Structural Modification of Mevinolin[1]

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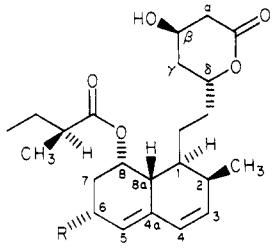
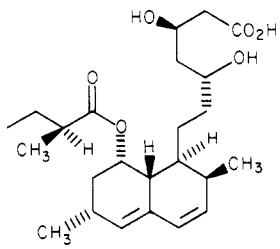
Received May 22, 1982

Synthetic strategies are described for modifying the side-chain ester and lactone moieties of mevinolin (1), a potent, competitive HMG-CoA reductase inhibitor isolated from cultures of *Aspergillus terreus*. A general route for preparing side-chain ether analogues of 1 is disclosed. Central to the success of this multistep route is the use of a method for reversibly masking the lactone moiety as a hemiacetal ether. The merit of this strategy is demonstrated again in the route developed for elaborating mevalonate analogue 11 from 1. Finally, a new, versatile, and efficient method is presented for homologating five- and six-membered lactones and is used to prepare carboxylate 27, a homologue of 1.

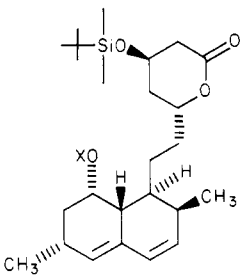
Mevinolin (1) is a highly functionalized, fungal metabolite isolated from cultures of *Aspergillus terreus*. The structure and absolute configuration of this novel β-hydroxy δ-lactone were determined by a combination of physical techniques.[2,3] Mevinolinic acid (3), the dihydroxy



1, R = CH_3
2, R = H



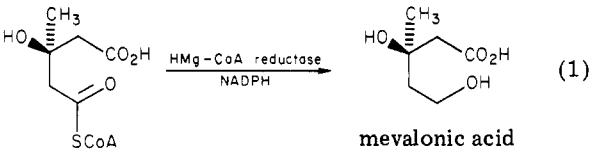
3



4a, X = RCO
b, X = H

acid form of lactone 1, is the most potent inhibitor (K_i = 0.6 nM)[2] of 3-hydroxy-3-methylglutaryl–coenzyme A reductase [HMG-CoA reductase; mevalonate:NADP$^+$ oxidoreductase (CoA acylating), EC 1.1.1.34][4] reported to date and is an effective hypocholesterolemic agent in several animal species[2] and man.[5] Previously, a related natural product of structure 2[6] was isolated from cultures of *Penicillium citrinum* (ML-236B)[7] and *Penicillium brevicompactum* (compactin)[8] by workers at Sankyo[7] and Beecham,[8] respectively. Compound 2 was shown to inhibit HMG-CoA reductase and to lower plasma cholesterol levels in experimental animals[9] and man.[10]

Since a major rate-limiting step (eq 1) in cholesterogenesis is catalyzed by HMG-CoA reductase[4] and hypercholesterolemia is a known primary risk factor[11,12] for coronary artery disease, the major cause of death in western countries, it was deemed important to delineate the structural features of mevinolin responsible for its HMG-CoA reductase inhibitory activity. Achievement of this objective first required the design and development of synthetic strategies for selectively modifying key structural features of 1. Our initial efforts in this regard focused on the modification of the side chain ester and the lactone moieties of mevinolin. Since a viable route for replacing the 2(*S*)-methylbutyl moiety in 1 with other acyl groups was disclosed recently,[13] herein we report our progress in the synthesis of side-chain ether analogues of 1, the mevalonate analogue 11, and carboxylate 27, a homologue of 1.



HMG-CoA mevalonic acid (1)

Elaboration of Side-Chain Ether Analogues. As noted previously, treatment of axial β-(*tert*-butyldimethylsiloxy)valerolactones (e.g., 4a) with fluoride led to

(1) The lactone homologation route has been presented: Lee, T.-J.; Holtz, W. J.; Smith, R. L. 11th Northeast Regional Meeting of the American Chemical Society, Rochester, New York, Oct 1981; Abstract No. 223.

(2) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, J.; 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.

(3) Recently, Endo reported isolation of monacolin K from a *Monascus* species. From the physical data presented, it appears that monacolin K may be identical with or very similar to mevinolin: (a) Endo, A. *J. Antibiot.* **1979**, *32*, 852. (b) Endo, A. *Ibid.* **1980**, *33*, 334.

(4) Rodwell, V. W.; Nordstrom, J. L.; Mitschell, J. J. *Adv. Lipid Res.* **1976**, *14*, 1.

(5) (a) Tobert, J. A.; Hitzenberger, G.; Kukovetz, W. R.; Holmes, I. B.; Jones, K. H. *Artherosclerosis* **1982**, *1*, 61. (b) Tobert, J. A.; Bell, G. D.; Birtwell, J.; James, I.; Kukovetz, W. R.; Pryor, J. S.; Buntinx, A.; Holmes, I. B.; Chao, Y.-S.; Bolognese, J. A. *J. Clin. Invest.* **1982**, *69*, 913.

(6) Although no sterochemical information was reported by the workers at Sankyo,[7] the X-ray crystal structure of compactin (2) was reported by the Beecham scientists.[8] Note that the relative configuration in Figure 1 of their paper does not agree with the crystal coordinates. We present the correct relative sterochemical configuration of compactin as 2. The absolute configuration of 2 has not been reported.

(7) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.

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

(9) (a) Tsujita, Y.; Kuroda, M.; Tanzawa, K.; Kitano, N.; Endo, A. *Artherosclerosis* **1978**, *32*, 307. (b) Kuroda, M.; Tsujita, Y.; Tanzawa, K.; Endo, A. *Lipids* **1979**, *14*, 585.

(10) (a) Yamamoto, A.; Judo, H.; Endo, A. *Artherosclerosis* **1980**, *35*, 259. (b) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *N. Engl. J. Med.* **1981**, *305*, 478.

(11) Kannel, W. B.; Castelli, W. P.; Gordon, T.; McNamara, P. M. *Ann. Intern. Med.* **1971**, *74*, 1.

(12) Stamler, J. *Arch. Surg. (Chicago)* **1978**, *113*, 21.

(13) Willard, A. K.; Smith, R. L. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 337.

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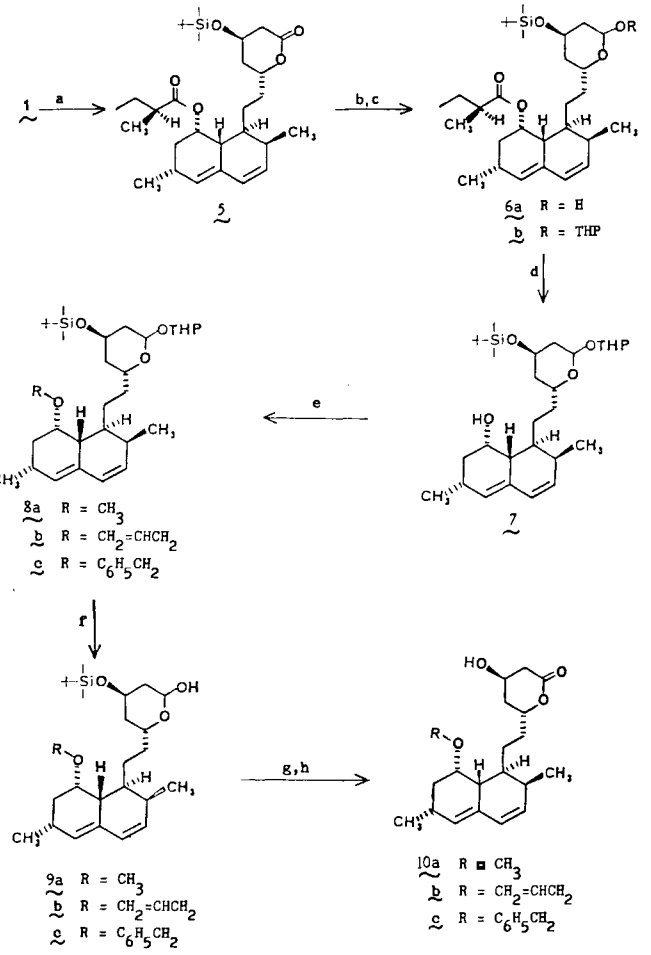
Scheme I

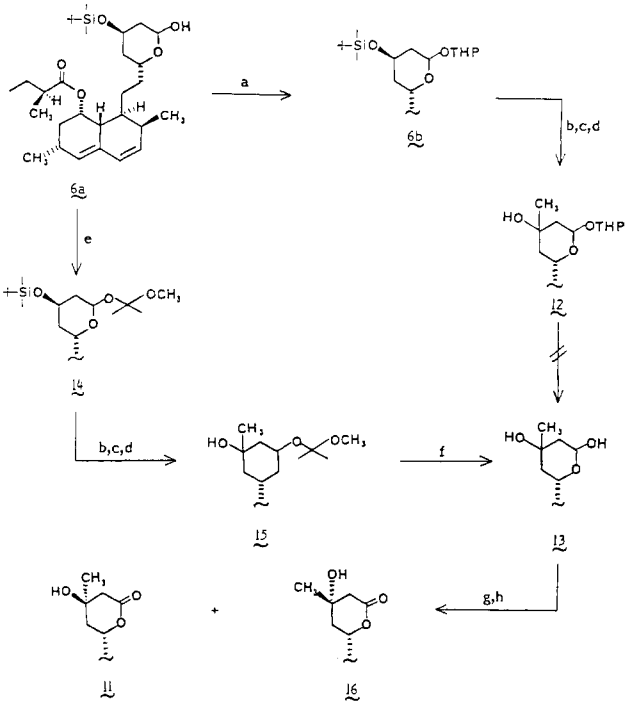


[a] $(CH_3)_3CSi(CH_3)_2Cl$, imidazole, DMF, 16 h. [b] DIBAH, THF, −78 °C. [c] Dihydropyran, CH_2Cl_2, PPTS (catalyst), room temperature, 16 h. [d] $LiAlH_4$, ether. [e] NaH, RX, DMF, Δ. [f] PPTS (catalyst), THF-H_2O-HOAc (3:1:1 v/v/v), room temperature; 36 h. [g] Ag_2CO_3/Celite, benzene, Δ. [h] n-$Bu_4N^+F^-\cdot 3H_2O$ (3 equiv) HOAc (4 equiv), THF, 44 h.

rapid and extensive destruction of the lactone ring.[13] Therefore, attempts to O-alkylate hindered axial alcohol **4b**[13] in the standard manner (i.e., excess RX, NaH, DMF) were anticipated to afford complex product mixtures. For preclusion of this possibility, a method for reversibly masking the lactone moiety as a hemiacetal ether was developed and utilized for ether analogue preparation as depicted in Scheme I.

Mevinolin was converted[14] to the *tert*-butyldimethylsilyl ether **5**[15] which, upon DIBAH reduction, gave a mixture of epimeric lactols **6a**.[16] Treatment of lactols **6a** with dihydropyran in the presence of pyridinium *p*-toluenesulfonate (PPTS, catalyst)[17] provided tetrahydropyranyl (THP) ethers **6b** (62% overall yield from 1). An attempt to saponify **6b** under conditions (LiOH, aqueous EtOH, reflux)[13] analogous to those used for deacylating the parent natural product **1** proved disappointing; the saponification remained incomplete after 2.5 days. In contrast, the reductive removal of the 2(*S*)-methylbutyryl moiety in **6b** with lithium aluminum hydride proceeded smoothly to afford alcohol **7** (70%). Generation of the corresponding alkoxide with NaH followed by alkylation with methyl iodide in DMF gave ether **8a** (65%). Selective removal of the THP group was accomplished cleanly in THF–H_2O–HOAc (3:1:1 v/v/v) in the presence of PPTS (catalyst) to give hemiacetals **9a** (50%).[18] Oxidation of **9a** with freshly prepared silver carbonate-on-Celite[19] followed by desilylation[13] of the resulting lactone with tetrabutylammonium fluoride (TBAF) trihydrate–HOAc (3 and 4 equiv, respectively) in THF completed the synthesis of methyl ether **10a** in 95% yield. Allyl ether **10b** and benzyl ether **10c** were prepared in an analogous manner from intermediate **7** in yields comparable to that obtained for **10a**.

Scheme II



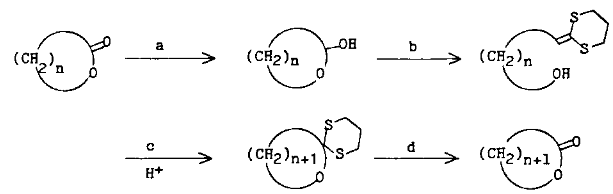
[a] Dihydropyran, CH_2Cl_2, PPTS (catalyst), room temperature, 16 h. [b] n-$Bu_4N^+F^-\cdot 3H_2O$, THF. [c] Me_2SO-TFAA, Et_3N, CH_2Cl_2, −78 °C. [d] CH_3Li, Et_2O-THF, −78 °C. [e] $CH_2=C(OCH_3)CH_3$, CH_2Cl_2, PPTS (catalyst), 0 °C. [f] THF-HOAc-H_2O (3:1:1 v/v/v), room temperature, 1 h. [g] Ag_2CO_3-Celite, benzene, Δ. [h] Separation by liquid chromatography.

Conversion to the Mevalonate Analogue 11. The hydroxy-bearing carbon in both HMG-CoA and mevalonic acid, the respective substrate and product of the reduction catalyzed by HMG-CoA reductase (eq 1), is substituted with a methyl group and is identical in absolute configuration to the β-carbon in mevinolin. To allow the biological consequences of replacing the β-methine proton in lactone **1** with a methyl group to be determined, we devised a synthetic route (Scheme II) for converting **1** to the mevalonate analogue **11**.

Diether **6b** was converted to a mixture of tertiary carbinols **12** in three steps involving desilylation with TBAF trihydrate[14] in THF followed by oxidation of the resulting alcohol with trifluoroacetic anhydride–activated dimethyl sulfoxide[20] and 1,2-addition of methyllithium to the newly

(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(15) Satisfactory elemental analyses and/or spectral data consistent with the assigned structures were obtained for all new compounds.
(16) The resistance of the 2(*S*)-methylbutyryl moiety in **5** to DIBAH reduction is attributed to steric hindrance attending the 1,3-diaxial interaction between the 6α-methyl and 8α-ester substituents.
(17) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(18) This yield is based on the consumption of THP ether **8a**; 33% of the starting material (**8a**) was recovered.
(19) For a comprehensive review of this oxidation method, see: McKillop, A.; Young, D. W. *Synthesis* **1979**, 401.
(20) (a) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. (b) Huang, S. L.; Omura, K.; Swern, D. *Ibid.* **1976**, *41*, 3329.

Scheme III

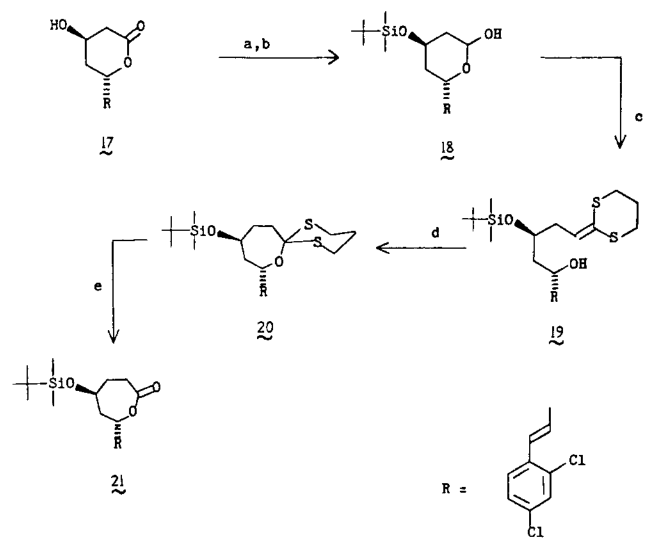


generated ketone. Attempts to deblock the THP ethers **12** under a variety of mildly acidic conditions[21] failed to provide lactols **13**; ether cleavage was accompanied by extensive dehydration of the acid-sensitive tertiary alcohol under all conditions studied. Masking the lactol hydroxyl group as a mixed ketal[22] with enhanced sensitivity to mild acid hydrolysis provided a reasonable solution to this problem. Treatment of starting lactols **6a** with excess 2-methoxypropene in dichloromethane at 0 °C in the presence of PPTS (catalyst) gave mixed ketals **14** in 91% yield.[23,24] By use of the three-step sequence described above for elaborating **12** from **6b**, mixed ketals **14** were converted to tertiary alcohols **15**. Hydrolysis of mixed ketals **15** in THF–HOAc–H_2O (3:1:1 v/v/v) at 20 °C proceeded cleanly to give the desired lactols which, upon oxidation with freshly prepared silver carbonate-on-Celite[19] in benzene heated at reflux, afforded a 1:1 mixture of epimeric lactones **11** and **16** in 22% overall yield from **6a**. Separation of this epimeric mixture into target lactone **11** [NMR ($CDCl_3$) δ 4.56, (br m, δ-CH)] and its epimer **16** [NMR, ($CDCl_3$) δ 4.14, (br m, δ-CH)] was achieved readily by liquid chromatography and served to complete Scheme II.

Homologation of the Lactone Ring. Our approach to this task centered on the development of a lactone homologation method which would be compatible with the complex and sensitive structural features of mevinolin. Cognizant of the reported ease[25] with which hydroxy-bearing ketene dithioacetals undergo intramolecular cyclization to masked lactones and having mevinolin-derived lactol intermediates available for study, we conceived the general lactone homologation route shown in Scheme III. Ample precedence[25,26] exists for the key step in this route, i.e., step c involving protonation of the ketene dithioacetal to generate a dithienium carbocation poised for intramolecular, nucleophilic interception by the appended hydroxyl group.

To test the validity of the above route, we initiated model studies on lactone **17** (Scheme IV). Lactol mixture **18** was prepared in 85% yield from β-hydroxy lactone **17** by sequential *tert*-butyldimethylsilylation[14] and reduction with DIBAH. Treatment of lactols **18** in THF with the carbanion (2.5 equiv) derived from diethyl (1,3-dithian-2-yl)phosphonate[27] and *n*-butyllithium in THF afforded ketene dithioacetal **19** as a viscous oil. Cyclization of **19** in dichloromethane at 20 °C in the presence of PPTS (catalyst) proceeded smoothly to afford, after chromatography on silica gel, crystalline dithio ortho lactone **20** in 92% overall yield[28] from lactols **18**. An attempt to deblock **20** with mercuric chloride–cadmium carbonate in aqueous acetonitrile failed to afford the target caprolactone **21** in a satisfactory yield. This failure likely stemmed from detrimental interaction between the mercuric ion and the olefinic linkage. On the other hand, ortho dithio lactone **20** was converted cleanly to lactone **21** (88%) with silver nitrate (2 equiv) and cadmium carbonate (2.2 equiv) in CH_3CN–THF–H_2O (3:1:1 v/v/v) at 20 °C. Application of steps b–e (Scheme IV) to dihydro-5-phenyl-2(3*H*)-furanone afforded 6-phenyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one in 45% overall yield.

Scheme IV



[a] $(CH_3)_3CSi(CH_3)_2Cl$, imidazole, DMF. [b] DIBAH, THF, THF, −78 °C. [c] $(EtO)_2P(O)C(Li)$(1,3-dithian-2-yl), THF, −78 °C then room temperature, 19 h. [d] PPTS (catalyst), CH_2Cl_2, room temperature. [e] $AgNO_3$–$CdCO_3$, CH_3CN–THF–H_2O (3:1:1 v/v/v).

Having established the validity of the proposed lactone homologation method, we investigated the elaboration of carboxylate **27** from mevinolin (Scheme V). Treatment of lactols **6a** with the freshly prepared phosphonate carbanion (4.6 equiv)[27] in THF gave ketene dithioacetal **22** in 43% yield.[29] Acid-catalyzed (PPTS) cyclization of **22** provided masked lactone **23** (88%) as an oil which was deblocked by the silver nitrate–cadmium carbonate procedure to afford caprolactone **24** in 97% yield. Desilylation[13] of **24** with TBAF·$3H_2O$–HOAc (3 and 4 equiv, respectively) in THF resulted in a 4:1 mixture (82% combined yield) of butyrolactone **25** [IR (neat) 1780 cm^{-1}] and caprolactone **26** [IR (neat) 1715 cm^{-1}]. The formation of

(21) For example, treatment of **12** in THF–HOAc–H_2O (3:1:1 v/v/v) at 20 °C for 72 h in the presence of pyridinium *p*-toluenesulfonate (PPTS, catalyst) afforded a trace of desired **13**; more acidic conditions (e.g., the use of 0.012 N HCl in THF–HOAc–H_2O (3:1:1 v/v/v) at 20 °C) led to complex reaction mixtures resulting, at least in part, from dehydration of the tertiary alcohol moiety.

(22) Newman, M. S.; Vander Zwan, M. C. *J. Org. Chem.* **1973**, *38*, 2910 and references cited therein.

(23) The conversion of **6a** to **14** is very sensitive to temperature: at temperatures above 0 °C, significant dehydration of **6a** to the corresponding glycal is observed, whereas at lower temperatures, the reaction rate is severely retarded.

(24) Mixed ketals **14** and the subsequent intermediates involved in the transformation of **14** to lactols **13** proved sensitive to silica gel (e.g., partial deketalization was observed under typical chromatographic conditions), and, accordingly, these compounds were used directly without purification.

(25) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829.

(26) For examples of intramolecular cyclization via dithienium carbocation interception, see: (a) Andersen, N. H.; Yamamoto, Y.; Denniston, A. D. *Tetrahedron Lett.* **1975**, 4547. (b) Kozikowski, A. P.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 2236. (c) Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, 207.

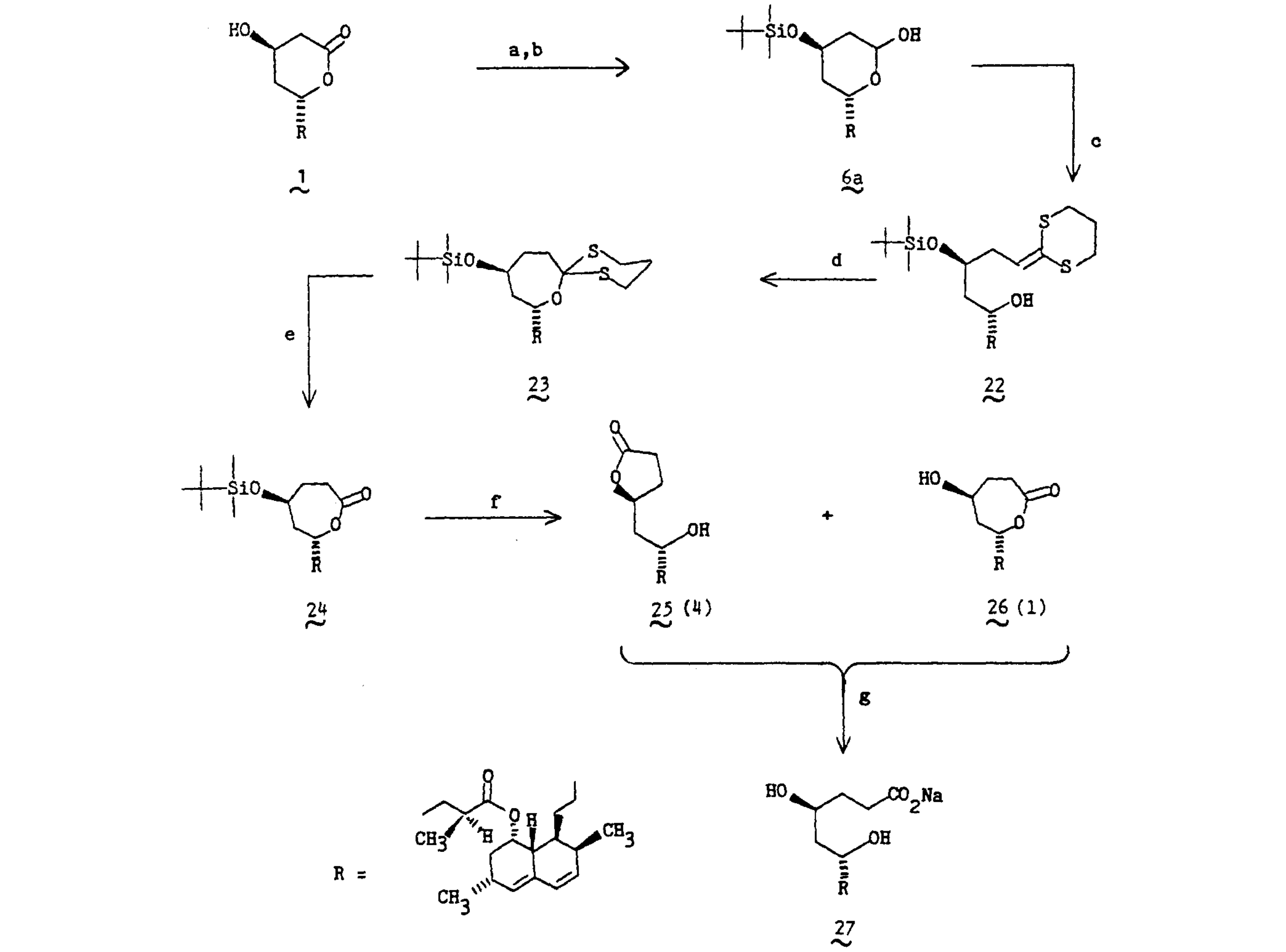
(27) Kruse, C. G.; Broekhof, N. L. J. M.; Wijsman, A.; Van der Gen, A. *Tetrahedron Lett.* **1977**, 885.

(28) The sequence **18** → **19** → **20** is effected most conveniently by utilizing the crude Wittig product **19** directly in the acid-catalyzed cyclization step without prior purification. The second step (i.e., **19** → **20**) is terminated when **19** can no longer be detected in the reaction millieux by TLC analysis.

(29) This yield is based on consumed lactol **6a**; 57% of starting **6a** was recovered.

(30) Julia, M.; Rouault, A. *Bull. Soc. Chim. Fr.* **1959**, 1833.

Scheme V



[a] $(CH_3)_3CSi(CH_3)_2Cl$, imidazole, DMF. [b] DIBAH, THF, −78 °C. [c] $(EtO)_2P(O)$–(2-lithio-1,3-dithiane), THF, −78 °C then room temperature, 19 h. [d] PPTS (catalyst), CH_2Cl_2, room temperature. [e] $AgNO_3$–$CdCO_3$, CH_3CN–THF–H_2O (3:1:1 v/v/v). [f] 3 equiv of n-$Bu_4N^+F^-\cdot 3H_2O$, 4 equiv of HOAc, THF. [g] 1 equiv of NaOH.

25 is ascribed to acid-catalyzed translactonization of **26**. Brief exposure of the lactone mixture or either constituent lactone to aqueous sodium hydroxide (1.1 equiv) at 20 °C afforded a single carboxylate (**27**), thereby confirming the stereochemical and skeletal commonality of lactones **25** and **26**.

Summary

Impetus for our studies on the structural modification of mevinolin derives from the remarkable ability of this natural product to competitively inhibit HMG-CoA reductase and, more importantly, to lower serum cholesterol levels in experimental animals and man. In this paper, synthetic sequences are described for (a) elaborating side-chain ether analogues, (b) converting mevinolin to the mevalonate analogue **11**, and (c) homologating the lactone ring. Central to the success of the route devised to side-chain ether analogues was the use of a method for reversibly masking the lactone moiety as a hemiacetal ether. Likewise, the employment of this strategy proved to be of paramount importance in the synthesis of mevalonate analogue **11**. Furthermore, in this instance, protection of the lactol moiety as the mixed ketal ether derived from 2-methoxypropene, rather than the THP ether, was required for smooth deprotection of the lactol ether in the presence of the acid-labile tertiary alcohol. Finally, a versatile and efficient method based on the facile, intramolecular interception of a dithienium carbocation by an appended hydroxyl group was developed for homologating five- and six-membered lactones. Carboxylate **27** was elaborated from mevinolin by using this method. In view of the mild reaction conditions employed therein, this new homologation method may prove particularly attractive for expanding lactones bearing sensitive functional groups. The demonstrated inertness of dithio ortho lactones (e.g., **20** and **23**) to common nucleophilic reagents[25] should afford ample opportunity for manipulating a variety of functional groups at the masked lactone stage. Such a strategy is frequently required for the successful elaboration of complex structures.

The synthetic sequences described above have been used to prepare a wide array of mevinolin derivatives. Their syntheses and the results of their biological evaluation will be reported in future publications from these laboratories.

Experimental Section

General Methods. Proton NMR spectra were recorded on a Varian EM390 spectrometer; chemical shifts are reported in δ units with Me_4Si as the internal standard (unless otherwise specified). IR spectra were taken on a Perkin-Elmer 297 infrared spectrophotomer and are reported in reciprocal centimeters with polystyrene as the reference standard. Mass spectra were taken on a VG Micromass MM7035 mass spectrometer. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5). A solution of *tert*-butyldimethylsilyl chloride (180 mg, 1.2 mmol) in DMF (2.4 mL) was added to a stirred mixture of **1** (300 mg, 0.741 mmol) and imidazole (204 mg, 3 mmol) in DMF (3 mL) while the temperature was maintained at 0 °C. The resulting mixture was stirred at room temperature for 16 h, poured into cold water, and extracted with ether. The ethereal extract was washed with hydrochloric acid (0.05 N) and aqueous sodium bicarbonate (5%), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to leave **5** as a pale yellow, oily residue (0.441 g) which was used directly in the next reaction without further purification: NMR ($CDCl_3$) δ 0.08 (6 H, s), 0.89 (9 H, s), 1.08 (3 H, d), 1.10 (3 H, d), 2.57 (2 H, d), 4.3 (1 H, m), 4.6 (1 H, m), 5.4 (1 H, m), 5.54 (1 H, m), 5.8 (1 H, dd), 6.0 (1 H, d).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (6a). A solution of diisobutylaluminum hydride (1 M in hexane, 0.9 mL) was added via a syringe under a nitrogen atmosphere to a stirred solution of **5** (0.441 g) in THF (15 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 0.5 h. Methanol (0.15 mL) was added and the mixture stirred for 10 min. The cooling bath was removed followed by the addition of water (0.6 mL), Celite (0.6 g), and Na_2SO_4 (3 g). The resulting mixture was stirred at room temperature for 0.5 h and filtered. The collected solid was washed with ether. The combined filtrate and washings were concentrated at reduced pressure to give **6a** as a colorless oil (0.45 g) which was used directly in the subsequent reaction without further purification. An analytical sample was obtained after chromatographic purification: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, S), 1.07 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.5–4.2 (2 H, m), 4.3 (1 H, m), 5.1 (1 H, m), 5.4 (1 H, m), 5.55 (1 H, m), 5.8 (1 H, dd, J = 10, 6 Hz), 6.05 (1 H, d, J = 10 Hz). Anal. Calcd for $C_{30}H_{52}O_5Si$: C, 69.18; H, 10.07. Found: C, 68.93; H, 10.25.

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran (6b). Dihydropyran (0.6 mL, 6.74 mmol) was added dropwise to a stirred mixture of **6a** (0.45 g) and PPTS (20 mg, 0.08 mmol) in methylene chloride (2 mL). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 16 h, poured into cold water, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to afford an oily residue which was applied to a silica gel column. Elution with methylene chloride–acetone (50:1 v/v) produced **6b** (0.281 g, 0.46 mmol, 62% overall from **1**) as a colorless, glassy oil: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.07 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.4–4.1 (4 H, m), 4.3 (1 H, m), 4.9–5.3 (2 H, m), 5.4 (1 H, m), 5.55 (1 H, m), 5.8 (1 H, dd, J = 10, 6 Hz), 6.02 (1 H, d, J = 10 Hz).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-8(*S*)-hydroxy-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran (7). A solution of **6b** (96 mg, 0.159 mmol) in ether (2.5 mL) was added to a stirred suspension of lithium aluminum hydride (35 mg, 0.92 mmol) in ether (3 mL). The resulting mixture was heated at reflex under a nitrogen atmosphere for 15 min, cooled to room temperature, and stirred for 16 h. The reaction mixture was treated successively with water (35 μL), 20% sodium hydroxide (35 μL), and water (105 μL). The resulting mixture was stirred at room temperature for 1 h and filtered. The filtrate was concentrated to yield an oily residue which was applied to a silica gel column. Elution of the column with methylene chloride–acetone (50:1 v/v) gave **7** (58 mg, 0.111 mmol, 70%) as a colorless, glassy oil: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.20 (3 H, d), 3.3–4.4 (5 H, m), 4.9–5.3 (2 H, m), 5.57 (1 H, m), 5.8 (1 H, dd, J = 10, 6 Hz), 6.08 (1 H, d, J = 10 Hz). Anal. Calcd for $C_{30}H_{52}O_5Si$: C, 69.18; H, 10.07. Found: C, 68.61; H, 10.37.

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-8(*S*)-methoxy-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran (8a). To a stirred suspension of sodium hydride (50% oil dispersion, 38 mg, 0.75 mmol, washed with petroleum ether prior to use) in DMF (1 mL) was added a solution of **7** (44 mg, 0.084 mmol) in DMF (1 mL) at room temperature under a nitrogen atmosphere. The resulting mixture was heated on a steam bath for 10 min and cooled to room temperature. Methyl iodide (0.1 mL, 1.6 mmol) was added, and the resulting reaction mixture was heated on a steam bath for 10 min. The mixture was cooled to room temperature, poured into cold water, and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid and aqueous sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was evaporated to leave an oily residue which was applied to a silica gel column. Elution with methylene chloride–acetone (50:1 v/v) afforded **8a** (29 mg, 0.054 mmol, 65%) as a colorless, glassy oil: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.15 (3 H, d, J = 7 Hz), 3.34 (3 H, s), 3.4–4.1 (4 H, m), 4.26 (1 H, m), 4.9–5.3 (2 H, m), 5.5 (1 H, m), 5.75 (1 H, dd, J = 10, 6 Hz), 6.0 (1 H, d, J = 10 Hz).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-8(*S*)-methoxy-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (9a). Powdered PPTS (20 mg, 0.08 mmol) was added in one portion to a stirred mixture of **8a** (82 mg, 0.153 mmol) in THF (2 mL), acetic acid (0.8 mL), and water (0.6 mL). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 36 h, poured into cold water, and extracted with ether. The ethereal extract was washed with water and aqueous sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to provide an oily residue which was subsequently applied to a silica gel column. Elution of the column with methylene chloride–acetone (50:1 v/v) first gave the starting **8a** (26 mg, 0.049 mmol). Continued elution with the same eluant produced **9a** (23 mg, 0.051 mmol, 49% based on consumed starting material) as a colorless, glassy oil: NMR ($CDCl_3$) δ 1.14 (3 H, d, J = 7 Hz), 3.34 (3 H, s), 3.6–4.4 (3 H, m), 5.0–5.3 (1 H, m), 5.55 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.0 (1 H, d, J = 10 Hz).

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-8(*S*)-methoxy-2(*S*),6-(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10a). A mixture of **9a** (23 mg, 0.051 mmol) and freshly prepared silver carbonate-on-Celite (1.6 g) in benzene (7.5 mL) was heated at reflux under a nitrogen atmosphere for 0.5 h. The reaction mixture was cooled to room temperature. The insoluble solid was collected and washed with ether. The combined filtrate and washings were evaporated on a rotary evaporator to leave the crude 4(*R*)-(*tert*-butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a(*S*)-hexahydro-8(*S*)-methoxy-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (24 mg) as a classy oil which was used directly in the next step without further purification: NMR ($CDCl_3$) δ 0.80 (6 H, s), 0.90 (9 H, s), 1.12 (3 H, d), 2.58 (2 H, d), 3.33 (3 H, s), 3.7 (1 H, m), 4.3 (1 H, m), 4.7 (1 H, m), 5.5 (1 H, m), 5.74 (1 H, dd), 5.97 (1 H, d).

The glassy oil was dissolved in THF (3 mL) and treated successively with acetic acid (25 μL, 0.44 mmol) and a solution of tetrabutylammonium fluoride trihydrate (0.32 M in THF, 0.75 mL, 0.24 mmol). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 44 h, poured into cold water, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to yield an oily residue which was applied to a silica gel column. Elution with methylene chloride–acetone (9:1 v/v) provided **10a** (17 mg, 0.051 mmol, 100%) as a colorless, glassy oil. This oil solidified on standing; recrystallization from ether–hexane gave fine needles: mp 110–111 °C; NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 2.66 (2 H, m), 3.34 (3 H, s), 3.7 (1 H, m), 4.37 (1 H, m), 4.7 (1 H, m), 5.5 (1 H, m), 5.74 (1 H, dd, J = 10, 6 Hz), 5.97 (1 H, d, J = 10 Hz). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.03; H, 9.05.

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-(allyloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran (8b). Compound **8b** was prepared from **7** by the same procedure described for the preparation of **8a** but with allyl chloride instead of methyl iodide: NMR ($CDCl_3$) δ 0.07

(6 H, s), 0.90 (9 H, s), 1.12 (3 H, d, J = 7 Hz), 3.4–4.4 (7 H, m), 4.9–5.5 (4 H, m), 5.51 (1 H, m), 5.7–6.2 (3 H, m).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-(allyloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (9b). Compound **9b** was prepared from **8b** by using a procedure similar to that described in the preparation of **9a**: NMR ($CDCl_3$) δ 1.13 (3 H, d, J = 7 Hz), 3.4–4.5 (5 H, m), 5.0–5.6 (5 H, m), 5.6–6.2 (3 H, m).

6(*R*)-[2-[8(*S*)-(Allyloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10b). Compound **10b** was prepared from **9b** by using a procedure similar to that described in the preparation of **10a**: mp 102–103 °C; NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 7 Hz), 1.13 (1 H, d, J = 7 Hz), 2.67 (2 H, m), 3.6–4.0 (2 H, m), 4.1–4.5 (2 H, m), 4.5–4.9 (1 H, m), 5.5 (1 H, m), 5.6–6.2 (3 H, m). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.03; H, 9.21.

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-(benzyloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)oxy]-2,4,5,6-tetrahydro-2*H*-pyran (8c). Compound **8c** was prepared from **7** by the same procedure as that described in the preparation of **8a** but with benzyl chloride instead of methyl iodide: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.15 (3 H, d, J = 7 Hz), 4.35 (1 H, d, J = 12 Hz), 4.75 (1 H, d, J = 12 Hz), 4.8–5.2 (2 H, m), 5.5 (1 H, m), 5.78 (1 H, dd, J = 10, 6 Hz), 6.03 (1 H, d, J = 10 Hz), 7.3 (5 H, br s).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-(benzyloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (9c). Compound **9c** was prepared from **8c** by using a procedure similar to that described in the preparation of **9a**: NMR ($CDCl_3$) δ 1.13 (3 H, d, J = 7 Hz), 5.5 (1 H, m), 5.75 (1 H, dd, J = 10, 6 Hz), 6.0 (1 H, d, J = 10 Hz), 7.3 (5 H, br s).

6(*R*)-[2-[8(*S*)-(Benzyloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10c). Compound **10c** was prepared from **9c** by using a procedure similar to that described in the preparation of **10a**: mp 110–112 °C; NMR ($CDCl_3$) δ 0.85 (3 H, d, J = 7 Hz), 1.15 (3 H, d, J = 7 Hz), 2.53 (2 H, m), 3.91 (1 H, M), 4.30 (1 H, d, J = 12 Hz), 4.68 (1 H, d, J = 12 Hz), 5.52 (1 H, m), 5.75 (1 H, dd, J = 10, 6 Hz), 6.00 (1 H, d, J = 10 Hz), 7.33 (5 H, s). Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 76.15; H, 8.66.

4(*R*)-(*tert*-butyldimethylsiloxy)-6(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-2-(1-methoxy-1-methylethoxy)-3,4,5,6-tetrahydro-2*H*-pyran (14). A solution of PPTS (16 mg) in CH_2Cl_2 (2 mL) was added to a stirred mixture of 2-methoxypropene (1.5 mL) and **6a** (600 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 3 h, poured into aqueous sodium bicarbonate solution, and extracted with ether. The ethereal extract was dried over $MgSO_4$, filtered, and concentrated to provide **14** (600 mg, 1.01 mmol, 88%) as a colorless glassy oil which was used in the next step without purification: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.06 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.22 (3 H, s), 5.15 (1 H, m), 5.35 (1 H, m), 5.52 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.02 (1 H, d, J = 10 Hz).

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-2-(1-methoxy-1-methylethoxy)-3,4,5,6-tetrahydro-2*H*-pyran. A solution of tetrabutylammonium fluoride trihydrate (0.322 M in THF, 30 mL) was added to a stirred solution of **14** (600 mg, 1.01 mmol) in THF (10 mL) at ambient temperature. The resulting mixture was stirred under an atmosphere of nitrogen for 3 days, poured into aqueous sodium bicarbonate, and extracted with ether. This ethereal extract was dried ($MgSO_4$), filtered, and evaporated to give the crude title compound (700 mg) as a brownish oil: NMR ($CDCl_3$) δ 0.87 (3 H, t), 0.89 (3 H, d), 1.08 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 1.37 (3 H, s), 1.43 (3 H, s), 3.23 (3 H, s), 4.30 (1 H, m), 5.17 (1 H, dd, J = 9, 3 Hz), 5.37 (1 H, m), 5.52 (1 H, m), 5.78 (1 H, dd, J = 10, 6 Hz), 6.01 (1 H, d, J = 10 Hz).

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-2-(1-methoxy-1-methylethoxy)-3,4,5,6-tetrahydro-2*H*-pyran-4-one. Trifluoroacetic anhydride (0.337 mL, 2.4 mmol) was added to a solution of Me_2SO (0.232 mL, 0.3 mmol) in CH_2Cl_2 (3 mL) at −78 °C under an atmosphere of nitrogen. The resulting mixture was stirred at −78 °C for 0.5 h followed by the addition of a solution of aforementioned crude 6(*R*)-[2-[1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-2-(1-methoxy-1-methylethoxy)-3,4,5,6-tetrahydro-2*H*-pyran (700 mg) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at −78 °C for 1 h and subsequently treated with triethylamine (0.974 mL, 7 mmol). The resulting mixture was stirred at −78 °C for 0.5 h, allowed to warm up to room temperature, poured into cold water, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated to leave the title compound (520 mg) as a brownish oil which was used directly in the next reaction without purification: NMR ($CDCl_3$) δ 1.06 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 1.38 (3 H, s), 1.45 (3 H, s), 3.20 (3 H, s), 5.0 (1 H, t, J = 6 Hz), 5.35 (1 H, m), 5.52 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.02 (1 H, d, J = 10 Hz).

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-4-hydroxy-2-(1-methoxy-1-methylethoxy)-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (15). Methyllithium (1.4 M in ether, 0.95 mL, 1.33 mmol) was added dropwise to a solution of 6(*R*)-[2-[1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-yl]ethyl]-2-(1-methoxy-1-methylethoxy)-3,4,5,6-tetrahydro-2*H*-pyran-4-one (520 mg) in THF (10 mL) at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 0.5 h, quenched with aqueous ammonium chloride and extracted with ether. The extract was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated to provide crude **15** (500 mg) as a yellow, glassy oil which was used directly in the next step without purification: NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz), 0.90 (3 H, d, J = 7 Hz), 1.06 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.23 (3 H, s), 4.6–5.6 (1 H, two sets of dd), 5.36 (1 H, m) 5.53 (1 H, m), 5.78 (1 H, dd, J = 10, 6 Hz) 6.01 (1 H, d, J = 10 Hz).

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-2,4-dihydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (13). A solution of crude **15** (500 mg) in THF (6 mL), acetic acid (2 mL), and water (2 mL) was stirred at room temperature for 0.5 h, diluted with water, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried over $MgSO_4$, and evaporated to give crude **13** (380 mg) as a yellow, glassy oil which was used in the next reaction without purification: NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 1.07 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 5.3–5.6 (2 H, m), 5.78 (1 H, dd, J = 10, 6 Hz), 6.02 (1 H, d, J = 10 Hz).

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (11) and 6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-4(*S*)-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (16). Freshly prepared Fetizon's reagent (Ag_2CO_3-on-Celite, 0.7 g) was added to a stirred solution of **13** (380 mg) in benzene (15 mL). The resulting mixture was heated at reflux under a nitrogen atmosphere for 1.5 h, cooled to room temperature, filtered through a pad of Celite, and washed with portions of ether. The combined filtrate and washings were evaporated to leave an oily residue which was purified by column chromatography [silica gel, eluant = methylene chloride/acetone (9:1 v/v)] to give a 1:1 mixture of **11** and **16** (107 mg, 22% overall yield from **6a**). Separation of this mixture by HPLC on a Whatman Partisil-Pac cyano-bonded column with the eluant hexane–2-propanol (95:5 v/v) pumped at 8 mL/min gave **11** [38 mg; mp 145–147 °C; NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 1.07 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 1.35 (3 H, s), 4.56 (1 H, m), 5.40 (1 H, m), 5.53 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.02 (1 H, d, J = 10 Hz). Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.35; H, 9.28] and **16**: 31 mg; NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 1.07 (3 H, d,

J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 1.40 (3 H, s), 2.60 (1 H, s), 4.14 (1 H, m), 5.43 (1 H, m), 5.56 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.04 (1 H, d, J = 10 Hz); MS, m/e 418 (M), 298, 198.

6(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8-(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-4-hydroxy-4-methyl-2-[(tetrahydropyran-2-yl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran (12). Compound **12** was prepared from **6b** by following the reaction sequence described in the conversion of **14** to **15**: NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 7 Hz), 0.88 (3 H, d, J = 7 Hz), 1.05 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 3.1–4.3 (3 H, m), 4.5–5.2 (2 H, m), 5.36 (1 H, m) 5.5 (1 H, m), 5.76 (1 H, dd, J = 10, 6 Hz), 6.0 (1 H, d, J = 10 Hz).

(*E-trans*)-4-(*tert*-Butyldimethylsiloxy)-6-[2-(2,4-dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one. To a solution of **17** (2.87 g, 10 mmol) and imidazole (2.04 g, 30 mmol) in DMF (10 mL) was added a solution of *tert*-butyldimethylsilyl chloride (1.95 g, 13 mmol) in DMF (5 mL). The resulting mixture was stirred at room temperature for 16 h, poured into cold water, and extracted with ether–methylene chloride. The organic extract was washed with dilute hydrochloric acid and aqueous sodium bicarbonate, dried over $MgSO_4$, filtered, and evaporated to yield a solid residue. The solid residue was triturated in hexane at −10 °C (ice–acetone bath). The title compound (3.6 g, 9.0 mmol, 90%) was collected by filtration: NMR ($CDCl_3$) δ 0.10 (6 H, s), 0.90 (9 H, s), 2.65 (2 H, d, J = 4 Hz), 4.40 (1 H, m), 5.39 (1 H, m), 6.22 (1 H, dd, J = 15, 6 Hz), 7.02 (1 H, d, J = 15 Hz), 7.1–7.6 (3 H, m).

(*E*)-4β-(*tert*-Butyldimethylsiloxy)-6α-[2-(2,4-dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-ol (18). Diisobutylaluminum hydride (0.85 M in hexane, 3.53 mL, 3 mmol) was added to a stirred solution of (*E-trans*)-4-(*tert*-butyldimethylsiloxy)-6-[2-(2,4-dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (0.802 g, 2 mmol) in THF (15 mL) at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 0.5 h and then treated successively with methanol (0.4 mL), water (0.4 mL), Celite (0.8 g), and THF (15 mL). The resulting mixture was allowed to warm to room temperature, stirred for 15 min, and treated with anhydrous Na_2SO_4 (3 g). The solids were collected by filtration, and the filtrate was evaporated to give the desired **18** (0.76 g, 1.89 mmol, 94%) as a solid: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.9 (9 H, s), 3.14 (1 H, d, J = 6 Hz), 4.1–5.5 (3 H, m), 6.10 (1 H, dd, J = 16, 6 Hz), 6.88 (1 H, d, J = 16 Hz), 7.08 (1 H, dd, J = 8, 2 Hz), 7.18 (1 H, d, J = 2 Hz), 7.34 (1 H, d, J = 8 Hz).

(*E-trans*)-5-(*tert*-Butyldimethylsiloxy)-7-[2-(2,4-dichlorophenyl)ethenyl]-2,2-(trimethylenedithio)hexahydrooxepin (20). *n*-Butyllithium (2.1 M in hexane, 1.47 mL, 3.1 mmol) was added to a stirred solution of diethyl (1,3-dithian-2-yl)-phosphonate (760 mg, 3.1 mmol) in THF (12 mL) at −70 °C under a nitrogen atmosphere. The resulting mixture was stirred at −70 °C for 10 min, warmed to room temperature, and stirred for 1 h. Subsequently, the reaction mixture was cooled to −70 °C and treated with a solution of **18** (500 mg, 1.24 mmol) in THF (3 mL). The resulting mixture was stirred at −70 °C for 0.5 h, warmed to room temperature, and stirred overnight. The reaction mixture was poured into saturated brine and extracted with ether. The ethereal extract was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to yield an oily residue from which pure **19** could be isolated by chromatography and characterized: NMR ($CDCl_3$) δ 0.15 (6 H, s), 0.92 (9 H, s), 3.17 (1 H, br s), 4.08 (1 H, m), 4.50 (1 H, q, J = 6 Hz), 5.98 (1 H, t, J = 6 Hz), 6.20 (1 H, dd, J = 16, 6 Hz), 7.20 (1 H, d, J = 16 Hz), 7.21 (1 H, dd, J = 8, 2 Hz), 7.40 (1 H, d, J = 2 Hz), 7.50 (H, d, J = 8 Hz).

For expediency, the above oil residue was used directly in the following reaction without purification. A solution of the oily residue in methylene chloride (50 mL) was treated with powdered PPTS (50 mg). The resulting mixture was stirred at room temperature for 4 h, poured into cold water, and extracted with ether. The ethereal extract was washed and aqueous sodium bicarbonate, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave an oily residue which was applied to a silica gel column. Elution of the column with methylene chloride–hexane (9:1 v/v) produced **20** (600 mg, 1.18 mmol, 96% overall yield) which solidified on standing. Recrystallization from acetonitrile–water gave an analytical sample: mp 86–87 °C; NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 3.2–3.8 (2 H, m), 4.17 (1 H, m), 4.73 (1 H, q, J = 6 Hz), 6.21 (1 H, dd, J = 16, 6 Hz), 7.11 (1 H, d, J = 16 Hz), 7.20 (1 H, dd, J = 8, 2 Hz), 7.40 (1 H, d, J = 2 Hz), 7.48 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{23}H_{34}Cl_2O_2S_2Si$: C, 54.63; H, 6.78. Found: C, 54.93; H, 6.89.

(*E-trans*)-5-(*tert*-Butyldimethylsiloxy)-7-[2-(2,4-dichlorophenyl)ethenyl]hexahydrooxepin-2-one (21). To a stirred mixture of **20** (32 mg, 0.063 mmol) in acetonitrile (3 mL), THF (1 mL), and water (0.5 mL) was added successively powdered cadmium carbonate (24 mg, 0.14 mmol) and a solution of silver nitrate (20 mg, 0.12 mmol) in water (0.5 mL). The resulting mixture was stirred at room temperature for 1 h, filtered through a pad of Celite, and washed with portions of ether. The combined filtrate and washings were washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave **21** (23 mg, 0.055 mmol, 88%) as an oil which solidified on standing: mp 108–110 °C; IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (6 H, s), 0.93 (9 H, s), 2.3–2.6 (1 H, m), 3.0–3.4 (1 H, m), 4.25 (1 H, m), 4.47 (1 H, q, J = 6 Hz), 6.20 (1 H, dd, J = 16, 6 Hz), 6.98 (1 H, d, J = 16 Hz), 7.20 (1 H, dd, J = 8, 2 Hz), 7.38 (1 H, d, J = 2 Hz), 7.46 (1 H, d, J = 8 Hz).

5-Phenyltetrahydrofuran-2-ol. To a solution of dihydro-5-phenyl-2(3*H*)-furanone (500 mg, 3.1 mmol) in THF (50 mL) was added diisobutylaluminum hydride (0.89 M in hexane, 12.5 mL, 11.2 mmol) at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 0.5 h, treated with methanol (0.64 mL), and removed from the cooling bath. Water (2.5 mL), Celite (8 g), and sodium sulfate (8 g) were added to the mixture, which was stirred for 1 h and filtered. Concentration of the filtrate gave an oily residue which was purified by chromatography on a silica gel column [eluant = methylene chloride–acetone (9:1 v/v)] to give the title compound (350 mg, 2.13 mmol, 70%) as a colorless viscous oil: NMR ($CDCl_3$) δ 1.7–2.6 (4 H, m), 4.34 (1 H, m), 4.8–5.3 (1 H, m), 5.60 (1 H, m), 7.2 (5 H, m).

6-Phenyl-2,2-(trimethylenedithio)tetrahydropyran. *n*-Butyllithium (2.1 M in hexane, 2.53 mL, 5.3 mmol) was dropwise added to a stirred solution of diethyl (1,3-dithian-2-yl)phosphonate (1.3 g, 5.3 mmol) in THF (20 mL) at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 10 min, allowed to warm to room temperature, and stirred for 0.5 h. After cooling to −78 °C, a solution of 5-phenyltetrahydrofuran-2-ol (0.35 g, 2.13 mmol) in THF (4 mL) was added. The resulting mixture was stirred at −78 °C for 15 min and then at room temperature for 2 h, quenched with water, and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and filtered. The filtrate was evaporated to give an oily residue. This residue was dissolved in methylene chloride (25 mL), PPTS (25 mg) was added, and the resulting solution was stirred at room temperature overnight. The reaction mixture was concentrated, and the resulting residue was purified by column chromatography on silica gel. Elution of the column with methylene chloride gave the title compound (0.40 g, 1.50 mmol, 70%) as a solid. The analytical sample was recrystallized from hexane: mp 99–101 °C; NMR ($CDCl_3$) δ 1.5–2.3 (8 H, m), 2.3–2.7 (2 H, m), 2.7–3.1 (1 H, m), 3.2–3.8 (1 H, m), 4.97 (1 H, dd, J = 11, 1 Hz), 7.4 (5 H, m). Anal. Calcd for $C_{14}H_{18}OS_2$: C, 63.11; H, 6.81. Found: C, 62.97; H, 6.90.

6-Phenyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one. To a stirred solution of 6-phenyl-2,2-(trimethylenedithio)tetrahydropyran (210 mg, 0.79 mmol) in acetonitrile (37 mL), THF (12.4 mL) and water (6.2 mL) was added powdered cadmium carbonate (295 mg, 1.7 mmol) followed by a solution of silver nitrate (250 mg, 1.47 mmol) in water (6.2 mL). The resulting mixture was stirred at room temperature until the starting material had been consumed as indicated by TLC. The reaction mixture was filtered through a pad of Celite and washed with portions of ether. The filtrate and the washings were combined, washed with water, dried, and filtered. Evaporation of the filtrate gave the title compound as an oily residue which solidified on standing (130 mg, 0.74 mmol, 93%). The analytical sample was recrystallized from methylcyclohexane: mp 69–70 °C (lit.[30] mp 74–76 °C); NMR ($CDCl_3$) δ 1.8–2.3 (4 H, m), 2.6 (2 H, m), 5.35 (1 H, m), 7.4 (5 H, s). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.35; H, 7.16.

2-[3(*S*)-(*tert*-Butyldimethylsiloxy)-7-[1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]-5(*R*)-hydroxyheptylidene]-

1,3-dithiane (22). *n*-Butyllithium (2.1 M in hexane, 4.05 mL, 8.5 mmol) was added dropwise under a nitrogen atmosphere to a stirred solution of diethyl (1,3-dithian-2-yl)phosphonate (2.18 g, 8.5 mmol) in THF (40 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 15 min, warmed to room temperature, and stirred for 0.5 h. The resulting brownish orange solution was cooled to −78 °C and treated with a solution of **6a** (1.0 g, 1.93 mmol) in THF (20 mL). The resulting mixture was stirred at −78 °C for 0.5 h and then at room temperature overnight. The reaction mixture was poured into aqueous ammonium chloride and extracted with ether. The ethereal extract was washed with sodium bicarbonate solution, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave an oily residue which was purified by preparative TLC to yield desired **22** (0.222 g, 0.36 mmol, 43% based on the unrecovered starting material) as a colorless, glassy oil: IR (film) 3500, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (6 H, s), 0.90 (9 H, s), 1.04 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 3.60 (1 H, m), 3.97 (1 H, q, J = 6 Hz), 5.3–5.6 (2 H, m), 5.78 (1 H, dd, J = 10, 6 Hz), 5.92 (1 H, t, J = 6 Hz), 6.00 (1 H, d, J = 10 Hz); MS, calcd for $C_{34}H_{58}O_4S_2Si$ m/e 622.3543, found 622.3518. Also a significant amount of the starting **6a** (0.575 g, 1.10 mmol, 57%) was recovered.

5(*S*)-(*tert*-Butyldimethylsiloxy)-7(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-2,2-(trimethylenedithio)hexahydrooxepin (23). A mixture of **22** (185 mg, 0.30 mmol) and PPTS (40 mg) in methylene chloride (15 mL) was stirred at room temperature for 6 h, diluted with ether, and washed with aqueous sodium bicarbonate. The organic phase was separated, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave an oily residue which was purified by preparative TLC to provide **23** (163 mg, 0.262 mmol, 88%) as a glassy oil: IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.04 (3 H, s), 0.07 (3 H, s), 0.90 (9 H, s), 1.05 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.1–3.5 (2 H, m), 3.8–4.2 (2 H, m), 5.35 (1 H, m), 5.53 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.05 (1 H, d, J = 10 Hz); MS, calcd for $C_{34}H_{58}O_4S_2Si$ m/e 622.3543, found 622.3530.

5(*S*)-(*tert*-Butyldimethylsiloxy)-7(*R*)-[2-[1,2,6,7,8,8a-(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]hexahydrooxepin-2-one (24). A solution of silver nitrate (85 mg, 0.5 mmol) in water (0.5 mL) was added dropwise to a stirred mixture of **23** (163 mg, 0.26 mmol) in acetonitrile (6 mL), THF (2 mL), and water (1 mL) containing powdered cadmium carbonate (103 mg, 0.6 mmol). The resulting mixture was stirred at room temperature for 1 h and then filtered through a pad of Celite. The filtrate was diluted with ether and washed with water. The organic phase was separated, dried ($MgSO_4$), and filtered. Concentration of the filtrate gave **24** (135 mg, 0.25 mmol, 97%) as a colorless, glassy oil: IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.90 (9 H, s), 1.08 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.0–3.4 (1 H, m), 4.18 (1 H, m), 4.63 (1 H, m), 5.36 (1 H, m), 5.53 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.02 (1 H, d, J = 10 Hz); MS, calcd for $C_{31}H_{52}O_5Si$ m/e 532.3586, found 532.3581.

7(*R*)-[2-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8-(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]ethyl]-5-(*S*)-hydroxyhexahydrooxepin-2-one (26) and 5(*S*)-[5-[1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2-(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]-2(*R*)-hydroxybutyl]dihydro-2(3*H*)-furanone (25). A solution of tetrabutylammonium fluoride trihydrate (0.322 M in THF, 10 mL, 3.22 mmol) was added to a stirred solution of **24** (135 mg, 0.25 mmol) in THF (1 mL) and acetic acid (0.36 mL, 6.3 mmol). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 5 days, warmed to 60 °C, and stirred for 22 h. The reaction mixture was poured into cold water and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave an oily residue which was purified by preparative TLC to provide a 4:1 mixture of **25** and **26** (85 mg, 0.204 mmol, 82% combined yield). Separation of this mixture by HPLC [Whatman Partisil-Pac, cyano-bonded column; eluant = hexane–2-propanol (9:1 v/v)] afforded **26** [15 mg; IR (film) 3450, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 1.06 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.0–3.4 (1 H, m), 4.23 (1 H, m), 4.65 (1 H, m), 5.3–5.6 (2 H, m), 5.78 (1 H, dd, J = 10, 6 Hz), 6.03 (1 H, d, J = 10 Hz); MS, calcd for $C_{25}H_{38}O_5$ m/e 418.2717, found 418.2711] followed by **25**: 49 mg; IR (film) 3500, 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 3.74 (1 H, m), 4.71 (1 H, m), 5.4–5.7 (2 H, m), 5.8 (1 H, dd, J = 10, 6 Hz), 6.03 (1 H, d, J = 10 Hz); MS, calcd for $C_{25}H_{38}O_5$ m/e 418.2717, found 418.2720.

Sodium 8-[1,2,6,7,8,8a(*S*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutyryl]oxy]-1(*S*)-naphthyl]-4-(*S*),6(*R*)-dihydroxyoctanoate (27). The addition of sodium deuteriooxide (0.8 N in D_2O, 0.1 mL) to a mixture of **25** (22 mg, 0.053 mmol) in methanol-d_4 (0.3 mL) and D_2O (0.2 mL) readily yielded a solution of **27**: NMR (D_2O–MeOH-d_4, with sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the zero reference) δ 0.86 (3 H, t, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 1.05 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 3.5–3.9 (2 H, m), 5.35 (1 H, m), 5.53 (1 H, m), 5.80 (1 H, dd, J = 10, 6 Hz), 6.00 (1 H, d, J = 10 Hz). Similarly, treatment of **26** with 1 equiv of sodium deuteriooxide in D_2O and methanol-d_4 produced a solution of **27** whose NMR spectrum was identical with that obtained for **27** derived from **25**.

Acknowledgment. Appreciation is extended to Mr. J. Lago for supplying mevinolin, Dr. H. Ramjit for mass spectra, and Dr. W. C. Randall and his staff for elemental analyses. We are indebted to Dr. C. S. Rooney for helpful discussions and to Dr. P. S. Anderson and Dr. R. Hirschmann for their support and encouragement throughout the course of this investigation.