1**, is prepared in an efficient ten-step sequence from Danishefsky's diene and ethyl (*Z*)-crotonate. Functional group manipulations give coupling precursors **36–39**. Enantiomerically homogeneous alcohol **5** is obtained in high yield by the sequence (±)-**28** → **5** + **50** → **51** + **52**; **52** → **5**. This compound is an important precursor to several analogues of **1** which have been synthesized and are undergoing biological evaluation.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran were distilled from sodium/benzophenone immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored over 4-Å molecular sieves. Dichloromethane was distilled from phosphorus pentoxide. Boiling points and melting points are uncorrected. Infrared (IR) spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined on the following spectrometers: Varian EM 390, UCB 200, or UCB 250 (superconducting, FT instruments operating at 200 and 250 MHz, respectively). ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer or at 62.89 MHz with the UCB 250. All NMR spectra were determined with $CDCl_3$ as the solvent. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants(s) in hertz. Mass spectra were obtained with Atlas MS-12, consolidated 12-110B, or Kratos MS-50 mass spectrometers. Ultraviolet (UV) spectra were recorded on a Varian 219 UV spectrometer. Gravity column chromatography was done with Merck silica gel 60 (70–230 mesh ASTM), and flash chromatography[31] was done with MN silica gel 60 (230–400 mesh ASTM). Thin layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 μm) and compound visualization was effected with a 5% solution of 12-molybdophosphoric acid in ethanol or a solution of 10% vanillin and 5% sulfuric acid in 95% ethanol. High-pressure liquid chromatography (HPLC) was done with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters Prep LC/system 500 (preparative). Porasil columns were used unless otherwise indicated. Capillary GLPC analysis was done with a Hewlett Packard 5790A series gas chromatograph (12 m, cross-linked methylsilicone, programmed, 45 °C, 3 °C/min). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

Ethyl But-2-ynoate (13). To a solution of 85 mL (60 g, 1.5 mol) of propyne in 1000 mL of ether at −78 °C was added 667 mL (1.0 mol) of 1.5 M *n*-butyllithium in hexanes. The white slurry was stirred under nitrogen at −78 °C for 30 min, and 134 mL (152 g, 1.4 mol) of ethyl chloroformate was added in a single portion. The reaction mixture was allowed to warm to 0 °C over a period

(30) Neilson, D.; Peters, D. *J. Chem. Soc.* **1962**, 1519.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

of approximately 3 h. The system was immersed in an ice bath, and the mixture was stirred overnight during which time the ice gradually melted and the temperature rose to approximately 25 °C. The mixture was poured onto 400 g of ice, and the layers were separated. The aqueous phase was extracted with ether (2 × 200 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated with a rotary evaporator (bath temperature 10 °C). The crude product was distilled at aspirator pressure and the fraction boiling at 65 °C was collected to obtain 112 g (quantitative yield) of **13** as a colorless liquid (lit. 105 °C (190 mm));[32] IR (film) 2250, 1700, 1260 cm^{-1}; ^1H NMR δ 1.23 (t, 3 H, J = 7), 1.95 (s, 3 H), 4.07 (q, 2 H, J = 7).

Ethyl (*Z*)-Crotonate. In an oven-dried, 250-mL round-bottomed flask with a septum-capped side arm equipped with a magnetic stirring bar were placed 0.40 g of 5% $Pd/BaSO_4$, 0.40 g of quinoline, and 200 mL of anhydrous ether. The system was attached to an atmospheric hydrogenation apparatus, flushed with hydrogen, and charged with 23.2 mL (22.4 g, 200 mmol) of ethyl but-2-ynoate (**13**). The progress of the reaction was monitored by hydrogen uptake (ca. 4.5 L of H_2) and ^1H NMR spectroscopy. When the reaction was complete (8 h), the catalyst was removed by suction filtration through a pad of Celite. The ether was removed with a rotary evaporator (bath temperature 0 °C) to obtain 22.8 g (100% crude yield) of ethyl (*Z*)-crotonate as a pale yellow liquid. Capillary GLPC analysis revealed that the ratio of *Z* and *E* isomers is reproducible in the range 58–59:1 [t_R of ethyl (*Z*)-crotonate, 2.5 min; ethyl (*E*)-crotonate, 2.95 min]. The material may be distilled at atmospheric pressure: bp 128–132 °C (lit.[33] bp 129–130.5 °C); ^1H NMR δ 1.23 (t, 3 H, J = 7), 2.05 (dd, 3 H, J = 2, 7), 4.03 (q, 2 H, J = 7), 5.62 (dq, 1 H, J = 2, 12), 6.19 (dq, 1 H, J = 7, 12).

(3*RS*,4*SR*,5*SR*)- and (3*SR*,4*SR*,5*SR*)-4-Carbethoxy-3-methoxy-5-methyl-1-[(trimethylsilyl)oxy]cyclohexene (6). In a thick-walled glass tube equipped with a magnetic stirring bar were placed 22.0 g (193 mmol) of ethyl (*Z*)-crotonate and 34.0 g (198 mmol) of 1-methoxy-3-[(trimethylsilyl)oxy]butadiene.[13] The solution was purged with nitrogen for a period of 10 min, the tube was sealed at −78 °C, and after warming to room temperature, it was immersed in an oil bath heated to 150 °C. The mixture was stirred at 150 °C for 48 h. The crude orange oil was distilled at reduced pressure to obtain 43.0 g (78% yield) of **6**: bp 80 °C (0.20 mm); IR (film) 1730, 1665 cm^{-1}; ^1H NMR δ 0.20 and 0.23 (two s, 9 H), 1.03 and 1.06 (two d, 3 H, J = 8), 1.17 (t, 3 H, J = 7.5), 3.38 and 3.40 (two s, 3 H), 4.19 (q, 2 H, J = 7.5), 4.95 and 5.02 (two m, 1 H); ^{13}C NMR δ 0.13, 14.2, 16.7, 18.4, 28.0, 28.7, 35.8, 36.2, 47.9, 48.7, 55.6, 56.5, 59.5, 59.8, 75.2, 77.2, 101, 103, 152, 153, 171, 172. Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.58; H, 8.91.

4-Carbethoxy-1-methoxy-5-methyl-1,3-cyclohexadiene (14): IR (film) 2960, 1690, 1640, 1560, 1450, 1380, 1285, 1245, 1200 cm^{-1}; ^1H NMR δ 1.01 (d, 3, J = 6.9), 1.29 (t, 3, J = 7.1), 2.03 (dd, 1, J = 1.0, 16.7), 2.73 (ddd, 1, J = 2.1, 8.8, 16.7), 2.89 (ddq, 1, J = 1.0, 6.9, 8.8), 3.65 (s, 3), 4.19 (dq, 2, J = 2.2, 7.1), 5.08 (dd, 1, J = 2.1, 6.6), 7.08 (d, 1, J = 6.6); UV (methanol) λ_{max} 319 nm (ϵ 8900); HRMS, calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1093.

(4*RS*,5*RS*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5-methylcyclohex-2-en-1-one (8). Under a nitrogen atmosphere, into a flame-dried 2-L round-bottomed flask equipped with a pressure-equalizing addition funnel and a magnetic stirring bar, were placed 10.2 g (256 mmol) of 95% lithium aluminum hydride and 1 L of ether. To the stirring suspension, at −78 °C, was added a solution of 73.1 g (256 mmol) of ester **6** in 510 mL of ether over a period of 2 h. The reaction mixture was allowed to warm to −20 °C over a period of 2 h and poured into a vigorously stirring mixture of 1 L of ether, 38.9 mL of water, and 9.7 mL of 15% aqueous sodium hydroxide in a 3-L Morton flask. The resulting suspension was stirred at room temperature until TLC showed no **15** remaining (1.5 h). Magnesium sulfate was added, and the suspension was stirred for an additional 45 min. The solids were removed by suction filtration, and the solvent was removed with a rotary evaporator to obtain 38.5 g of crude alcohol **7**[34] as a pale yellow viscous liquid: IR (film) 3450, 1665 cm^{-1}; ^1H NMR δ 0.99 (d, 3 H, J = 6.7), 2.45 (m, 3 H), 3.77 (d, 2 H, J = 6.8), 6.05 (dd, 1 H, J = 2.3, 10.2), 6.94 (dd, 1 H, J = 3.4, 10.2); HRMS, calcd for $C_8H_{12}O_2$ 140.0838, found 140.0831.

The crude alcohol **7** was placed in a 2-L round-bottomed flask equipped with a rubber septum and a magnetic stirring bar. The system was placed under a nitrogen atmosphere and charged with 390 mL of dichloromethane. To this stirring solution were added 48.9 mL (35.5 g, 351 mmol) of triethylamine, 2.01 g (16.4 mmol) of 4-(dimethylamino)pyridine (DMAP), and 48.4 g (322 mmol) of *tert*-butylchlorodimethylsilane. The reaction mixture was stirred at room temperature for 27 h and partitioned between 400 mL of hexanes and 400 mL of water, and the layers were separated. The organic phase was washed with water (500 mL, 2 × 300 mL), concentrated to a volume of 100 mL with a rotary evaporator, diluted with 500 mL of hexanes, and washed with an additional three 300-mL portions of water. The aqueous washings were combined and extracted with three 300-mL portions of hexanes. The combined organic fractions were dried over magnesium sulfate, the solvent was removed with a rotary evaporator, and the crude product was distilled under vacuum to obtain 46.6 g (72% yield from **6**) of silyl ether **8** as a pale yellow liquid, bp 109–129 °C (3 mm). The product was judged to contain less than 10% of β-methoxy ketone **16** by its ^1H NMR spectrum: IR (film) 1680, 1250 cm^{-1}; ^1H NMR δ 0.06 and 0.07 (two s, 6 H), 0.89 (s, 9 H), 1.0 (d, 3 H, J = 7), 2.47 (m, 2 H), 2.66 (m, 1 H), 3.74 (m, 2 H), 6.07 (dd, 1 H, J = 2.3, 10), 6.83 (dd, 1 H, J = 4, 10); ^{13}C NMR δ −5.60, 15.24, 18.04, 25.71, 30.79, 42.61, 44.77, 62.51, 129.81, 149.88, 199.48. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.30. Found: C, 66.17, H, 10.23.

(3*RS*,4*SR*,5*SR*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-methoxy-5-methylcyclohexanone (16): IR (film) 2920, 1710, 1455, 1250 cm^{-1}; ^1H NMR δ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.06 (d, 3 H, J = 7.0), 2.12 (m, 2 H), 2.42 (m, 3 H), 2.70 (dd, 1 H, J = 7.7, 14.3), 3.28 (s, 3 H), 3.71 (ddd, 1 H, J = 3.7, 3.7, 7.4), 3.87 (d, 2 H, J = 4.9); ^{13}C NMR δ −5.9, 17.5, 17.8, 25.6, 31.4, 43.4, 47.4, 56.4, 59.7, 79.4, 210 ppm. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.88; H, 10.56. Found: C, 62.59; H, 10.61.

2-[3,3-(Propylenedioxy)propyl]-1,3-dithiane.[11] Under a nitrogen atmosphere, in a 500-mL round-bottomed flask equipped with a rubber septum and magnetic stirring bar were placed 24.0 g (200 mmol) of 1,3-dithiane and 500 mL of THF. To this stirring solution, at −78 °C, was added 133 mL (200 mmol) of 1.5 M *n*-butyllithium in hexanes. The mixture was stirred for 0.5 h at −78 °C. The system was warmed to −20 °C and stirred for an additional period of 2 h at this temperature. The reaction mixture was cooled to −78 °C, and 52.1 mL (53.7 g, 300 mmol) of HMPA was added. The mixture was stirred at −78 °C for 15 min, and 41.0 g (210 mmol) of 2-(2-bromoethyl)-1,3-dioxane[35] was added in a single portion. After 45 min, the reaction mixture was poured into 800 mL of water and extracted with three 400-mL portions of ether. The ether solution was washed with four 200-mL portions of water and a 200-mL portion of saturated aqueous sodium chloride and dried over sodium sulfate. The solvent was removed with a rotary evaporator, and the crude product was recrystallized from ca. 500 mL of petroleum ether to obtain 41.9 g of 2-[3,3-(propylenedioxy)propyl]-1,3-dithiane as white needles. The slurry was cooled to −20 °C and the crystalline product was collected by suction filtration. An additional 2.3 g of product was obtained by concentration of the mother liquor followed by recrystallization of the residue. The total yield of material with mp 59–61 °C was thus 44.2 g (94%): IR (film) 3010, 1380, 1215 cm^{-1}; ^1H NMR δ 1.35 (m, 1 H), 1.82 (m, 5 H), 2.09 (m, 2 H), 2.84 (m, 4 H), 3.75 (m, 2 H), 4.02 (t, 1 H, J = 6.7), 4.08 (m, 2 H), 4.54 (t, 1 H, J = 4.7). Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.24; H, 7.74. Found: C, 51.29; H, 7.76.

(3*RS*,4*RS*,5*RS*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-methyl-5-[[3,3-(propylenedioxy)propyl]-1,3-dithian-2-yl]cyclohexanone (10). To a 0.40 M solution of 3.74 g (16 mmol) of 2-[3,3-(propylenedioxy)propyl]-1,3-dithiane in THF, at −78 °C, was added 10.7 mL (16 mmol) of 1.5 M *n*-butyllithium in hexanes. The resulting solution was stirred at −78 °C for 15 min, allowed to warm to −20 °C, and stirred at −20 °C for 2 h.

(32) "Handbook of Chemistry and Physics", 52nd ed.; Weast, R. C., Ed.; Chemical Rubber Company: Cleveland, OH; p c-227.
(33) Von Auwers, K. *Liebigs Ann. Chem.* **1923**, *432*, 46.
(34) The alcohol **7** decomposes upon attempted distillation.
(35) Faas, U.; Hilgert, H. *Chem. Ber.* **1954**, *87*, 1343.

The system was cooled to −78 °C, 5.56 mL (5.73 g, 32 mmol) of HMPA was added, and the deep yellow solution was stirred at −78 °C for 30 min. A 0.40 M solution of 4.06 g (16 mmol) of enone 8 in THF was added at a rate of 0.50 mL min^{-1} with a syringe pump. The reaction mixture was stirred at −78 °C for 7 h and allowed to warm to 0 °C. The mixture was poured into 300 mL of hexanes and washed with NH_4Cl/NH_4OH pH 7 buffer, H_2O (4 × 100 mL), and brine. The organic phase was dried ($MgSO_4$) and concentrated with a rotary evaporator. The crude product was purified by preparative HPLC using 3:7 ether/hexanes as the eluant to obtain 5.78 g (74%)[36] of **10** as a light yellow oil that solidified on standing. An analytical sample, mp 79 °C, was obtained by recrystallization from hexanes: IR (film) 1720, 1140 cm^{-1}; ^1H NMR δ 0.03 and 0.04 (two s, 6 H), 0.86 (s, 9 H), 1.10 (d, 3 H, J = 7), 2.98 (dq, 2 H, J = 3, 10), 3.58 (dd, 1 H, J = 3, 10), 3.75 (t, 2 H, J = 10), 3.90 (dd, 1 H, J = 3, 10), 4.10 (dd, 2 H, J = 5, 12), 4.56 (t, 1 H, J = 5); ^{13}C NMR δ −5.77, 18.0, 18.2, 25.0, 25.7, 29.1, 29.6, 29.9, 30.2, 30.6, 32.0, 38.5, 40.0, 40.4, 44.1, 59.6, 63.5, 66.6, 102, 212. Anal. Calcd for $C_{24}H_{44}O_4S_2Si$: C, 58.97; H, 9.07. Found: C, 59.23; H, 9.07.

(1*SR*,2*SR*,8a*RS*)-8-(1,3-Dithian-2-yl)-1-(hydroxymethyl)-2-methyl-4-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene (11). Into a 2-L round-bottomed flask equipped with a rubber septum, a magnetic stirring bar, and a reflux condenser were placed 40.8 g (83.6 mmol) of acetal **10**, 450 mL of methanol, and 42.4 mL of 10% aqueous hydrochloric acid. The stirring mixture was heated at reflux under a nitrogen atmosphere for a period of 45 min. The reaction mixture was cooled to room temperature and brought to pH 7 (pH paper) with saturated aqueous sodium bicarbonate, and the majority of the solvent was removed with a rotary evaporator. The residue was partitioned between 300 mL of water and 400 mL of chloroform, the layers were separated, and the aqueous phase was extracted with two 200-mL portions of chloroform. The combined organic fractions were washed with water and brine and dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. To the resulting yellow solid was added 25 mL of ether, and the heterogeneous mixture was heated to boiling. Cooling of the mixture in an ice bath followed by suction filtration (10 mL ether rinse, 10 mL benzene rinse) gave 17.3 g of **11** as an off-white solid. The mother liquor was concentrated with a rotary evaporator, and the resulting orange oil was triturated with ether to obtain, after cooling for several days, 1.10 g of additional product as a yellow solid. The overall yield of useful product was thus 18.4 g (74%). The analytical sample, mp 177 °C, was obtained by recrystallization from benzene: IR ($CHCl_3$) 3650, 1680, 1620 cm^{-1}; ^1H NMR δ 1.12 (d, 3 H, J = 6.4), 1.53 (t, 1 H, J = 5), 3.19 (dt, 1 H, J = 4, 12), 4.87 (m, 2 H), 6.65 (m, 1 H); ^{13}C NMR δ 18.0, 24.4, 24.7, 24.9, 25.1, 25.5, 25.9, 26.1, 26.5, 30.3, 30.6, 33.4, 40.4, 43.0, 46.0, 55.2, 63.2, 135.7, 136, 202. Anal. Calcd for $C_{15}H_{22}O_2S_2$: C, 60.36; H, 7.43. Found: C, 60.26; H, 7.47.

(1*SR*,2*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-(1,3-dithian-2-yl)-2-methyl-4-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene (12). To a 0.50 M solution of 1.52 g (5.10 mmol) of alcohol **11** in dichloromethane were added 25 mg (0.20 mmol) of DMAP, 0.92 mL (0.67 g, 6.63 mmol) of triethylamine, and 0.96 g (6.38 mmol) of *tert*-butylchlorodimethylsilane. After being stirred at room temperature for 8 h, the mixture was poured into ether and washed with H_2O (3 × 25 mL) and brine. The organic solution was dried ($MgSO_4$) and concentrated with a rotary evaporator to obtain 2.00 g (95%) of **12** as a white crystalline solid, mp 101–104 °C. An analytical sample, mp 104 °C, was obtained by recrystallization from hexane: IR ($CHCl_3$) 1680, 1620 cm^{-1}; ^1H NMR δ 0.03 and 0.06 (two s, 6 H), 0.86 (s, 9 H), 1.10 (d, 3 H, J = 6.7), 3.19 (dt, 1 H, J = 4, 14), 3.69 (dd, 1 H, J = 4, 10.5), 4.05 (dd, 1 H, J = 2.5, 10.5), 6.61 (m, 1 H); ^{13}C NMR δ −5.72, 18.1, 24.2, 25.5, 25.8, 25.9, 30.3, 33.4, 39.6, 43.3, 45.8, 55.4, 64.1, 135, 136, 202. Anal. Calcd for $C_{21}H_{36}O_2S_2Si$: C, 61.11; H, 8.79. Found: C, 61.21; H, 8.86.

(1*SR*,2*SR*,4*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-(1,3-dithian-2-yl)-4-hydroxy-2-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (19). To a 0.10 M solution of 2.00 g (4.85 mmol) of enone **12** in methanol was added 1.28 g (4.85 mmol) of $CeCl_3 \cdot xH_2O$. The mixture was stirred at room temperature for 10 min, 0.184 g (4.85 mmol) of $NaBH_4$ was added in three portions, and the mixture was stirred at room temperature for 20 min longer. To the system was added 20 mL of NH_4Cl/NH_4OH pH 7 buffer solution, followed by 20 mL of H_2O. The mixture was extracted with dichloromethane (3 × 50 mL). The combined dichloromethane extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (20/1) with 15:85 ether/hexanes as the eluant to obtain 1.84 g (92% yield) of **19** as a white crystalline solid: mp 43–45 °C; IR (CCl_4) 3610, 1250 cm^{-1}; ^1H NMR δ 0.09 (s, 6 H), 0.91 (s, 9 H), 1.0 (d, 3 H, J = 7), 3.67 (dd, 1 H, J = 5.4, 10.3), 3.96 (dd, 1 H, J = 5.1, 10.3), 4.35 (m, 1 H), 5.77 (m, 1 H); ^{13}C NMR δ −5.5, 17.4, 18.2, 23.0, 25.3, 25.6, 25.9, 26.3, 29.6, 33.6, 40.6, 42.6, 46.8, 55.8, 64.3, 68.5, 116, 138. Anal. Calcd for $C_{21}H_{38}O_2S_2Si$: C, 60.81; H, 9.23. Found: C, 61.02; H, 9.25.

Reaction of 19 with Pyridinium *p*-Toluenesulfonate (PPTS). To a 0.03 M solution of 6.10 g (14.7 mmol) of alcohol **19** in 1,2-dichloroethane was added 0.37 g (1.47 mmol) of PPTS.[37] The reaction mixture was heated at reflux for 3 h and then diluted with an equal volume of ether and washed with half-saturated brine. The organic phase was dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (15/1) with 2:98 ether/hexanes as the eluant to obtain 3.79 g (65% yield) of **20** as a colorless oil: IR (film) 3025, 1460, 1260 cm^{-1}; ^1H NMR δ 0.03 (s, 6 H), 0.86 (s, 9 H), 1.09 (d, 3 H, J = 8), 3.58 (dd, 1 H, J = 7.1, 9.9), 3.71 (dd, 1 H, J = 4.3, 9.9), 5.52 (m, 1 H), 5.84 (m, 1 H), 6.21 (dd, 1 H, J = 2.4, 9.7); ^{13}C NMR δ −5.44, 18.7, 25.6, 25.9, 26.1, 27.0, 30.4, 30.9, 40.1, 40.8, 46.2, 55.3, 62.9, 122, 129, 131. Anal. Calcd for $C_{21}H_{36}OS_2Si$: C, 63.57; H, 9.14. Found: C, 63.20; H, 9.01.

Also isolated was 0.35 g (6% yield) of **21** as a white crystalline solid: mp 110–113 °C (from methanol); IR ($CDCl_3$) 3020, 2950, 1420, 1250 cm^{-1}; ^1H NMR δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.92 (s, 9 H), 0.93 (d, 3 H, J = 8.7), 1.85 (m, 2 H), 2.08 (m, 3 H), 2.37 (m, 2 H), 2.60 (m, 2 H), 2.85 (m, 3 H), 3.20 (m, 1 H), 3.60 (dd, 1 H, J = 10.7, 10.7), 4.95 (dd, 1 H, J = 5.2, 10.0), 5.53 (m, 1 H), 5.71 (dd, 1 H, J = 5.8, 9.4), 5.89 (d, 1 H, J = 9.6); ^{13}C NMR δ −5.17, −4.98, 0.98, 14.0, 18.2, 23.4, 25.1, 26.0, 27.0, 30.2, 34.5, 43.0, 43.3, 52.6, 64.0, 124, 128, 133, 134. Anal. Calcd for $C_{21}H_{36}OS_2Si$: C, 63.57; H, 9.15. Found: C, 63.84; H, 9.07.

[(2,4,6-Triisopropylphenyl)sulfonyl]hydrazone of (1*SR*,2*SR*,8a*RS*)-8-(1,3-Dithian-2-yl)-1-(hydroxymethyl)-2-methyl-4-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene (22). Into a 100-mL round-bottomed flask equipped with a rubber septum and magnetic stirring bar were placed 11.3 g (38.0 mmol) of [(2,4,6-triisopropylphenyl)sulfonyl]hydrazine, which was finely powdered with a glass stirring rod, and 37 mL of methanol. To the vigorously stirring suspension was added 11.2 g (37.6 mmol) of enone **12** with the aid of 15 mL of methanol as a rinse. The suspension was stirred rapidly, and the system was charged with 0.37 mL of concentrated hydrochloric acid. After a period of approximately 10 min, the reaction mixture thickened substantially, and stirring was continued for 20 min. The reaction mixture was refrigerated for several hours, the product was collected by suction filtration and rinsed with 15–20 mL of cold methanol, and residual methanol was removed under reduced pressure to obtain 17.6 g (81%) of **22** as an off-white solid which was judged to be pure by its ^1H NMR spectrum. An analytical sample, mp 124 °C dec, was prepared by recrystallization from methanol: IR ($CHCl_3$) 3600, 2950, 1600 cm^{-1}; ^1H NMR δ 1.13 (d, 3 H, J = 7), 1.26 (d, 18 H, J = 7), 1.45–3.00 (complex, 16 H), 3.14 (t, 2 H, J = 7), 3.51 (m, 1 H), 3.75 (m, 1 H), 4.24 (m, 2 H), 6.03 (m, 1 H), 7.16 (s, 2 H). Anal. Calcd for $C_{30}H_{46}N_2O_3S_3$: C, 62.24; H, 8.01; N, 4.84. Found: C, 62.13; H, 7.95; N, 4.76.

(1*SR*,2*SR*,8a*RS*)-8-(1,3-Dithian-2-yl)-1-(hydroxymethyl)-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (23). Under a nitrogen atmosphere, into a 1-L round-bottomed flask equipped with a rubber septum and magnetic stirring bar, were placed 17.6 g (30.4 mmol) of **22** and a mixture of 177 mL of hexanes and 17.7 mL of *N,N,N',N'*-tetramethylethylenediamine

(36) Compound **10** has been obtained on a scale of 146 mmol (37.0 g of compound 8) in 57% yield, after purification by flash chromatography.

(37) Prepared by the method in ref 20.

(TMEDA). To the stirring suspension, at −78 °C, was added 81.2 mL (122 mmol) of 1.5 M *n*-butyllithium in hexanes with a syringe. The reaction mixture was stirred at −78 °C for 15 min, the dry ice/acetone bath was replaced with an ice bath, and stirring was continued for 1 h at 0 °C. The mixture gradually became orange-brown and a relatively small amount of suspended solid remained. The reaction was quenched carefully with 250 mL of saturated aqueous ammonium chloride, and the light yellow mixture was stirred for 30 min at 0 °C. To the system was added 200 mL of ether and 100 mL of water, and the mixture was poured through a plug of glass wool into a separatory funnel (the filtered solids were rinsed with each portion of ether used for extraction). The layers were separated, and the aqueous phase was extracted with three 150-mL portions of ether. The combined organic fractions were washed with two 75-mL portions of brine and dried over magnesium sulfate, and the solvent was removed with a rotary evaporator to obtain 13.8 g of crude **23** as a yellow solid/oil mixture which was used in subsequent transformations without further purification. An analytical sample, mp 110–112 °C, was prepared by silcia gel column chromatography with 1:2 ether/hexanes as the eluant: IR ($CHCl_3$) 3615, 3445, 2950, 1415 cm^{-1}; ^1H NMR δ 0.98 (d, 3 H, J = 7.6), 1.20–3.00 (complex, 13 H), 3.28 (t, 1 H, J = 15), 3.70 (m, 1 H), 4.53 (m, 1 H), 5.55 (m, 1 H), 5.68 (dd, 1 H, J = 6, 9), 5.93 (d, 1 H, J = 10). Anal. Calcd for $C_{15}H_{22}OS_2$: C, 63.74; H, 7.85. Found: C, 63.98; H, 7.84.

(1*SR*,2*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-(1,3-dithian-2-yl)-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (21). Under a nitrogen atmosphere, into a 1-L round-bottomed flask equipped with a rubber septum and magnetic stirring bar, were placed 13.8 g of crude diene alcohol **23** and 125 mL of dichloromethane. To the stirring solution were added 16.2 mL (11.8 g, 118 mmol) of triethylamine, 192 mg (1.57 mmol) of DMAP, and 8.80 g (58.4 mmol) of *tert*-butylchlorodimethylsilane. The reaction mixture was stirred at room temperature for 24 h and partitioned between 350 mL of ether and 200 mL of water, and the layers were separated. The organic phase was washed with two 200-mL portions of water and 100 mL of brine. The combined aqueous washings were extracted with two 100-mL portions of ether, the combined organic fractions were dried over magnesium sulfate, and the solvent was removed with a rotary evaporator to obtain 19 g of crude product as a light brown solid. To this solid was added 20 mL of methanol, and the mixture was heated to boiling. Cooling of the mixture, followed by suction filtration (product rinsed with a small amount of cold methanol) gave 8.86 g (74% yield from **22**) of **21** as an off-white solid. The product obtained was found to be identical with the minor product isolated from the PPTS-catalyzed dehydration of **19** by ^1H NMR spectroscopy.

Treatment of (1*SR*,2*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-(1,3-dithian-2-yl)-2-methyl-1,2,3,7,8,8a-hexahydronaphthalene (20) with $HgCl_2/CdCO_3$. In a 250-mL round-bottomed flask were placed 1.20 g (3.03 mmol) of thioketal **20** and 75 mL of 4:1 acetonitrile/water. To this solution were added 2.09 g (12.1 mmol) of cadmium carbonate and 2.47 g (9.10 mmol) of mercuric chloride. The system was equipped with a reflux condenser, and the stirring mixture was heated at 60 °C under a nitrogen atmosphere for 3 h. After being cooled to room temperature, the mixture was diluted with 75 mL of ether and filtered through a Celite pad (solids rinsed repeatedly with ether). The ether solution was washed with several portions of 5 M aqueous ammonium acetate, followed by water and saturated aqueous sodium chloride. The organic solution was dried over magnesium sulfate and concentrated with a rotary evaporator. The resulting light yellow oil was purified by column chromatography (30 g of silica gel) with 1:2 ether/hexanes as the eluant to obtain 240 mg (26%) of (1*SR*,2*SR*)-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-8-hydroxy-2-methyl-1,2,3,4-tetrahydronaphthalene (**24**) as a light yellow oil (repurified by using 16:1 hexanes/ether as the eluant to give an analytical sample as a colorless oil) and 120 mg (21%) of (1*SR*,2*SR*)-8-hydroxy-1-(hydroxymethyl)-2-methyl-1,2,3,4-tetrahydronaphthalene (**25**) as a white solid, mp 93–101 °C.

Compound 24: IR (film) 3325 (br), 3060, 2950, 1580, 1460 cm^{-1}; ^1H NMR δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.90 (s, 9 H), 1.06 (d, 3 H, J = 8.9), 1.46 (m, 1 H), 1.65 (m, 1 H), 1.92 (m, 1 H), 2.90 (m, 2 H), 3.14 (m, 1 H), 3.67 (dd, 1 H, J = 11.2, 11.2), 4.15 (dd, 1 H, J = 3.3, 11.2), 6.71 (d, 1 H, J = 7.8), 6.77 (d, 1 H, J = 7.8), 7.07 (dd, 1, J = 7.8, 7.8), 8.22 (s, 1 H). Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.86. Found: C, 70.37; H, 9.70.

Compound 25: IR ($CHCl_3$) 3600, 3300, 3000, 2925, 1580, 1450 cm^{-1}; ^1H NMR δ 1.17 (d, 3 H, J = 8), 1.51 (m, 1 H), 1.67 (m, 1 H), 1.95 (m, 1 H), 2.28 (br s, 1 H), 2.88 (m, 2 H), 3.17 (m, 1 H), 3.75 (m, 1 H), 4.19 (m, 1 H), 6.75 (d, 1 H, J = 8), 6.78 (d, 1 H, J = 8), 7.07 (dd, 1 H, J = 8, 8), 7.87 (br s, 1 H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.11; H, 8.64.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-hydroxy-2-methyl-1,2,3,7,8,8a-hexahydronaphthalene (29). Under a nitrogen atmosphere, into a 250-mL round-bottomed flask was placed a mixture of 1.50 g (8.8 mmol) of silver nitrate, 1.07 g (8.0 mmol) of N-chlorosuccinimide, and 1.9 g (16 mmol) of 2,4,6-collidine in 100 mL of 4:1 acetonitrile/water. To this stirring mixture, cooled in an ice/acetone bath, was rapidly added 800 mg (2.02 mmol) of thioketal **20** in 10 mL of 80% acetonitrile/water which contained enough THF to dissolve the thioketal. After 20 min, the mixture was treated successively with 8 mL of saturated aqueous sodium sulfite, 8 mL of saturated aqueous sodium carbonate, and 8 mL of brine. The mixture was diluted with 100 mL of 1:1 hexanes/dichloromethane and filtered through a Celite pad, and the Celite was rinsed well with 1:1 hexanes/dichloromethane. The solution was washed with 5 M aqueous $Cu(NO_3)_2$ and then brine (until the brine no longer became colored). The aqueous washings were extracted with ether, and the combined organic fractions were dried over sodium sulfate. Concentration with a rotary evaporator afforded 0.75 g of crude ketone **26**.

The ketone was reduced immediately with L-Selectride as follows. Under a nitrogen atmosphere, in a 250-mL round-bottomed flask equipped with a rubber septum were placed the crude ketone **26** and 20 mL of THF. The stirring solution was cooled to −78 °C, and 6.00 mL (6.00 mmol) of 1 M L-Selectride in THF was added dropwise with a syringe. After 0.5 h the cooling bath was removed, and the solution was stirred for an additional period of 1 h. The system was immersed in an ice bath, and after 15 min, 2.6 mL of 10% aqueous sodium hydroxide was cautiously added, followed by 2.6 mL of 30% hydrogen peroxide. The ice bath was removed, and the reaction mixture was stirred for 1 h. The mixture was diluted with 50 mL of water, and the resulting solution was extracted with three 100-mL portions of ether. The combined ether fractions were washed sequentially with saturated aqueous sodium bisulfite, water, and brine. The organic phase was dried over sodium sulfate, and the solvent was removed with a rotary evaporator. The crude brown oil which remained was purified by column chromatography on 30 g of silica gel, with 1:9 ether/hexanes as the eluant, to give 280 mg (45% yield from thioketal **20**) of **29** as a colorless oil: IR (film) 3450, 1260 cm^{-1}; ^1H NMR δ 0.06 (s, 6 H), 0.83 (d, 3 H, J = 7), 0.88 (s, 9 H), 3.58 (dd, 1 H, J = 6.1, 10), 3.75 (dd, 1 H, J = 5.7, 10), 4.16 (m, 1 H), 5.52 (m, 1 H), 5.62 (m, 1 H), 6.09 (d, 1 H, J = 10); ^{13}C NMR δ −5.63, −5.53, 14.1, 18.1, 24.9, 25.8, 28.3, 33.7, 34.2, 38.9, 39.9, 64.7, 65.4, 122, 127, 130.

(1*SR*,2*SR*,8*SR*,8a*RS*)-8-(Hydroxymethyl)-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,3,7,8,8a-hexahydronaphthalene (32 and 33). Under a nitrogen atmosphere, into a 250-mL round-bottomed flask equipped with a rubber septum and magnetic stirring bar were placed 0.28 g (0.91 mmol) of alcohol **29** and 20 mL of dichloromethane. To the stirring solution were added 0.62 mL (0.45 g, 4.5 mmol) of triethylamine, 26 mg (0.21 mmol) of DMAP, and 0.64 mL (0.60 g, 3.2 mmol) of (*S*)-2-methylbutyric anhydride. The mixture was stirred at room temperature for 84 h, during which time 0.36 mL (1.82 mmol) of additional anhydride, 0.34 mL (3.4 mmol) of triethylamine, and a small amount of DMAP were added to the system. The system was charged with 8 mL of methanol, and the mixture was stirred for 45 min. Ether was added and the mixture was washed with two portions of 10% aqueous HCl, two portions of saturated aqueous $NaHCO_3$, H_2O, and brine. The organic solution was dried ($MgSO_4$), and the solvent was removed with a rotary evaporator to obtain 352 mg (97%) of crude **30** and **31** as a light yellow oil. The crude product was used without further purification.

Under a nitrogen atmosphere, into a 50-mL round-bottomed flask equipped with a rubber septum and magnetic stirring bar were placed 337 mg (0.86 mmol) of crude silyl ethers **30** and **31**

and 25 mL of THF. To the stirring solution was added 2.15 mL (2.15 mmol) of 1 M *n*-Bu_4NF in THF. After 14 h, TLC showed no silyl ether remaining. The reaction mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The solution was dried over magnesium sulfate and concentrated with a rotary evaporator. The crude product was purified by column chromatography (25 g of silica gel), gradually increasing the polarity of the eluant from 1:4 ether/hexanes to 2:5 ether/hexanes to obtain 220 mg (92%) of **32** and **33** as a light yellow oil: IR (film) 3425 (br), 3020, 2960, 1720, 1460, 1380 cm^{-1}; ^1H NMR δ 0.91 (d, 3 H, J = 8), 0.92 (t, 2 H), 1.11 (d, 3 H, J = 8), 1.45 (m, 1 H), 1.67 (m, 4 H), 1.95 (m, 1 H), 2.34 (m, 6 H), 3.60 (m, 1 H), 3.86 (m, 1 H), 5.47 (m, 2 H), 5.62 (m, 1 H), 6.12 (d, 1 H, J = 10). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.09; H, 9.30.

(1*SR*,2*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-hydroxy-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (28). Under a nitrogen atmosphere, into a 2-L round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed a mixture of 12.1 g (70.8 mmol) of silver nitrate, 8.56 g (64.4 mmol) of *N*-chlorosuccinimide (NCS), 17.2 mL (15.8 g, 130 mmol) of 2,4,6-collidine, and 760 mL of 4:1 acetonitrile/water. The system was immersed in an ice/acetone bath, and to the vigorously stirring mixture was added a solution of 6.40 g (16.2 mmol) of thioketal **21** in a mixture of 96 mL of acetonitrile and ca. 25–30 mL of THF. Immediate TLC analysis of the reaction mixture indicated that no **21** remained. To the system were added sequentially at 1 min intervals 96 mL of saturated aqueous sodium sulfite, 96 mL of saturated aqueous sodium carbonate, and 96 mL of brine. Chloroform (800 mL) was added, the mixture was filtered through a Celite pad, the solids were rinsed well with chloroform, and the layers were separated. The aqueous phase was extracted with two 400-mL portions of chloroform. The combined organic fractions were washed with four 150-mL portions of 5 M cupric nitrate and two portions of water and dried over sodium sulfate, and the solvent was removed with a rotary evaporator to obtain 6.3 g of crude ketone **27**: IR (film) 3020, 2950, 1715, 1255 cm^{-1}; ^1H NMR δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9), 0.94 (d, 3 H, J = 7.0), 2.24 (m, 1 H), 2.52 (m, 5 H), 3.01 (d, 1 H, J = 12), 3.59 (dd, 1 H, J = 8.59, 9.8), 3.84 (dd, 1 H, J = 5.2, 10), 5.64 (m, 1 H), 5.76 (dd, 1 H, J = 5.6, 9.7), 6.01 (d, 1 H, J = 9.7).

Under an argon atmosphere, into a 2-L round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed the crude ketone **27** and 250 mL of THF. To the stirring solution, at −78 °C, was added 48.6 mL (48.6 mmol) of 1 M L-Selectride in THF with a syringe. The reaction mixture was stirred for 7.5 h at −78 °C and 75 min at room temperature. The system was cooled to 0 °C, cautiously charged with 21.2 mL of 10% aqueous sodium hydroxide and 21.2 mL of 30% hydrogen peroxide, and the mixture was stirred for 1 h at room temperature. The reaction mixture was partitioned between 650 mL of ether and 480 mL of water, the layers were separated, and the aqueous phase was extracted with three 300-mL portions of chloroform. The combined organic fractions were washed with 250 mL of 10% aqueous sodium bisulfite and brine and dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. The resulting brown oil (6.7 g) was purified by column chromatography (approximately 70 g of silica gel) with 1:6 ether/hexanes as the eluant to obtain 3.63 g (73% yield from thioketal **21**) of alcohol **29** as a light yellow liquid which crystallized upon standing in a refrigerator: mp 46–49 °C; IR ($CHCl_3$) 3450, 3000, 2930 cm^{-1}; ^1H NMR δ 0.05 (s, 6 H), 0.88 (d, 3 H, J = 8), 0.92 (s, 9 H), 1.71 (m, 1 H), 2.03 (m, 3 H), 2.40 (m, 3 H), 3.70 (m, 3 H), 4.22 (br s, 1 H), 5.67 (m, 2 H), 5.98 (d, 1 H, J = 12). Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.46. Found: C, 70.4; H, 10.5.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-[(2-methoxyethoxy)methoxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (34). Under a nitrogen atmosphere, into an oven-dried 25-mL round-bottomed flask equipped with a rubber septum were placed 600 mg (1.95 mmol) of alcohol **28** and 6 mL of dichloromethane. To the stirring solution were added 3.38 mL (2.51 g, 19.4 mmol) of *N*,*N*-diisopropylethylamine, 60.0 mg (0.49 mmol) of DMAP, and 2.01 mL (2.19 g, 17.6 mmol) of (methoxyethoxy)methyl chloride. The mixture became turbid and then clear yellow. After 22 h, the reaction mixture was diluted with ether, and the resulting suspension was washed successively with three portions of water, two portions of 10% aqueous HCl, and a single portion of brine (all 10–15-mL portions). The aqueous washings were combined and extracted twice with ether (5 mL each). The combined organic fractions were dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. The crude product was purified by column chromatography (ca. 10 g of silica gel), with 1:2 ether/hexanes as the eluant, to obtain 701 mg (91%) of pure **34** as a light yellow liquid: IR (film) 3025, 2940, 1460 cm^{-1}; ^1H NMR δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 0.94 (d, 3 H, J = 7), 1.60 (m, 1 H), 2.02–2.63 (m, 6 H), 3.40 (s, 3 H), 3.51–3.91 (m, 6 H), 3.99 (br s, 1 H), 4.81 (d, 1 H, J = 7.6), 4.89 (d, 1 H, J = 7.6), 5.55 (br s, 1 H), 5.73 (m, 1 H), 5.95 (d, 1 H, J = 9.1). Anal. Calcd for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.16. Found: C, 66.74; H, 10.15.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-(Hydroxymethyl)-8-[(2-methoxyethoxy)methoxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (35). Under a nitrogen atmosphere, into a 500-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 2.20 g (5.52 mmol) of silyl ether **34** and 23 mL of THF. To the stirring solution was added 13.8 mL (13.8 mmol) of 1 M tetrabutylammonium fluoride (TBAF) in THF with a syringe. The reaction mixture was stirred at room temperature for 7 h, diluted with 150 mL of ether, and cautiously washed with two portions of saturated aqueous sodium bicarbonate and a portion of brine. The combined aqueous washings were extracted with two 25-mL portions of ether, the combined organic fractions were dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. The resulting crude product (2.3 g) was purified by column chromatography (35 g of silica gel) with 1:2 ether/hexanes as the eluant to obtain 1.56 g (quantitative yield) of alcohol **35** as a pale yellow oil which partially crystallized upon standing in a refrigerator: IR (film) 3430, 3015, 2930, 1445, 1365 cm^{-1}; ^1H NMR δ 0.98 (d, 3 H, J = 7), 1.58 (m, 1 H), 2.20 (m, 5 H), 2.68 (m, 2 H), 3.42 (s, 3 H), 3.54 (m, 4 H), 4.12 (m, 3 H), 4.74 (d, 1 H, J = 7.5), 4.90 (d, 1 H, J = 7.5), 5.58 (br s, 1 H), 5.77 (m, 1 H), 5.97 (d, 1 H, J = 9.7). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.84; H, 9.05.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-[[(Methylsulfonyl)oxy]methyl]-8-[(2-methoxyethoxy)methoxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (36). Into an oven-dried, 100-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 1.26 g (4.48 mmol) of alcohol **35** and 14 mL of dichloromethane. The flask was immersed in an ice bath, and 1.06 mL (772 mg, 7.63 mmol) of triethylamine was added followed by 0.38 mL (566 mg, 4.94 mmol) of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for approximately 4 h and was partitioned between ether and brine. The layers were separated, and the organic phase was washed with two portions of 10% aqueous HCl and one portion each of saturated aqueous sodium bicarbonate and brine (all ca. 30-mL portions). The combined aqueous washings were extracted with ether. The combined organic extracts were dried over magnesium sulfate and concentrated with a rotary evaporator. Residual solvent was removed under high vacuum to obtain 1.55 g (96%) of methanesulfonate ester **36** as a viscous yellow oil which was used in subsequent transformations without further purification. An analytical sample was prepared by silica gel chromatography: IR (film) 3020, 2925, 1450, 1350, 1235, 1170 cm^{-1}; ^1H NMR δ 1.01 (d, 3 H, J = 7), 1.59 (m, 1 H), 2.20 (m, 3 H), 2.40 (m, 2 H), 2.54 (m, 1 H), 3.04 (s, 3 H), 3.38 (s, 3 H), 3.54 (m, 2 H), 3.70 (m, 1 H), 3.84 (m, 1 H), 4.02 (br s, 1 H), 4.25 (m, 1 H), 4.63 (m, 1 H), 4.79 (d, 1 H, J = 7.2), 4.90 (d, 1 H, J = 7.2), 5.61 (br s, 1 H), 5.71 (m, 1 H), 5.98 (d, 1 H, J = 9.6). Anal. Calcd for $C_{17}H_{28}O_6S$: C, 56.64; H, 7.83. Found: 55.65; H, 7.66.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-[(Phenylsulfonyl)methyl]-8-[(2-methoxyethoxy)methoxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (39). Under a nitrogen atmosphere, into a 25-mL round-bottomed flask equipped with a reflux condenser were placed 406 mg (1.13 mmol) of methanesulfonate ester **36** and 6 mL of THF. To the stirring solution was added 1.27 g (7.77 mmol) of sodium benzenesulfinate followed by 2.05 g (5.55 mmol) of tetrabutylammonium iodide. The mixture was heated under reflux, and additional sodium benzenesulfinate was added after 3.5 h (500 mg, 3.04 mmol) and 6.5 h (200 mg, 1.22 mmol). After 7 h the mixture was partitioned between ether and water. The

layers were separated, and the organic phase was washed with water and brine. The aqueous washings were extracted with ether, and the combined organic fractions were dried over magnesium sulfate and concentrated with a rotary evaporator. The crude product was purified by column chromatography (ca. 5 g of silica gel), with 2:1 ether/hexanes as the eluant, to obtain 243 mg (53%) of pure sulfone **39** as a highly crystalline white solid: mp 83.5–87.5 °C; IR (film) 3020, 2930, 1445, 1305, 1140, 1085 cm^{-1}; ^1H NMR δ 1.01 (d, 3 H, J = 6.9), 1.58 (m, 1 H), 1.95–2.37 (m, 4 H), 2.52 (m, 1 H), 2.94 (m, 1 H), 3.15 (dd, 1 H, J = 11.9, 14.0), 3.34 (s, 3 H), 3.54 (m, 3 H), 3.72 (m, 2 H), 3.94 (br s, 1 H), 4.69 (s, 2 H), 5.56 (br s, 1 H), 5.72 (m, 1 H), 5.94 (d, 1 H, J = 9.6), 7.59 (m, 3 H), 7.95 (d, 2 H, J = 6.9); mass spectrum (70 eV); m/z 406 (parent), 59 (base). Anal. Calcd for $C_{22}H_{30}O_5S$: C, 64.99; H, 7.44. Found: C, 65.03; H, 7.40.

Reaction of (1*SR*,2*SR*,8*SR*,8a*RS*)-1-[[(Methylsulfonyl)oxy]methyl]-8-[(2-methoxyethoxy)methoxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (36) with Tetrabutylammonium Bromide and Sodium Benzenesulfinate. Under a nitrogen atmosphere, into a 10-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar were placed 105 mg (0.292 mmol) of methanesulfonate ester **36** and 1.5 mL of THF. To the stirring solution was added 228 mg (1.39 mmol) of sodium benzenesulfinate followed by 448 mg (1.39 mmol) of tetrabutylammonium bromide. The mixture was heated at reflux for 1 h and partitioned between ether and water. The layers were separated, and the organic phase was washed with brine. The aqueous washings was extracted with ether, and the organic fractions were combined and dried over magnesium sulfate. The solvent was removed with a rotary evaporator, and the crude product mixture was purified by column chromatography (2 g of silica gel) with 2:1 ether/hexanes as the eluant to obtain 35.5 mg (35%) of bromide **44** as a faint yellow oil and 30.6 mg (26%) of sulfone **39** as a white solid, identified by its ^1H NMR spectrum (vide supra).

Compound 44: IR (film) 3020, 2920, 1445, 1365, 1260 cm^{-1}; ^1H NMR δ 0.94 (d, 3 H, J = 7.0), 1.59 (m, 1 H), 2.20 (m, 5 H), 2.73 (m, 1 H), 3.23 (m, 1 H), 3.40 (s, 3 H), 3.66 (m, 3 H), 3.93 (m, 1 H), 4.04 (m, 1 H), 4.12 (br s, 1 H), 4.74 (d, 1 H, J = 7.6), 4.93 (d, 1 H, J = 7.6), 5.58 (br s, 1 H), 5.75 (m, 1 H), 5.97 (d, 1 H, J = 9.1); mass spectrum (70 eV), m/z 344, 346 (parent), 43 (base); HRMS, calcd for $C_{16}H_{25}O_3Br$ 344.0988, found 344.1001.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-(Iodomethyl)-8-[(2-methoxyethoxy)methoxy]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (37). Under a nitrogen atmosphere, into a 500-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar were placed 1.90 g (5.27 mmol) of methanesulfonate ester **36** and 28 mL of THF. To the stirring solution was added 11.7 g (31.7 mmol) of tetrabutylammonium iodide. The system was immersed in an oil bath (90–95 °C), and the mixture was heated at reflux for 135 min, at which time TLC indicated that no **36** remained. The reaction mixture was cooled to room temperature and partitioned between 250 mL of ether and 100 mL of water. The mixture was poured through a plug of glass wool into a separatory funnel, the solids were rinsed well with ether, the layers were separated, and the organic phase was washed with 50 mL of brine. The combined aqueous washings were extracted with ether, the combined organic fractions were dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. The resulting solid/oil mixture was purified by column chromatography (19 g of silica gel) with 1:2 ether/hexanes as the eluant to obtain 1.80 g of pure iodide **37** as a white crystalline solid: mp 39–41 °C; IR (film) 3020, 2920, 1445, 1245 cm^{-1}; ^1H NMR δ 0.88 (d, 3 H, J = 7.0), 1.55 (m, 1 H), 2.19 (m, 5 H), 2.69 (m, 1 H), 2.93 (dd, 1 H, J = 9.6, 12.0), 3.42 (s, 3 H), 3.64 (m, 3 H), 3.91 (m, 2 H), 4.18 (br s, 1 H), 4.73 (d, 1 H, J = 7.5), 4.92 (d, 1 H, J = 7.5), 5.57 (br s, 1 H), 5.74 (m, 1 H), 5.95 (d, 1 H, J = 9.7); mass spectrum (70 eV), m/z 392 (parent), 59 (base); HRMS, calcd for $C_{16}H_{25}O_3I$ 392.0850, found 392.0857.

(1*SR*,2*SR*,8*SR*,8a*RS*)-2-Methyl-8-[(2-methoxyethoxy)methoxy]-1-[(triphenylphosphonio)methyl]-1,2,6,7,8,8a-hexahydronaphthalene Iodide (38). Under an argon atmosphere, into a 100-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar were placed 355 mg (0.90 mmol) of iodide **37** and 0.9 mL of THF. To the stirring solution was added 237 mg (0.90 mmol) of triphenylphosphine, and the system was immersed in a heating bath (100 °C). The THF gradually evaporated as the system was heated at 100 °C for a period of 13 h. The resulting yellow oil was triturated with ether, causing the formation of a thick wax. The ether rinse contained 119 mg of a mixture of triphenylphosphine and cyclic ether **42**. The wax was purified by column chromatography (10 g of silica gel) with successively 1:1 ether/ethyl acetate, ethyl acetate, and isopropyl alcohol as the eluant to obtain 328 mg (55% yield) of **38** as a light yellow solid: mp 73–77 °C; IR ($CHCl_3$) 3010, 2930, 1260 cm^{-1}; ^1H NMR δ 0.73 (d, 3 H, J = 6.8), 1.70–2.93 (complex, 7 H), 3.05–3.55 (complex, 4 H), 3.16 (s, 3 H), 3.86 (br t, 1 H, J = 16), 4.18 (m, 1 H), 4.67 (br s, 1 H), 4.69 (d, 1 H, J = 5.4), 4.77 (d, 1 H, J = 5.4), 5.44 (dd, 1 H, J = 6.3, 9.4), 5.56 (br s, 1 H), 5.86 (d, 1 H, J = 9.4), 7.77 (m, 9 H), 7.97 (m, 6 H); MS (FAB), m/z 527 (parent – I, base).

(1*SR*,2*SR*,8*SR*,8a*RS*)-8-Hydroxy-1-(hydroxymethyl)-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (40). Under a nitrogen atmosphere, into a 50-mL round-bottomed flask equipped with a magnetic stirring bar was placed 93.4 mg (0.30 mmol) of silyl ether **28**. To the system was added 4.0 mL of a 5% solution of 40% aqueous HF in acetonitrile. The resulting solution was stirred at room temperature for 20 min, diluted with 30 mL of chloroform, and washed with 15 mL of saturated aqueous $NaHCO_3$ and 15 mL of brine. The combined aqueous washings were extracted with 20 mL of chloroform, the combined organic fractions were dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude solid (65.4 mg) was heated in 5–10 mL of hexanes, cooled, and filtered to obtain 56.9 mg of pure diol **40** as a white solid: mp 130.5–132 °C; IR ($CHCl_3$) 3640, 3475, 3000, 2950 cm^{-1}; ^1H NMR δ 0.87 (d, 3 H, J = 7.0), 1.66–2.92 (complex, 9 H), 3.72 (dd, 1 H, J = 3.3, 10), 3.85 (dd, 1 H, J = 8.2, 10), 4.28 (br s, 1 H), 5.61 (m, 1 H), 5.68 (dd, 1 H, J = 5.8, 9.6), 5.96 (d, 1 H, J = 9.7); HRMS, calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1305.

(1*SR*,2*SR*,8*SR*,8a*RS*)-8-Hydroxy-[[(methylsulfonyl)oxy]methyl]-2-methyl-1,2,6,7,8,8a-hexahydronaphthalene (41). Under a nitrogen atmosphere, into a 100-mL round-bottomed flask equipped with a magnetic stirring bar were placed 53.4 mg (0.28 mmol) of diol **40** and 1 mL of dichloromethane. To the stirring solution was added 0.085 mL (61.7 mg, 0.61 mmol) of triethylamine. The system was cooled to 0 °C and charged with a solution of 0.020 mL (30.2 mg, 0.26 mmol) of methanesulfonyl chloride in 0.25 mL of dichloromethane. After being stirred at 0 °C for 15 min, 40 mL of dichloromethane was added, and the solution was washed with 15 mL of 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The combined aqueous washings were extracted with 25 mL of dichloromethane, the combined organic fractions were dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude product (87.1 mg) was purified by column chromatography (2 g of silica gel) with ether as the eluant to obtain 65.6 mg (88% yield) of **41** as a colorless oil: IR ($CHCl_3$) 3610, 3410, 2950, 1350 cm^{-1}; ^1H NMR δ 0.97 (d, 3 H, J = 7.0), 1.61–2.61 (complex, 8 H), 3.02 (s, 3 H), 4.06 (br s, 1 H), 4.25 (m, 1 H), 4.57 (m, 1 H), 5.58 (m, 1 H), 5.68 (dd, 1 H, J = 5.9, 9.6), 5.95 (d, 1 H, J = 9.7); HRMS, calcd for $C_{13}H_{20}O_4S$ 272.1083, found 272.1091.

If an excess of methanesulfonyl chloride is used, the corresponding dimesylate is isolated as white needles: mp 100–101 °C; IR ($CHCl_3$) 3015, 2940, 1355, 1330 cm^{-1}; ^1H NMR δ 1.01 (d, 3 H, J = 7.0), 1.80 (m, 1 H), 2.19–2.70 (complex, 6 H), 3.07 (s, 3 H), 3.09 (s, 3 H), 4.22 (t, 1 H, J = 10), 4.63 (dd, 1 H, J = 4.5, 10), 5.15 (m, 1 H), 5.61 (m, 1 H), 5.73 (dd, 1 H, J = 5.9, 10), 5.96 (d, 1 H, J = 10). Anal. Calcd for $C_{14}H_{22}O_6S_2$: C, 47.98; H, 6.33. Found: C, 47.99; H, 6.22.

Treatment of Methanesulfonate Ester 41 with Sodium Hydride. Under an argon atmosphere, into a round-bottomed flask equipped with a magnetic stirring bar were placed 19.2 mg (0.070 mmol) of methanesulfonate ester **41** and 0.8 mL of THF. To the stirring solution, at room temperature, was added 10.0 mg of 50% sodium hydride mineral oil dispersion (0.21 mmol of NaH). The addition was accompanied by a vigorous evolution of gas. The mixture was stirred at room temperature for 10 h and partitioned between 20 mL of ether and 5 mL of H_2O. The layers were separated, the organic phase was washed with brine, and the combined aqueous washings were extracted with 10 mL of ether. The combined organic fractions were dried ($MgSO_4$), the solvent was removed with a rotary evaporator, and the crude

product was purified by column chromatography (1 g of silica gel) to obtain 12.3 mg of ether **42** as a colorless oil: IR ($CHCl_3$) 2960 cm^{-1}; ^1H NMR δ 0.98 (d, 3 H, J = 7.2), 1.97–2.64 (complex, 7 H), 3.58 (dd, 1 H, J = 7.9, 11), 3.99 (dd, 1 H, J = 6.4, 7.9), 4.26 (m, 1 H), 5.60 (m, 1 H), 5.67 (dd, 1 H, J = 5.0, 9.7), 6.12 (d, 1 H, J = 10); HRMS; calcd for $C_{12}H_{16}O$ 176.1202, found 176.1196.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (48 and 49). Under a nitrogen atmosphere, into a 50-mL round-bottomed flask equipped with rubber septum and a magnetic stirring bar were placed 376 mg (1.22 mmol) of alcohol **28** and 4 mL of dichloromethane. To the stirring solution were added 74.2 mg (0.61 mmol) of DMAP, 0.95 mL (692 mg, 6.85 mmol) of triethylamine, and 0.98 mL (908 mg, 4.88 mmol) of (*S*)-2-methylbutyric anhydride. The reaction mixture was stirred at room temperature for 12 h, diluted with 75 mL of ether, and washed consecutively with 20-mL portions of 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The combined aqueous washings were extracted with ether. The combined organic fractions were dried over magnesium sulfate, the solvent was removed with a rotary evaporator, and residual (*S*)-2-methylbutyric anhydride was removed in vacuo (4–5 h, 75 °C, 0.05 mm) to obtain 481 mg (quantitative yield) of **48** and **49** as a light yellow liquid. The crude ester, contaminated with a trace of anhydride, was used without further purification. An analytical sample (colorless liquid) was prepared by column chromatography: IR (film) 3025, 2970, 2870, 1730, 1465, 1260 cm^{-1}; ^1H NMR δ 0.01, 0.04 (s, 6), 0.87 (s, 9), 0.93 (complex, 6), 1.12, 1.13 (d, 3, J = 7.0), 1.38–2.62 (complex, 10), 3.50 (t, 1, J = 9.8), 3.70 (dd, 1, J = 4.0, 9.8), 5.18 (br s, 1), 5.55 (br s, 1), 5.75 (dd, 1, J = 4.0, 9.6), 5.97 (d, 1, J = 9.6). Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.35; H, 10.27. Found: C, 70.17; H, 10.26.

(1*SR*,2*SR*,8*SR*,8a*RS*)-1-(Hydroxymethyl)-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (5 and 50). Under a nitrogen atmosphere, into a 100-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 358 mg (0.91 mmol) of **48** and **49** and 5 mL of THF. The system was charged with 2.73 mL (2.73 mmol) of 1 M TBAF in THF, and the solution was stirred at room temperature for 9 h. The reaction mixture was diluted with 100 mL of ether and washed carefully with two 20-mL portions of saturated aqueous sodium bicarbonate followed by brine. The combined aqueous washings were extracted with ether, the combined organic fractions were dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. The resulting orange liquid was purified by column chromatography (7 g of silica gel) with 1:2 ether/hexanes as the eluant, and residual solvent was removed in vacuo (65 °C, 0.05 mm) to obtain 256 mg (quantitative yield) of **5** and **50** as a pale yellow viscous oil which became a white solid upon cooling: mp 42–50.5 °C; IR (film) 3425, 2920, 1710, 1450 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.15; H, 9.22.

(1*SR*,2*SR*,8a*RS*)-8-(1,3-Dithian-2-yl)-2-methyl-1-[[(*S*)-(*O*-methylmandelyl)oxy]methyl]-4-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene (53 and 54). Under a nitrogen atmosphere, into a 25 mL-round-bottomed flask equipped with rubber septum and a magnetic stirring bar were placed 150 mg (0.50 mmol) of alcohol **11** and 2 mL of dichloromethane. To the stirring solution were added 24 mg (0.20 mmol) of DMAP, 0.32 mL (230 mg, 2.25 mmol) of triethylamine, and 280 mg (1.51 mmol) of (*S*)-*O*-methylmandelyl chloride in 2 mL of dichloromethane. The syringe which delivered the acid chloride was rinsed with 2 mL of dichloromethane, and the rinse was added to the system. The mixture was stirred for 30 min at room temperature, diluted with dichloromethane, and washed successively with two 10-mL portions of 10% aqueous hydrochloric acid, two 10-mL portions of saturated aqueous sodium bicarbonate, and brine. The dichloromethane solution was dried over magnesium sulfate, the solvent was removed with a rotary evaporator, and the resulting yellow oil was purified by column chromatography (25 g of silica gel) to obtain 200 mg (91% yield) of **53** and **54** as a white foam: IR ($CHCl_3$) 3000, 2960, 2020, 1745, 1680, 1620, 1260, 1175 cm^{-1}; ^1H NMR δ 0.93, 1.02 (2 d, 3 H, J = 6.8, 6.1), 1.63–3.26 (complex, 15 H), 3.36, 3.37 (2 s, 3 H), 4.18 (dd, 1 H, J = 4.9, 12), 4.40 (m, 1 H), 4.68 (s, 1 H), 6.63 (m, 1 H), 7.37 (m, 5 H). Anal. Calcd for $C_{24}H_{30}O_4S_2$: C, 64.54; H, 6.77. Found: C, 64.36; H, 6.82.

(1*SR*,2*SR*,8*SR*,8a*RS*)-2-Methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1-[[(*R*)-(*O*-methylmandelyl)oxy]methyl]-1,2,6,7,8,8a-hexahydronaphthalene (51 and 52). Under a nitrogen atmosphere, into a 10-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 83.4 mg of ester alcohols **5** and **50** and 1 mL of dichloromethane. To the stirring solution were added 0.16 mL (115 mg, 1.12 mmol) of triethylamine, 12 mg (0.10 mmol) of DMAP, and 208 mg (0.75 mmol) of (*R*)-*O*-methylmandelyl chloride in 1 mL of dichloromethane. The syringe which delivered the acid chloride was rinsed with 1 mL of dichloromethane, and the rinse was added to the system. The mixture was stirred 30 min at room temperature, diluted with ether, and washed successively with two 5-mL portions of 10% aqueous hydrochloric acid, two 5-mL portions of saturated aqueous sodium bicarbonate, and brine. The ether solution was dried over magnesium sulfate, the solvent was removed with a rotary evaporator, and the crude product was purified by column chromatography (10 g of silica gel) with 1:4 ether/hexanes as the eluant to obtain 112 mg (88% yield) of **51** and **52** as a colorless viscous oil which was analytically pure; IR (mixture, film) 2850, 1730, 1450, 1175 cm^{-1}. The two diastereomers could be separated by HPLC.

Compound 51: ^1H NMR δ 0.69 (d, 3 H, J = 6.8), 0.87 (t, 3 H, J = 7.4), 1.12 (d, 3 H, J = 7.0), 1.50 (m, 3 H), 2.14 (m, 5 H), 2.36 (m, 2 H), 3.41 (s, 3 H), 3.98 (dd, 1 H, J = 9.7, 11), 4.21 (dd, 1 H, J = 4.0, 11), 4.74 (s, 1 H), 5.00 (br s, 1 H), 5.57 (m, 2 H), 5.94 (d, 1 H, J = 9.6), 7.48 (m, 5 H).

Compound 52: ^1H NMR δ 0.72 (d, 3 H, J = 6.8), 0.79 (t, 3 H, J = 7.4), 1.06 (d, 3 H, J = 7.0), 1.37 (m, 1 H), 1.62 (m, 2 H), 2.11 (m, 5 H), 2.35 (m, 2 H), 3.40 (s, 3 H), 3.99 (t, 1 H, J = 10.4), 4.23 (dd, 1 H, J = 3.9, 11), 4.74 (s, 1 H), 5.10 (br s, 1 H), 5.59 (m, 2 H), 5.93 (d, 1 H, J = 9.7), 7.35 (m, 5 H). Anal. (mixture of **51** and **52**) Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 72.99; H, 7.96.

(1*SR*,2*SR*,8*SR*,8a*RS*)-2-Methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1-[[(*S*)-(*O*-methylmandelyl)oxy]methyl]-1,2,6,7,8,8a-hexahydronaphthalene (55 and 56). Under a nitrogen atmosphere, into a 500-mL round-bottomed flask equipped with a rubber septum and a magnetic stirring bar were placed 690 mg (2.48 mmol) of a mixture of **5** and **50**, 31.7 mg (0.26 mmol) of DMAP, 436 mg (2.63 mmol) of (*S*)-*O*-methylmandelic acid, and 4 mL of dichloromethane. To this stirring solution, at 0 °C, was added 542 mg (2.63 mmol) of 1,3-dicyclohexylcarbodiimide. After being stirred for 20 min at 0 °C and 12 h at room temperature, the reaction mixture was diluted with ether, and the white solids were removed by suction filtration. The filtrate was washed with 1 M aqueous phosphoric acid, saturated aqueous sodium bicarbonate, and brine. The combined aqueous washings were extracted with ether, the combined organic fractions were dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude yellow oil was purified by column chromatography (20 g of silica gel) with 1:3 ether/hexanes as the eluant to obtain 996 mg (94% yield) of **55** and **56**; IR (mixture, film) 3025, 2970, 1750, 1730, 1450 cm^{-1}. The diastereomers were separated by HPLC.[38]

Compound 55: ^1H NMR δ 0.68 (d, 3 H, J = 6.8), 0.86 (t, 3 H, J = 7.4), 1.10 (d, 3 H, J = 7), 1.57 (m, 3 H), 2.03–2.45 (complex, 7 H), 3.41 (s, 3 H), 4.00 (t, 1 H, J = 11), 4.19 (dd, 1 H, J = 4, 11), 4.74 (s, 1 H), 4.99 (br s, 1 H), 5.60 (m, 2 H), 5.94 (d, 1 H, J = 9.6), 7.39 (m, 5 H).

Compound 56: ^1H NMR δ 0.72 (d, 3 H, J 6.8), 0.83 (t, 3 H, J = 7.4), 1.06 (d, 3 H, J = 7), 1.42 (m, 1 H), 1.62 (m, 2 H), 2.13 (m, 5 H), 2.36 (m, 2 H), 3.40 (s, 3 H), 3.96 (dd, 1 H, J = 10, 11), 4.24 (dd, 1 H, J = 3.8, 11), 4.74 (s, 1 H), 5.12 (br s, 1 H), 5.56 (m, 2 H), 5.92 (d, 1 H, J = 9.7), 7.38 (m, 5 H). Anal. (mixture of **55** and **56**) Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.03. Found: C, 73.18; H, 8.20.

(1*S*,2*S*,8*S*,8a*R*)-1-(Hydroxymethyl)-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (5). Under an argon atmosphere, into a 100-mL round-bottomed flask

(38) Parameters for HPLC: two μ-Porasil semipreparative columns and one Pirkle-type 1A semipreparative column in series; 25–35 mg/injection, 1:4 ether/hexanes, 4 mL min^{-1}; t_R of compound **56**, 43 min; compound **55**, 53 min.

(39) The symbol ΣSi is used to represent the *tert*-butyldimethylsilyl radical.

equipped with a rubber septum and magnetic stirring bar was placed 142 mg (0.33 mmol) of diester **55**. The system (cooled to 0 °C) was charged with 7.17 mL (0.66 mmol) of 0.092 M potassium hydroxide in methanol, and the solution was stirred for 5.5 h, during which time the ice bath melted and the cooling bath was maintained at 10–20 °C. After being warmed to room temperature and stirred for a further period of 40 min, the reaction mixture was diluted with 70 mL of ether and washed with 10 mL of brine and 10 mL of water. The combined aqueous washings were extracted with 25 mL of ether, the combined organic fractions were dried over magnesium sulfate, and the solvent was removed with a rotary evaporator. The crude material (140 mg) was purified by column chromatography (6 g of silica gel) with 1:2 ether/hexanes as the eluant to obtain 92.4 mg (quantitative yield) of **5** as a white crystalline solid. This material was recrystallized from spectrophotometric grade pentane by slow evaporation at room temperature to afford small white needles: mp 64.5–65.5 °C; $[\alpha]^{25}_D$ +328° (*c* 0.42, $CHCl_3$); ^1H NMR δ 0.89 (t, 3 H, J = 7.4), 0.99 (d, 3 H, J = 7.0), 1.14 (d, 3 H, J = 7.0), 1.40–2.64 (complex, 11 H), 3.58 (t, 1 H, J = 10), 3.79 (dd, 1 H, J = 4.5, 10), 5.20 (m, 1 H), 5.58 (m, 1 H), 5.76 (dd, 1 H, J = 5.4, 9.7), 5.99 (d, 1 H, J = 9.7). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.19; H, 9.26. The stereostructure of **5** was verified by single-crystal X-ray analysis.

(1*R*,2*R*,8*R*,8a*S*)-1-(Hydroxymethyl)-2-methyl-8-[(*S*)-(2-methylbutyryl)oxy]-1,2,6,7,8,8a-hexahydronaphthalene (50). This compound was prepared from diester **56** by the procedure described for the preparation of alcohol **5**. After purification by column chromatography, the compound was obtained as white crystals: mp 78–82 °C, $[\alpha]^{25}_D$ −342 °C (*c* 0.54, $CHCl_3$); ^1H NMR δ 0.90 (t, 3 H, J = 7.4), 0.98 (d, 3 H, J = 7), 1.14 (d, 3 H, J = 7)8 1.14 (d, 3 H, J = 7), 1.26 (br s, 1 H), 1.45 (m, 1 H), 1.67 (m, 2 H), 1.95–2.63 (complex, 7 H), 3.58 (dd, 1 H, J = 10), 3.77 (dd, 1 H, J = 4.4, 10), 5.21 (br s, 1 H), 5.58 (m, 1 H), 5.76 (dd, 1 H, J = 5.9, 9.7), 5.99 (d, 1 H, J = 9.7). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.55; H, 9.44.

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Supplementary Material Available: Experimental details containing positional thermal parameters of non-hydrogen atoms, bond lengths, bond angles, and torsion angles for compound **5** (10 pages). Ordering information is given on any current masthead page.

Mechanism of the Oxidation of Alkyl Aryl and Diphenyl Sulfides by Chromium(VI)

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The mechanism of Cr(VI) oxidation of organic sulfur compounds has been investigated by studying the rates of oxidation of 17 alkyl aryl sulfides and 6 diphenyl sulfides respectively in 50% (v/v) aqueous acetic acid and 75:25 acetic acid–water (v/v) mixtures. The oxidation follows second-order kinetics at constant $[H^+]$ and ionic strength. Those sulfides containing electron-releasing groups in the benzene ring accelerate the rate while those with electron-attracting groups retard the rate. A good correlation is found to exist between log k_2 and Hammett σ constants for both aryl methyl and diphenyl sulfides. The excellent correlations obtained between log k values and oxidation potentials/ionization energies and the absence of any retardation on the rate of oxidation in the presence of Mn(II) suggest that the mechanism presumably involves a one-electron-transfer process. That the oxidation is susceptible to steric congestion at the reaction center, sulfur, has been revealed by the excellent correlation between the logarithm of rate coefficients of alkyl phenyl sulfides, C_6H_5SR (R = Me, Et, *n*-Pr, *i*-Pr, and *t*-Bu) and Taft's steric substituent constant, E_s.

Although chromium(VI) is widely used as an oxidant in the preparation of sulfoxides[1] from the corresponding sulfides, the formulation of a detailed mechanism for this reaction is impeded by the lack of kinetic data. In spite of the extensive studies on the mechanism of the oxidation of sulfides to sulfoxides by several oxidants like peroxydisulfate ion,[2] peroxydiphosphate ion,[3] bromine,[4] hydrogen peroxide,[5] peroxybenzoic acid,[6] (diacetoxyiodo)benzene,[7] chloramine-T,[8] bromamine-T,[8] and chlorine,[9] kinetics of oxidation by metal ion oxidants has received little attention. However, the oxidation of alkyl phenyl sulfides by Mn^{3+} has been proposed to proceed by a one-electron-transfer mechanism[10] as the rate of oxidation increases with a decrease in the values of half-wave (oxidation) potential and ionization energy.

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